FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

ANESTHETIC & LIFE SUPPORT DRUGS ADVISORY COMMITTEE

8:12 a.m

Tuesday, November 18, 2003

Holiday Inn
Montgomery Village Avenue
Gaithersburg, Maryland

ATTENDEES

COMMITTEE MEMBERS:

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ATTENDEES (Continued)

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FOOD AND DRUG ADMINISTRATION STAFF:

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MEHUL DESAI, M.D.
ROBERT MEYER, M.D.
DR. MARTIN POLLOCK
BOB RAPPAPORT, M.D.
LESTER SCHULTHEIS, M.D., PH.D.
ARTHUR SIMONE, M.D., PH.D.

ATTENDEES (Continued)

ALSO PRESENT:

ABU ALAM, PH.D.
BRUCE F. CULLEN, M.D.
T.J. GAN, M.B., F.R.C.A.

C O N T E N T S

P R O C E E D I N G S

(8:12 a.m.)

DR. KATZ: Good morning. I wonder if everybody could make their way to their seats.

My name is Nathaniel Katz. I will be co-chair of the meeting today.

Welcome. Let me begin by welcoming everybody to this meeting of the Anesthetic & Life Support Drugs Advisory Committee. This meeting will be about the use of droperidol.

I would like to give a special welcome to Terese Horlocker, who was the chair of this committee before I became chair, and she has kindly agreed to join us today and to actually chair this meeting since droperidol is more within her area of expertise as an anesthesiologist than it is in mine as a neurologist. So we're grateful to her for agreeing to join us.

Terry, would you like to make any introductory comments?

DR. HORLOCKER: Thank you. It's certainly an honor to be here, and I'm looking forward to a truly educational session. Also as an anesthesiologist, I'm very interested in the outcome of these proceedings. Droperidol has been around since 1970, but the ongoing case reports of prolonged QT leading to torsade de pointes, as well as some

of the clinical investigations led to the FDA placing a black box warning in December of 2001. That action took away one of our major front line drugs for the treatment and prevention of nausea and vomiting, as well as a great rescue medication, or at least severely limited its use. So it's not surprising that this caused a lot of controversy within the anesthesia commission. However, the FDA has always promised to convene an advisory committee panel to discuss these proceedings, and thus here we are today.

In my opening comments, what I want to do is to say to the advisory committee we are not here to discuss the relative efficacy and risk of the other antiemetic drugs. We want to focus on droperidol. And as you've all reviewed your questions, we want to really focus on the labeling and also what recommendations we can make to the FDA to make this drug as safe as possible to administer to our patients.

Thank you.

DR. KATZ: Thank you very much.

Let me just remind everybody around the table of a couple of different mechanical issues here. When you do want to speak, just raise your hand later during the discussion, and Dr. Horlocker will recognize you, more or less, in the order that your hand goes up. We'll try to be

as fair as possible about that, given the need to make sure that the discussion is on point.

When you do speak, you have to press this little microphone button in front of you where it says "mic," and when you're done speaking, you need to turn it off unless you want everybody to hear all your whispered comments that you make to your neighbor. And it creates a lot of feedback, so try to remember that, and we'll remind you.

With that, what I'd like to do, since many of us don't know each other and Dr. Horlocker has not met some of you, I'd like to go ahead and have everyone around the table introduce themselves. So if we could start at that end please.

DR. MEYER: I'm Dr. Bob Meyer. I'm the Director of the Office of Drug Evaluation II in the Center for Drugs at FDA.

DR. RAPPAPORT: I'm Bob Rappaport. I'm the Director of the Division of Anesthetics, Critical Care, and Addiction Drug Products in the Center for Drug Evaluation and Research.

DR. CHANG: Nancy Chang, same division. I'm the medical team leader for anesthetics.

DR. RODEN: Dan Roden, clinical pharmacology and electrophysiology at Vanderbilt.

DR. KOWEY: Peter Kowey. I'm one of your other token cardiologists for the day. I'm Professor of Medicine at Jefferson and head of cardiovascular diseases at LanKenau Hospital, Main Line Health in Phillie.

DR. SHAFER: Steve Shafer, anesthesiologist and clinical pharmacologist at Stanford, UCSF, and anesthesiologist at the Palo Alto VA Health Care System.

DR. HOLMBOE: Eric Holmboe. I'm a general internist from Yale University, and my role here is as a member of the Drug Safety and Risk Management Advisory Committee.

DR. KAHANA: Madelyn Kahana. I'm a professor of pediatrics and anesthesiology at the University of Chicago.

MS. CLIFFORD: Johanna Clifford. I'm the Exec Sec to this meeting.

DR. HORLOCKER: Terese Horlocker, Mayo Clinic, co-chair.

DR. BRIL: I'm Vera Bril. I'm a professor of neurology at the University of Toronto.

DR. ROSE: I'm Carol Rose. I'm an anesthesiologist at the University of Pittsburgh Medical Center, and I have a particular interest in anesthesia for electroconvulsive therapy at Western Psychiatric Institute and Clinic in Pittsburgh.

DR. BITETTI: I'm Janice Bitetti. I'm on the faculty at George Washington University and anesthesia.

DR. WLODY: I'm David Wlody. I'm an anesthesiologist at the State University of New York Downstate Medical Center in Brooklyn, New York.

DR. CRAWFORD: Good morning. Stephanie Crawford, University of Illinois, Chicago, College of Pharmacy, and also a guest member from the Drug Safety and Risk Management Advisory Committee.

DR. BOBEK: Mary Beth Bobek, University of North Carolina, Chapel Hill School of Pharmacy.

DR. EISENACH: Jim Eisenach, anesthesiologist, Winston-Salem, North Carolina.

DR. BALSER: Jeff Balser, Chair, Anesthesiology at Vanderbilt, Nashville, Tennessee.

DR. GILLETT: Jim Gillett, Professor of Toxicology and patient rep for Esophageal Cancer Awareness Association, Cornell University.

DR. McLESKEY: Charlie McLeskey, anesthesiologist by training. I work for Abbott Laboratories, and I'm the industry representative to the committee.

DR. KATZ: Thank you very much, everybody, and with that, Johanna Clifford will read the conflict of interest statement.

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has been determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

Dr. Nathaniel Katz has been granted a waiver under 18 U.S.C. 208(b)(3) for consulting with two competitors on unrelated matters. He receives between $10,001 to $50,000 a year from each firm.

Dr. Dan Roden has been granted a 208(b)(3) waiver for consulting on unrelated matters for a firm that manufactures a competing product. He receives less than $10,000 a year. Also, for serving as an expert witness for a competitor on an unrelated matter, he receives greater than $50,000 a year. Dr. Roden has been granted a waiver under 21 U.S.C., section 355(n)(4) for owning stock in a competitor worth greater than $50,000, but less than $100,000.

DR. RODEN: My wife owns the stock.

MS. CLIFFORD: Okay, thank you.

DR. RODEN: In a blind trust.

MS. CLIFFORD: Thank you.

Dr. Robert Dworkin, who will be joining us later, has been granted a 208(b)(3) waiver for consulting with five competitors. He receives less than $10,000 a year from each firm. Also, Dr. Dworkin is a speaker for a competitor on unrelated matters. He receives from $5,001 to $10,000 a year.

Dr. Peter Kowey has been granted a 208(b)(3) waiver for consulting with four competitors on unrelated matters. He receives less than $10,000 a year from each firm. Also, Dr. Kowey is a member of a competitor's speaker's bureau. He lectures on unrelated matters and receives greater than $10,001 a year. Lastly, Dr. Kowey is a consultant to a competitor firm on unrelated matters. He receives greater than $10,000 a year.

Dr. Thomas Fleming has been granted a 208(b)(3) waiver for consulting with five competitors on unrelated matters. He receives less than $10,000 a year from each firm.

Dr. James Eisenach has been granted a 208(b)(3) waiver because his employer has a contract with a competitor for a study of an approved competing product. This study is funded for less than $100,000 a year.

Dr. Janice Bitetti has been granted a waiver

under 21 U.S.C., section 355(n)(4) for owning stock in a competitor valued between $5,001 to $25,000 a year.

A copy of these waiver statements can be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building. The signed disclosure statements are also available for public review at this meeting.

We would also like to note that Dr. Charles McLeskey is participating in this meeting as the acting industry representative acting on behalf of all regulated industry. Dr. McLeskey is an employee of Abbott Laboratories.

With respect to FDA's invited guests, Dr. Marek Malik has reported interests that we believe should be made public to allow the participants to objectively evaluate the comments. Dr. Malik has received research grants, consulting fees, and speaker's fees from a number of pharmaceutical companies; however, he has never received any grants, consulting or speaker's fees related to the product at issue or its competitors.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for

the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. BALSER: My conflicts of interest were submitted a few weeks ago, but were not read.

MS. CLIFFORD: Thanks, Dr. Balser. We'll take a look at that.

DR. KATZ: With that, I'll turn the meeting over to Dr. Horlocker, who will be chairing the meeting for the rest of the day.

DR. HORLOCKER: Dr. Rappaport, would you like to make your opening comments?

DR. RAPPAPORT: Good morning. Dr. Katz, Dr. Horlocker, members of the committee, and invited guests. Thank you for participating in this meeting today.

The purpose of today's session is to enlist your assistance in determining the best path forward for our ongoing risk analysis of the cardiovascular toxicity of droperidol, an important product in the anesthetic armamentarium.

As you are aware, in March of 2001, Janssen discontinued marketing of droperidol internationally except

in the United States where the generics firm Akorn had recently acquired the U.S. distribution rights from Janssen. Janssen's decision to discontinue marketing was based on concerns regarding the drug's potential to cause life-threatening ventricular dysrhythmias.

Shortly after the withdrawal was announced, the division held teleconferences with both Akorn and Janssen representatives and was informed of an existing internal analysis that had been performed by Janssen. We requested and received that document, and after review, we performed an internal review of our own postmarketing safety database for droperidol, as well as a thorough literature review. Those reviews led us to the conclusion that a real signal for an association between QT prolongation, torsade de pointes, and droperidol did indeed exist.

We held numerous telecons with Akorn, as we attempted to find ways to establish and evidence-based data set that would allow us to assure safe use of the drug and to avoid removing this widely administered product from the market. Although we were unable to fully achieve this goal, based on a clear demonstration of significant QT prolongation and torsade, the absence of a clear safety margin or clear prevention and management strategies and the existence of alternative treatments, we chose to take the relatively conservative approach of a labeling change.

In doing so, we also took into account the long marketing history of the drug, the importance of the drug to the community, and the use of relatively low doses in current practice. Thus, following our regulatory mandate to communicate serious safety signals to practitioners on an urgent basis, the agency placed a boxed warning on droperidol labels in November of 2001.

Due to the necessity for us to act on an urgent basis, we did not convene a meeting of this committee prior to instituting the changes in the label. And although in retrospect, it may have been prudent for us to have communicated more effectively at that time, the intensely negative responses to the label changes from some members of the medical community were not ignored.

In addition to publication of an article outlining the reasons for our action, we committed to conducting a pharmacokinetic/pharmacodynamic study to evaluate the dose-related effects of droperidol on the QT interval. You will hear a detailed presentation of that study later this morning from one of the original investigators who is now a medical officer in the Cardio-Renal Division of the agency.

Unfortunately, that study was discontinued prematurely due to significant neuropsychiatric adverse events and was therefore inconclusive.

Since the results of that study became available, we've been exploring the options for obtaining additional data that would satisfy the regulatory standards for a demonstration of safety and efficacy at doses lower than those currently labeled, as well as data that would clearly define the risks associated with use of the product in general. This task has turned out to be far more challenging than we had suspected and, indeed, it's not even clear to us at this time whether there is a reasonable path or if further efforts are even warranted.

The presentations today will focus not only on the cardiotoxicity profile of droperidol, but also on our efforts thus far to find an appropriate study design to fully elucidate that profile and the limitations that are inherent in the exploration of any low incidence, high morbidity adverse event.

Dr. Malik, one of the international medical community's leading experts on QT prolongation, will present the current thinking on evaluation and assessment of this often drug-induced toxicity. FDA staff will provide you with a history of the original product approval, a detailed portrait of the agency's assessments and actions since March of 2001, and the current status of our evaluation of risk assessment for this product.

In addition to seeking your assistance in

determining the most appropriate way for the agency to proceed with a significant public health concern, we will also be asking you to provide us with advice on how we might best communicate to the medical community the risks of cardiovascular toxicity that are associated with droperidol. There have been cases of torsade reported following the use of droperidol not only at the labeled doses, but also at the commonly used, unapproved lower doses. The literature establishes a clear relationship between droperidol and QT prolongation.

What further evidence, if any, is necessary in order to provide practitioners with a clear picture of the risk/benefit ratio for this product?

If more data is required, how may this best be obtained?

Based on the available data, is the current level of safety information in the label appropriate?

And are there other modes of risk communication that should be considered?

These are some of the questions you will be asked to address later today. Please keep these questions in mind as we chronicle this complex and often frustrating story for you.

And thank you again for your participation. I believe that we have a stimulating and challenging day

ahead of us, so I'll end here and I'll turn the meeting back to Dr. Horlocker.

DR. HORLOCKER: Thank you.

We'll proceed with our next speaker who is Dr. Simone.

DR. SIMONE: Good morning and welcome. I'm Art Simone, a medical officer in the Division of Anesthetic, Critical Care, and Addiction Drug Products. Together with Dr. Nancy Chang, anesthetics team leader in the division, we will present the history of droperidol from the submission of the new drug application to the placement of the boxed warning on the label.

Specifically, my goal is to provide the historical context of its approval from a regulatory, clinical, and safety perspective with emphasis on use of droperidol to prevent and treat perioperative nausea and vomiting. It is our hope that these presentations go beyond mere descriptions of FDA actions and provide some insight as to the basis for these actions.

Let us begin then with the new drug application for Inapsine. McNeil Laboratories submitted its NDA in June of 1968, including studies which it felt supported the claims of safety and efficacy for three general indications: for sedation or tranquilization in the perioperative setting, including all phases of anesthetic

care; neuroleptanalgesia, which is a tranquilized, stress-free state induced so patients may undergo and tolerate surgical and diagnostic procedures; and for prevention of nausea and vomiting.

Pharmacokinetic data regarding absorption, distribution, metabolism, and elimination in humans was not submitted with the NDA. Rather, a rat study of the elimination of tritiated droperidol was provided. However, even that was limited in its scope. A determination of all metabolic products was not performed, and metabolites that were detected were not assessed from a toxicology perspective. While this would constitute a serious deficiency by today's standards, it was acceptable in the 1960s.

The clinical studies submitted for agency review were, for the most part, conducted shortly after the 1962 Kefauver-Harris amendments to the federal Food Drug and Cosmetic Act. These amendments included requirements by sponsors to show their drug products were efficacious, as well as safe, in essence, enabling the FDA to perform risk/benefit analyses of new therapeutic agents.

The submitted studies were completed prior to the agency's issuance of a guidance on adequate and well-controlled studies which provided FDA's understanding and interpretation of how the amended act was to be

implemented. With this in mind, let us look at the clinical portion of the NDA.

McNeil provided the agency with a total of 54 phase II and phase III trials that were to serve as the basis for findings of safety and efficacy. The trials were conducted by 50 investigators and included 2,906 patients. In each trial, droperidol was used either as an adjunct to anesthesia or as a component of neuroleptanalgesia. Most of the trials were uncontrolled. 17 percent of the trials had only 1 patient. Few had formal protocols, and most were anecdotal in nature.

The clinical data were presented in three parts. These included tabulated and analyzed data collected from the 1,824 patients in 44 trials who received droperidol related to their anesthetic care; data from 1,197 patients involved in what were described as special studies such as otologic procedures, pneumocephalograms in pediatric studies. 115 patients were common to both parts I and II. Lastly, investigators were polled as to their opinions of droperidol's safety and efficacy when used as a neuroleptanalgesic.

In the part I studies, some of the 44 trials included evaluation for prevention and treatment of nausea and vomiting in the perioperative period, generally limited from the time of admission to the holding area to the time

of discharge from the recovery room. More than half the studies evaluated 10 patients or less. 5 of the studies included 70 or more patients.

Pertinent to current issues surrounding droperidol are the doses for which FDA has safety data. This slide provides a breakdown of the doses evaluated in part I studies. Although doses of less than 1 milligram were used, the number of patients receiving these doses were too small for the evaluation of safety and efficacy. In addition, many patients received doses at more than one period, further complicating the issue.

Routes of administration included intramuscular, intravenous, intravenous drip, and combination of an intravenous bolus and intravenous drip. The significant number of incidents of unreported routes of administration, which is listed in the last column, limits the usefulness of the data, particularly in the assessment of preoperative administration where there were 273 such cases.

Part II studies bring to the fore an interesting issue regarding safety monitoring. Even in the special study of epinephrine antagonism in which 5 patients were evaluated for the use of droperidol as an alpha adrenergic blocking agent, there was no electrocardiograph monitoring. Rather, manual intermittent blood pressure and

pulse rates were assessed as the primary determinants of cardiovascular status. In the 1960's, use of ECG monitoring was the exception, not the rule.

Part III of the clinical data included a survey of investigators regarding their opinion of the drug's safety and efficacy. 98 percent found it to be both safe and efficacious. It may be argued by some that the percentage has changed only minimally in the 30-plus years that droperidol has been marketed.

Let us turn our attention now to the efficacy data for droperidol, such as they were, relating to the prevention and treatment of nausea and vomiting. The salient point for each of these studies is the dose or the dose range studied.

The NDA submission noted the results of two studies in particular and combined data from several other studies where incidence of nausea and vomiting were assessed. In the part II study of droperidol use during pneumocephalography, evidence suggestive if not fully supportive of efficacy was shown at a dose of 0.15 milligram per kilogram or 10.5 milligrams for the average 70-kilogram adult.

In a study comparing three pharmacological approaches to neuroleptanalgesia, including droperidol with meperidine, chlorpromazine and meperidine, and

chlorpromazine used with fentanyl, droperidol significantly reduced the incidence of nausea and vomiting when given at a dose of 10 milligrams intravenously.

Lastly, an overall evaluation for nausea and vomiting during intraoperative and immediate post-operative periods -- that's in the recovery room -- was performed on a combination of several studies. An incidence of nausea and/or vomiting was found to be about 5 percent, with mean droperidol doses ranging from 5 to 7 milligrams.

That only one study, a prospective controlled trial provided the strongest evidence of efficacy is not the primary point to be made here. Rather, antiemetic doses tested ranged, for the most part, from 5 to 10 milligrams. Patients under 33.3 kilograms would have received less than 5 milligrams in the pneumocephalogram study, and that was the only study that would look at a dose that low.

Adverse event data for the part I trials included assessment made during the post-operative period; that is, the time in the recovery room. This table summarizes the cardiovascular events noted. These studies included the use of: droperidol alone; that is, other non-narcotic agents were used in the anesthetic; droperidol with Innovar, which is a droperidol and fentanyl fixed combination drug; and droperidol with fentanyl; or a

combination of all three. So, indeed, it's droperidol, droperidol and fentanyl; droperidol and fentanyl; or droperidol and fentanyl; and droperidol and fentanyl.

Even during this limited time frame, on the order of about 1 hour postoperatively, and scant monitoring which was in place, a substantial number of events were noted.

Cardiovascular adverse events noted among all patients exposed to droperidol are included in this table. In some of the studies, the actual incidences of hypo or hypertension were not reported. In these cases, the number of events was treated as 1 and the plus sign was added to indicate the number was actually greater. Often cutoff values defining hypo and hypertension or brady- or tachycardia were not prespecified, introducing the possibility of inconsistent and arbitrary reporting of these adverse events. Interesting to note are the episodes of arrhythmia reported despite the lack of routine electrocardiographic monitoring.

The next slide summarizes patient fatalities. Deaths are listed by time of occurrence relative to surgery. There's a peak occurrence from postoperative days 1 through 4, but a relatively substantial number of cases occurred through the first 24 hours as well. In fact, the 9 of the 2,906 patients who died during the intraoperative

and immediate postoperative period constitutes a death rate of .31 percent. If one looks at all deaths occurring up through postoperative day number 4, it's a rate of .96 percent.

In April of 1969, McNeil submitted an amendment to the new drug application satisfying deficiencies noted by the review staff, and in June 1970, Inapsine was approved for marketing in the United States.

Indications on the approved label were listed as preoperatively during induction and during maintenance for sedation or tranquilization, for anti-anxiety activity, and for reduction of the incidence of nausea and vomiting.

The dosing was described as shown based on when it was to be used perioperatively. You will note that there are no dosing recommendations for postoperative use or for the prevention or treatment nausea and vomiting.

So where did this leave us at the start of the new decade? Data provided by the sponsor was extremely limited in its usefulness for a safety evaluation that is applicable to the current question at hand. There was substantial incidence of results that were described as "not reported." Some concerned the routes of administration. Others concerned safety outcomes. For example, in some of the nausea and vomiting evaluations, it was assumed that neither occurred because there were no

reports of incidents occurring, and both were defined as adverse events. While this may not be a significant problem in and of itself, the scale to which it occurred, a total of 305 cases of no documentation for nausea and vomiting outcomes, raises concerns about the attention paid to gathering other safety and efficacy data.

Combining data from diverse protocols, especially large numbers of studies with small numbers of subjects, makes it difficult to derive meaningful dosing information and to discern possible safety issues. This is especially true when most of the data come from uncontrolled trials.

The mortality rates reported overall within the first 4 postoperative days and even within the first 24 hours following surgery are relatively high compared to the 1 in 10,000 mortality rates generally associated with anesthesia at that time. Without a control population, however, it is difficult at best to determine a role for droperidol in the increased mortality.

The same applies for the incidence of cardiac events that were seen, and although a case could be made that some of the serious adverse events were related to the patient's medical status preoperatively or to the nature of the surgeries they underwent, there is no way, without controls, to assess if droperidol added substantially to

these risk factors.

The sponsor also included literature from European studies involving droperidol. Such studies may be used to support a finding of safety and/or efficacy, although they're not without their limitations.

Despite these concerns, which are much easier to raise retrospectively, the approval of droperidol in 1970 was made in accordance with the clinical and regulatory standards of the time. From the perspective of the practice of medicine in anesthesia in the early 1960's when the studies were done, the level of monitoring in anesthesia was such that risks associated with many drugs would be nearly impossible to detect by the standards in place and the equipment available at the time. Indeed, it would be another 16 years before the American Society of Anesthesiologists would promulgate its first standards for basic monitoring, including continuous ECG monitoring.

Similarly, our understanding of drug actions and interactions on the cellular level were limited. It would be years before the issue of QTc prolongation would become a consideration for all new molecular entities and for some older entities not heretofore evaluated.

The 1950s and 1960s marked the beginning of an era for the development of new anesthetic agents. Given the limited armamentarium of the time, a higher level of

risk was acceptable in order to provide alternative agents in virtually all anesthetic drug classes. From a regulatory perspective, requirements for approval had recently been changed to include demonstration of efficacy. Safety evaluation was still evolving. Given the data presented, the practice of anesthesia at the time and the limited options for anesthetic drug products, a risk/benefit analysis supporting approval was not inappropriate.

Over the last three decades, the clinical use of droperidol has evolved. The introduction of new drugs with shorter duration of effect and fewer side effects have significantly reduced the use of neuroleptanalgesics and droperidol as a major component of balanced anesthetics. Nonetheless, droperidol has remained popular as an antiemetic. Indeed, from 1998 to 2001, unit sales of droperidol in the United States almost doubled from 5 million to nearly 10 million. The anesthesia community has observed that reduced off-label doses of droperidol, doses one-half to one-quarter of that currently labeled, seem to provide satisfactory control of perioperative nausea and vomiting, while reducing the incidence of dysphoria and excessive sedation. Emergency room physicians and psychiatrists have found droperidol to be a useful agent in the treatment of severely agitated patients, a use that is

off-label. Despite these changes in practice, the FDA has not been provided with the necessary evidence that use of droperidol at these doses and in these settings is safe and efficacious.

At the end of 2001, the labeled indications remained essentially unchanged from that of 1970. Droperidol was still only approved for use in the setting of an anesthetic to produce a tranquil state, induce or maintain a general anesthetic as an adjunct to regional anesthesia and as a neuroleptanalgesic agent.

Likewise, dosing information has also remained unchanged. For adults, starting doses were a minimum of 2.5 milligrams for all indications, and the lowest approved dose of 1.25 milligrams was reserved for supplementation purposes alone. There remains no labeled dose for the prevention or treatment of nausea and vomiting.

So where did this leave us at the turn of the century? We have a drug for which the FDA had no pharmacological profile for its use in humans and only scant information on its excretion in animals; a drug, which when used at labeled doses, is associated with cardiovascular events and mortality rates that by current standards suggest possible safety issues; a drug whose off-label administration constitutes a significant portion of its use; and a drug whose perhaps most popular use is

indicated although at doses, specifically the .625 milligram dose, for which the sponsor has not provided evidence of safety or efficacy to the FDA for its evaluation.

My colleague, Dr. Nancy Chang, will be picking up the story from here. I'd like to thank you for your attention, and I'd be happy to address any questions members of the committee may have.

DR. HORLOCKER: Are there any questions or points of clarification? There will be a building of the story by Dr. Chang who will discuss things after 2001. So please limit your questions to the pre-2001 for Dr. Simone. Any questions?

DR. HOLMBOE: Would you please just clarify the mortality data that you showed? I'm concerned that you're showing mortality data without context. In other words, these were deaths, probably some related to the surgery, and it's not clear to me exactly how this relates to the use of droperidol.

DR. SIMONE: The fatality data is that for all patients that participated in the trials. Sometimes there was no analysis offered by the people conducting the trials as to the actual cause of death. The trials in which it was used do run a gamut from extraction of molars to thoracotomies and cardiac surgeries. So there were

significant numbers that did occur in more complicated procedures where you would expect a higher death rate. But again, without a control study for comparison purposes, you don't know if the use of this drug seems to push the equation more towards one side or the other. So we have limited data to go by.

DR. HORLOCKER: Any other questions? Thank you, Dr. Simone. Dr. Chang. Oh, I'm sorry.

DR. RODEN: I was intrigued by the idea that the sales of this drug have doubled over a very short period of time, and I'd ask mostly my anesthesia colleagues around the table why has that happened.

DR. HORLOCKER: I would think it's because of the aggressive prophylaxis and treatment of postop nausea and vomiting, especially among the outpatient setting where that's such a point of patient satisfaction that we were very aggressive with trying to prevent nausea and then also treat it aggressively to facilitate discharge.

Does anybody else have other comments on that?

DR. RODEN: But this happened in the context of a drug that's never been studied at those doses and for which there's no data.

DR. HORLOCKER: I would actually differ with that, that there have been many studies. Droperidol is truly the gold standard, and then when ondansetron and some

of the other serotinergic medications came out, they were compared against these lower doses of droperidol.

DR. RODEN: Will we get an opportunity to hear those data?

DR. BALSER: There are studies at these doses. I think what the speaker meant was that the drug company hadn't submitted those data. Am I not correct?

DR. SIMONE: That's correct. The agency reviews the information submitted to it by the sponsor.

DR. RODEN: Well, are we going to hear those data sometime today?

DR. SIMONE: There will also be a discussion by Dr. Chang regarding the use during this time period, and she may be able to address some of the other drugs used as well.

DR. CHANG: We're not going to directly present the data that have been published in the literature because those data have not been submitted to us. We haven't been able to look at those and scrutinize them in any sort of a thorough way.

The other point I would make with respect to use is that we have seen an increase in use with all antiemetics. This isn't isolated to droperidol. All antiemetics have been steadily increasing in use over that period of time.

DR. HORLOCKER: Yes, sir.

DR. SHAFER: Just for the record, Dan -- I don't think this is even in doubt -- there are probably in the area of 20, 30, 40 well-done, large studies with thousands of patients. So I don't think the effectiveness of droperidol as an antiemetic at these doses is in doubt.

DR. HORLOCKER: And as Dr. Chang will point out, we have documented efficacy but nobody has done the true risk analysis of this. So even if we have the efficacy, we don't have a comparative risk analysis at these doses. So having half of the answer is not really helpful in this situation.

Dr. Fleming.

DR. FLEMING: So I'm still confused by this. We're not going to see the data that establishes the efficacy at these very low doses, and if we're not, can somebody confirm that there are proper placebo controls or, if not, how is it that we interpret efficacy?

DR. SIMONE: The determination of safety and efficacy is something that's under the purview of the FDA and that's based on the information that's provided to the agency by the sponsor. So we only have information delivered to us by the sponsor with which to address these issues.

DR. CHANG: The determination of safety and

efficacy has been made by the medical community, but that assessment has not been made by the FDA.

DR. HORLOCKER: Dr. Shafer, did you have an additional comment?

DR. SHAFER: Yes. I just want to comment when you said that they hadn't done safety, actually certainly all the studies that I'm aware of -- and again, there have been lots of them by our colleagues, including perhaps some people in the room here -- did in fact, document a pretty low incidence of safety problems. Now, whether there was a formal risk/benefit -- but certainly the studies didn't just report efficacy in the absence of any safety assessment.

DR. HORLOCKER: That's correct.

Dr. Eisenach.

DR. EISENACH: Well, yes, we did one of these studies 15 years ago with 400 subjects, and there are multiple studies that have been published in the last 15 years regarding low doses of droperidol in placebo-controlled and active-controlled trials. There is no doubt in the medical community from these well-controlled trials that these doses are effective.

Similarly, all these studies were done during the time of modern ECG monitoring and the ASA guidelines of the late '70s. Now, clearly, very large effects such as a

torsade de pointes would have been reported as part of that database. So I think it's unfortunate that the FDA took the case reports of problems and reviewed those for us but didn't provide us with a summary of the published data so we had an idea of what the denominator is.

Another reason perhaps for this large increase was several recent meta-analyses and reviews which suggested that droperidol was equally or more active than more expensive alternatives.

DR. HORLOCKER: I'd like to limit the discussion right now to just points of clarification because Dr. Chang is going to elaborate on the 2001 experience.

DR. BRIL: Well, I just wanted to make a point about efficacy data and what we've been presented with. In similar situations, it's what's presented to the regulatory agency and the trials you present with the safety data collected in a manner that the agencies require that would lead to the balancing of those studies. So the medical community can be convinced of efficacy of different interventions for different disorders very clearly from trials, but although safety is collected, it may not be in the form that would be acceptable to the agencies and reviewable by them. So there's a whole body of opinion that may say this is an effective safe treatment for

something, but it won't be labeled as such or approved as such. If you take some of these trials to the agency, then there are a lot of questions that arise because of the way they were run and things like that. So there's not a concurrence I think always with what happens.

DR. HORLOCKER: Dr. Chang, why don't you go ahead and we'll have a discussion after both your presentation and Dr. Simone's.

DR. CHANG: Good morning. I'm going to present to you a little bit of the agency's approach and the rationale behind that approach that led to the 2001 labeling changes for droperidol. I do want to emphasize that I am not trying to advocate a particular position or a particular action with respect to droperidol. The agency's approach to drug-induced QT prolongation has gone through a very rapid evolution in the last several years in response to an also very rapidly evolving science. So it's in that context that I'm going to present to you and as a group were going to present to you what we know about droperidol. I hope that we will be able to convey to you what a very difficult and complex regulatory issue this is, and I hope that you will take these issues into account as we try to work together and find the best path forward.

Probably the first major announcement of a potential problem with droperidol occurred in 1997 when the

French agency announced that they were concerned about a number of sudden deaths related to droperidol. Now, these deaths were occurring in large part in patients who were getting very large doses. A lot of these patients were alcoholics. But nevertheless, the agency estimated an incidence of sudden deaths at 1 per 55,000 vials, and because of that concern, they issued a Dear Doctor letter and they made a change to their labeling.

In early 2001, we found out from the British that Janssen was going to discontinue marketing of droperidol worldwide. Again, this was related to a risk/benefit assessment by Janssen looking at specifically the concern of QT prolongation related to droperidol. They chose to stop marketing all forms of droperidol, both oral and IV, although in their statement, they said that their primary concern was the use of oral doses in chronic conditions. With this statement, this was what prompted us to do our own analysis at FDA.

I'm going to present to you first the results of our postmarketing spontaneous reports. These numbers are going to be somewhat different from some of the numbers you've seen elsewhere for a couple of reasons. One is that the numbers have been updated to October of 2003, and the other is that these particular search terms have been narrowed down from some of the earlier search terms that

had been used. The largest contributor would be we have a large number of deaths related to droperidol that have not also been associated with one of these cardiac terms. That large number of patients has not been included in this particular analysis.

So the particular search terms we used here are QT prolongation, torsade de pointes, cardiac arrest, ventricular tachycardia, ventricular fibrillation, ventricular arrhythmia, and sudden death, and only those terms. Altogether from the time of marketing to October 2003, we had 89 events, 46 of which were fatal.

If you look at the QT and torsade cases only, we had 22 cases. At least 5 of them are fatal, and the "at least" is because in a number of these cases we don't know the outcome. 14 of those cases were specifically torsade. Almost all of them were by injection, and the doses that were reported ran the gamut, but you will note that we have out of those 7 cases that were at and below the lowest labeled dose of 2.5 milligrams. The onset was also variable. We have a large number of cases that occurred early after administration of droperidol, and others where the onset time is really not as clear.

This is a graphic of just the events related to doses less than or equal to 2.5 milligrams. Again, this is going back to the whole set of 89 patients.

Included in the less than 2.5 milligrams, out of those 89, we have 26: 10 deaths, 18 cardiac arrests, 6 cases of QT prolongation, and 3 cases of torsade. And I would note that these events are not mutually exclusive. So some of these events may be torsade and cardiac arrest, for example. At less than 1 milligram, 5 deaths, 9 cardiac arrests, 2 QT prolongations, and 1 torsade.

I'm going to present to you some of the case reports we've seen really just to give you a flavor of the case reports, and for reasons that I'm going into a little more later, I really don't want to spend a whole lot of time picking apart these case reports. This is really just to give you a sense of what it is that we see.

Our first example is a 60-year-old female who got 0.65 milligram of droperidol for nausea, had QT interval prolongation. And that's all we know. That's all we know. Unfortunately, this is not atypical. We see a lot of cases like this where the information is just simply incomplete.

This case is a little bit better. We've got a 44-year-old female, 115 pounds, had 1.25 milligrams of droperidol for nausea in the ER. She was being treated for UTI. The quote from the Medwatch report is that she then suffered adverse side effects including QT prolongation, chest pain, difficulty breathing, dizziness, extreme

agitation, et cetera. And again, that is a quote. No past medical history, and the only other medication she was getting was Levaquin. Again, that's all we know.

The third case example is a little more informative. A 52-year-old male who was undergoing a transjugular intrahepatic portal systemic shunt. He had a past medical history of alcohol abuse, cirrhosis, ascites, esophageal varices. He was a smoker, had COPD. During the course of the procedure, he got three doses of IV droperidol, each at 1.25 milligrams over the course of an hour and a half. His EKG was noted to be sinus rhythm throughout the procedure except with the second dose when he was noted to have some premature ventricular contractions.

The procedure was completed about 3 hours after the last dose of droperidol. He was sent to the unit about an hour and a half after that, and at 7:15, which was more than 7 hours after the last dose of droperidol, he was noted to be in torsade which progressed to ventricular fibrillation and then cardiac arrest. He was defibrillated. He was reported as having no evidence of ischemia, and 8 days later he expired for apparently unrelated causes.

The other medications he was given was gentamicin and vancomycin. Fentanyl was reported as being

550 milligrams. I think it's probably micrograms, but that's what we have. And 4 milligrams of versed during the course of the procedure. He was not reported as being hypokalemic but apparently he was receiving potassium, and he also received some heparin.

The next thing we looked at was the literature. There are a number of literature reports associating droperidol with QT prolongation. In 1994, Lischke, et al. reported on a study that they did in, again, relatively large doses of droperidol. That group found median QT increases of 37, 44, and 58 milliseconds in this surgical population. This was a surgical population that was generally healthy, that did not have prior cardiac disease.

Guy, et al. in 1991 reported a case of a 61-year-old woman who was a diabetic on oral hypoglycemics. She came in for a surgical procedure related to urinary stones. They gave her, as a premedication, a milligram of atropine, 50 milligrams of hydroxyzine, and then 12.5 milligrams of droperidol.

After the dose of droperidol, she had an episode of torsade. It resolved spontaneously. And then the next day, she was also noted to have several other incidents of torsade, for which they defibrillated her.

After they saw this very interesting case, well, they decided to rechallenge her. So they took her

and under electrocardiographic monitoring, they repeated the sequence. They gave her atropine. They gave hydroxyzine. No QT prolongation was noted after those two doses. After another dose of 12.5 milligrams of droperidol, she was noted to have a 60-millisecond prolongation of QT.

So that initiated a study of 55 patients, again at relatively high doses of droperidol, and the mean QT prolongation that was noted in those studies was from a mean of 387 to 423 milliseconds.

I would note too that for both of these studies, the Lischke and the Guy studies, the electrocardiogram was only looked at for the first 10 minutes after administration of droperidol. The onset and apparent peak effect occurred very early on at about 1 to 2 minutes, but there appeared to be a persistent effect at 10 minutes when monitoring was stopped.

Reilly in 2000 looked at a large cohort of psychiatric patients, inpatient and outpatient. They did electrocardiograms on them. And in that group of psychiatric patients, of 37 patients who were on droperidol, 6 of them were found to have a QTc interval of greater than 456 milliseconds. And the 456-millisecond cutoff was chosen as being 2 standard deviations away from a control population that they also studied.

They concluded from their study that droperidol was one of the most significant predictors of an abnormal corrected QT interval. That was when they looked at a number of variables, including demographics, including psychiatric diagnosis, including a large host of different medications.

Finally, Frye in 1995 reported two case reports of patients who were receiving infusions of droperidol after surgery for treatment of agitation, and those 2 patients had very impressive prolongations of corrected QT intervals. They had actually reported 3 different case reports of patients who received droperidol, and the third apparently did not have a QT prolongation.

Finally, we have some in vitro data from Drolet, et all. They studied three different in vitro models. They looked at isolated guinea pig hearts, looking at action potential durations. They looked at guinea pig ventricular myocytes, looking at the rapid component of the delayed rectifier potassium current and they looked at the HERG channel expressed in HEK293 cells.

I would note that for those who haven't followed this literature, the rapid component of the delayed rectifier potassium current is predominantly associated with the HERG channel, and of all the drugs that we know to be associated with clinically significant QT

prolongation, most if not all of them have been associated with significant block of IKr.

So anyway, Drolet, et al. found a significant effect of droperidol on IKr down to 10 nanomolar. The half maximal inhibitory concentration was 30 nanomolar. To put this into context, a 30 nanomolar IC50 is very similar to what we have seen for drugs such as cisapride, astemizole, and it is actually a higher affinity than for a drug such as terfenadine and moxifloxacin.

And I've put some reports there from the literature that also kind of put these levels into clinical context. So in other words, 10 nanomolar and 30 nanomolar are clinically relevant concentrations.

So at the conclusion of this, we made a few conclusions. We felt that there was very good evidence of a causal relationship between droperidol and QTc prolongation and torsade. The QTc effect at low doses of droperidol was not known, although it appeared to be dose-dependent. And although it was dose-dependent, we have seen serious cardiac adverse events at doses at and below the lowest-labeled dose of droperidol. In other words, we had no clear safety monitoring for droperidol with respect to QT prolongation.

Whenever a serious safety concern comes to light, it's appropriate to take a step back and do an

overall risk/benefit analysis. These are some of the components that the agency looks at in performing a risk/benefit analysis. If the drug is used to treat a very serious disease or condition, it is a lifesaving drug, of course that is a high benefit. If it is a drug that has no alternative therapies or a drug for which the alternatives are not as safe or not as efficacious, again this is a drug that would be considered to have a large benefit.

On the risk side, there is a perception that there may be some patient populations in which a higher risk may be tolerated. So, for example, in some instances we might tolerate a higher risk in a terminal cancer patient population than in young healthy pediatric patients.

The predictability of adverse events is very important. In other words, do we know what doses are associated with adverse events? Can we predict a population, a setting in which adverse events can occur? And do we know anything about drug interactions? Do we know anything about the metabolism of the drug? In this case we don't.

Safety margin is important. A drug with a very large safety margin for adverse events, of course, is associated with lower risk.

Is the risk manageable? Is the risk

preventable? Is the risk treatable? And what is the nature and the consequence of adverse events? Are the events reversible?

For droperidol, unfortunately, droperidol was not in a very strong position in this sort of a risk/benefit analysis. It is not a lifesaving drug. It is for a very important indication but it's not a lifesaving drug. There are alternative therapies from multiple drug classes, and those alternative therapies, as best we know, are reasonable safe and efficacious. This is used in a very diverse patient population from very sick patients to very healthy patients. It's used in old patients, young patients, pediatric patients.

As I've just discussed, we don't know very much about safe doses. We don't know very much about whether or not there may be populations that are safe, and although there are populations that we think are probably at higher risk, we don't know how much of a higher risk.

And as I said before, we don't even know details about the metabolism of this drug. So we can't even begin to try to predict how co-administration of other drugs might affect the profile of droperidol.

We have no clear safety monitoring for droperidol with respect to adverse events, and torsade is a very serious event. The mortality for torsade has been

reported to be as high as 30 percent.

Let's go on to the incidence of events. Usually our best estimate of incidence is in preapproval testing because we have a very well-controlled population. We have a lot of detailed data for all the patients, and we have detailed information about how the data were acquired and the disposition of those patients. Those preapproval data, of course, are limited because there are relatively small numbers. It's usually in a limited population. So generally speaking for most approvals, the population that studied is usually a little bit healthier than those that we're seeing in practice.

In this particular case, we have a problem where we have changes in clinical practice standards over time, changes in regulatory standards over time, and the preapproval data is simply not reassuring. We have a lot of deaths. We have a lot of events, and the safety monitoring was simply inadequate for us to make any sorts of conclusions from the preapproval data.

Let's look at the denominator. Let's go to postmarketing and let's think about the denominator. The denominator is the easier part. We can make some estimates of the denominator based on sales figures. So the peak sales figure for droperidol was about 10 million vials in 2001. It is a moving target, though, as was discussed

before. The sales for droperidol doubled over the time period of '98 to 2001. Of course, the sales figures don't tell us information about how many exposures and how many patients were exposed. Of course, furthermore, we don't know much about doses, duration, settings, and concomitants.

How about the numerator? I'm aware that at least one individual has been going around the country asking large rooms full of anesthesiologists how many of you have had a cardiac adverse event related to droperidol. I've tried this too. And if you ask a room full of anesthesiologists, how many of you have had an adverse cardiac event related to droperidol, nobody raises their hand.

But let's change the question. If you ask that same group of anesthesiologists -- and I've done this too -- how many of you have seen an adverse cardiac event, something that has concerned you enough to make an intervention, to do laboratories, to monitor a patient a little bit longer, to give another medication, everybody raises their hand. We see these events all the time, and it's not to say that all of these events are related to droperidol. It's just to say that when we have a drug that is used very commonly and we have an event that's seen very commonly, it's very difficult to distinguish at the level

of the individual whether or not these events may or may not be related.

There are a number of reports in the literature looking at cardiac events and morbidity and mortality in the perioperative setting.

Amar, et al. looked at a series of thoracic patients and found that 15 percent of those patients had at least one episode of ventricular tachycardia postoperatively.

O'Kelly in 1992 looked at 230 patients undergoing major noncardiac surgery. All of those patients either had coronary artery disease or had risk factors for coronary artery disease. And he found a 44 percent perioperative incidence of frequent or major ventricular arrhythmias defined as at least 30 ventricular ectopic beats in an hour or ventricular tachycardia.

In a generally healthy population, Forrest reported that 6.3 percent of these patients had a perioperative ventricular dysrhythmia.

And finally, if you look at mortality figures, Lagasse in 2002 looked at two university-based practices and found an overall perioperative mortality rate of 1 in 532 cases.

Similarly, Newland, looking at the cases in their particular teaching hospital, reported a 0.2

incidence of cardiac arrests in the perioperative setting.

We really expect under-reporting of events. Postmarketing safety reporting is voluntary. This is a drug that was approved in 1970. Anesthesiologists do not routinely monitor the QT interval. We have a high incidence of perioperative dysrhythmias. We work in a complex setting with multiple concomitants, and in that setting, we always have something else upon which to blame the arrhythmia. This is a sick patient. This is a patient who came into the operating room on multiple drugs. This is a patient who we've given multiple drugs to in the operating room. This is a patient who is undergoing surgical stress, who is undergoing fluid shifts, electrolyte shifts. In that setting, there's always something else to blame the arrhythmia on, and the last thing that the anesthesiologist is going to blame it on is that drug that they've been using safely for 30 years.

When we do get reports, of course, the submitted reports are often incomplete.

I'd also point out that QT and torsade were not even in the adverse event lexicons until the 1980s, over a decade after droperidol had been approved.

We have to take even very small signals very seriously. Even if we could figure out the incidence, what would be an acceptable incidence? Let's say we had a

serious event with an incidence of 1 in 1,000. The probability of at least 1 event -- let's take a busy institution. At a single busy institution, they might do 50 cases in a day. At that institution in a single day, they would have a 5 percent probability of experiencing at least 1 serious event. If they did 1,000 cases in a month, in a month they would have nearly a two-thirds chance of seeing at least 1 event.

Let's make the incidence 1 in 10,000. At that same single institution, it would be a pretty low chance of seeing an event in a single day. In a month, there would be nearly a 10 percent chance of seeing at least 1 event, and in 6 months, a nearly 50/50 chance of seeing at least 1 event at a single institution.

I'll put this into context in another way. When terfenadine was approved, terfenadine had been on the market for several years before we saw any reports of torsade related to terfenadine, which is Seldane. Over 100 million prescriptions had been written for terfenadine before we started seeing reports of adverse events. Remember that the peak sales for droperidol were 10 million in 2001.

If you take a drug like cisapride, which has also been strongly implicated with QT prolongation and torsade, the incidence rate that has been estimated for

cisapride has been reported as being 1 event per 110,000 prescriptions. And the fatality rate attributed to cisapride related to QT prolongation and torsade has been reported as being approximately 1 in 430,000 prescriptions.

Again, if these events represent preventable serious events, I think we have to take even very rare events like this very seriously.

The Rule of 3 states that if no events are observed, an upper bound for incidence is less than or equal to 3 over n with 95 percent confidence. If you put it another way, to rule out an event of 1 in 10,000 incidence with 95 percent confidence, we would require a clinical trial of 30,000, and that is assuming no events. If you take this and put it in a background where there is a very high background rate of events, you begin to appreciate how very difficult it would be for a particular individual, for a particular practice, for a particular institution to be able to discern these very rare events from their own experience. You can also begin to appreciate how very difficult it would be even in a controlled trial setting to be able to discern these events.

Just to say a word about the alternatives. Again, we have alternatives available from multiple drug classes. The agency did conduct a risk assessment of the

alternatives. You have heard, of course, the many limitations we have in trying to do a risk assessment for any particular drug, and within the constraints of what we could derive from such a risk assessment, there was no clear safety advantage for droperidol compared to the other drugs.

The other thing I would note that complicates it is that a lot of the other drugs are used in different populations and settings. So, for example, Zofran is used quite a lot in very sick cancer populations and at higher doses in those populations. So when we start looking at event rates or event reporting in drugs that are used in different populations and settings, again, it makes it very difficult to make any sort of comparisons.

So we were left in a situation where there was really a very high level of concern and, as Dr. Rappaport mentioned, a high level of urgency. We entered into multiple discussions with Akorn who is the NDA-holder for droperidol, and what became clear from those discussions was that Akorn was unable or unwilling to do any further studies of droperidol. The possibility of submitting a supplement to approve the lower doses of droperidol was discussed, and Akorn was told that we could look at a literature-based submission, although they were also warned that generally the agency is hesitant to base an approval

exclusively upon literature. Nevertheless, they were told that they could do so, but they opted not to do so because they did not have any data to support or elucidate the safety with respect to droperidol related to QT prolongation.

We conducted the risk assessment of alternatives, as I discussed.

In a situation like that, the agency actually has fairly limited options. We could do nothing. We could entertain some sort of labeling change or other sort of communication, or we could withdraw the drug from the market. We took into account, despite the very high level of concern, the 30-year marketing history for droperidol and the importance of this drug to the medical community and also the fact that in clinical practice generally very low doses are being used. And we took that into account when we decided on what we thought was a moderate action, and that was to go for a labeling change.

The labeling change that was implemented was a boxed warning. The warning stated that droperidol should be used after other drugs had been tried first. In other words, it was relegated to second-line status, and that again, was a reflection of the very high level of concern that we had for the drug at the time. It had precautions about taking care not to use it in patient populations and

settings that may be associated with high risk, and it also contained some wording that recommended that patients undergo a 12-lead baseline EKG and be monitored for 2 to 3 hours after administration of droperidol, that they should undergo ECG monitoring for 2 to 3 hours.

The recommendation for a baseline EKG and EKG monitoring was in accordance with the best and advice and guidance that we have with respect to these drugs that can prolong QT.

The 2 to 3 hours was chosen in this sort of a way. Based on the literature, the half-life for droperidol is estimated to be about 2 to 3 hours, the elimination half-life. The most conservative approach might have been to say, well, actually ECG monitoring should go on for two to three half-lives, when we're pretty sure that the drug is more or less gone. But when we started looking at a possible monitoring time of 6 to 9 hours, that seemed to be clinically impracticable. And the 2 to 3 hours was chosen as sort of a compromise between what might be clinically practicable and the pharmacokinetic considerations. In addition, what we knew about the clinical effect of droperidol was that with respect to sedation anyway, the sedation effect for droperidol lasts for about 2 to 4 hours. So that was the basis for the 2- to 3-hour recommendation.

And in addition, the indications were stripped down to an indication only for perioperative nausea and vomiting because that was thought to be the most important indication, and the other indications also were associated with much higher doses of droperidol. And the dosage section was rewritten to emphasize the lowest labeled doses.

At the same time, a Dear Healthcare Provider letter was issued and an FDA talk paper was also issued.

I just want to say a few words about what the label means to FDA and to others. The label is part of really the FDA mandate. The FDA was established and mandated to provide adequate labeling for safe use of drugs, and it's very much a part of what FDA is all about. There are a lot of implications to what is contained in the label, having to do with how a drug can be marketed. It is the statement of the evidence that the agency has of safety and effectiveness. It gives our best recommendations with respect to safe use of the drug when used according to the label, and unfortunately, in the community it has a lot of medical liability concerns associated with it as well.

This is a section taken out of the Code of Federal Regulations. The Code of Federal Regulations is the codification of our regulations. These have the force of law. The FDA and sponsors are required to abide by the

CFR. We are compelled to use warnings in labels to describe serious adverse reactions and potential safety hazards, limitations and use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association. A causal relationship need not be established. Special problems, particularly those that may lead to death or serious injury, may be required to be placed in a prominently displayed box. So from a purely regulatory standpoint, the boxed warning was a reflection of what the FDA is compelled to do by regulation.

There's also a very unfortunate disconnect between clinical practice and labeling. Clinicians simply don't practice according to labeling and often are unaware of what is contained in labeling.

I think most anesthesiologists probably don't know that to use Diprivan according to the label, you're supposed to administer it at a rate of 40 milligrams per 10 seconds, and that's in a healthy population. If you're going to use it in a somewhat sicker population, you're supposed to use it at a rate of 20 milligrams per 10 seconds, and that's an induction bolus dose of Diprivan.

I think most anesthesiologists aren't aware that fentanyl is not indicated for intrathecal use. Intrathecal use of fentanyl is off-label.

When the problems with cisapride came to light with respect to QT prolongation, cisapride underwent a number of boxed warnings, and those boxed warnings actually had quite a limited effect. Even after a number of Dear Healthcare Provider letters and a number of boxed warnings, there was clear evidence that practitioners were still prescribing cisapride along with drugs that would inhibit its metabolism.

So it leaves us in really a very difficult dilemma. When we have important safety information that might help clinicians to avoid a serious event, that might cause physicians to want to change their practice, how can we convey such information in a way that physicians will be aware of these and will act on these?

This is where we are right now. There is still an ongoing risk assessment of droperidol and the alternative drugs. As Dr. Rappaport stated, we conducted a clinical study of droperidol which will be presented later. The current meeting today, of course. And we have really attempted to engage in a dialogue with the anesthesia community.

I'm going to go on now and try to answer and discuss some of the issues that we've been hearing from the community.

One of the points that has come up is, well,

should droperidol be treated a little bit differently than the other drugs that prolong QT? Droperidol is used in a monitored setting. It's used by personnel who are trained to intervene in cases of cardiac arrhythmias or even cardiac arrest. It's generally used in a setting where the resources for rapid intervention are immediately available, and droperidol is used acutely and is generally a single-dose drug. Those certainly are reasonable arguments. We don't know the right answer to those yet.

But on the flip side of it, there are other factors that may increase the risk of droperidol in the perioperative setting; that is, that this is a setting where comorbidities are frequent, where co-medication is ubiquitous, where at the current time, QT monitoring really is not part of routine practice, and there are some settings where it is used that can also loosely be considered perioperative, that is, outpatient procedures where a patient really does not normally stay in the hospital very long after the procedure. There are non-OR procedures that are done in the GI suite, in the cath lab, in radiology. Of course, droperidol is often used in the post-anesthesia care unit at the conclusion of surgery, after which a patient will then go to an unmonitored inpatient setting or go home.

Just a few more issues that have been raised.

Practitioners have been very concerned about the alternative drugs. We hear this all the time. Well, how about ondansetron? Ondansetron prolongs the QT too. Why aren't you making a fuss about ondansetron? There are a few answers to that.

One is that at the present time, the agency simply does not have the tools to make comparative risk assessments. You've seen the limitations we have in interpreting postmarketing safety. The drugs are used in different settings. They're used in different patient populations. We simply are not at a place where we can make any good relative safety assessments.

The resource concern too with the agency is that unfortunately, because we don't have the tools to make these relative risk assessments and because we don't have the resources too to be looking at every drug and doing such a very intensive scrutiny of events, such as we've done with droperidol, we've had to take these cases really on a case-by-case basis. We are certainly aware of other drugs that prolong QT, and probably one day their day will come too. But we have to, at this present time, really just address things on a case-by-case basis when problems appear with a particular drug.

A lot of people have been concerned that droperidol is used really at much lower doses than we're

talking about. Again, the drug label is about directions for safe use of drug, our best recommendations for safe use of drug when the drug is used according to the label. As such, the boxed warning really is not about doses of droperidol less than 2.5 milligrams because the use of droperidol at doses less than 2.5 milligrams is off-label. We don't have data submitted to the agency to make a determination of safety and efficacy at less than 2.5 milligrams, and we really are not making any statement about the safety or lack of safety of droperidol at those doses. We simply don't have the data.

There has been a lot of emphasis on the case reports. People have refuted the case reports saying, well, there's a lot of concomitant medications here. This patient has a lot of risk factors, and so on and so forth. We could do a point/counterpoint for all of these cases. The point is that we are seeing cases. We have reasons to take even very small numbers of cases very seriously. And this is the setting in which we work. This is the setting where patients have concomitant medications, where patients have concomitant risk factors. It's the setting in which we work. Again, the case reports were not the sole basis for the warning.

A lot of the emphasis too has been focused on those cases less than 2.5 milligrams. The reason that at

the agency we've emphasized the doses really is just to say that we don't have a clear safety margin. It's not to try to make a clear statement about safety or lack of safety at those doses. We simply don't have the data.

Finally, as I stated before, the boxed warning from a purely regulatory standpoint is, first of all, something that we use according to the regulations and is really just a tool to try to emphasize particular safety information. We're certainly aware that in practice and in the community a boxed warning can have a different significance, and that's one of the items that certainly could be discussed today. But from a purely regulatory standpoint, a boxed warning is a tool to emphasize a particular warning.

As we've been trying to find a path forward, we have a number of ongoing concerns, of course. Again, we feel that there's strong evidence that droperidol can cause QT prolongation and torsade in humans. As you'll see later in the study that will be reported later, we feel that there's good evidence that droperidol can cause QT prolongation even down to doses of 2.5 milligrams and perhaps be associated with outlier responses as well. There's a growing concern in the literature that outlier responses may be seen with droperidol and with other drugs that prolong QT in patients who have silent mutations, and

so that these events may occur in an apparently idiosyncratic fashion and the predisposing mutations and polymorphisms might be as prevalent as several percent in the general population.

With these concerns and the difficulties I've discussed before about trying to discern very rare events against a noisy background, it really makes for a very difficult situation in trying to obtain definitive safety data or even trying to imagine how one might be able to design a study to give us definitive safety data. And you'll hear more about that later.

I think that's the last slide. Any questions?

DR. HORLOCKER: As the co-chair, I'm going to take the prerogative of the first question. Your third-to-the-last slide said that you were making no comments on the safety or the efficacy at the lower doses. Yet, the first line of your black box warning says that these reports have occurred at or below recommended doses. So by saying that, you actually are commenting on the off-label application. Could you address that?

DR. CHANG: I would say that, again, it's really intended to make a comment about the use of the drug when used according to the label in the sense that, again, this is an event that we've seen at all doses, and that when used according to the label, we really can't make any

recommendations about a particular dose at which these events will probably not occur.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: Nancy, thank you. I think you did a nice job of explaining sort of the FDA's dilemma when confronted by a serious problem and the tremendous difficulties in putting together the database for it.

Two questions. A problem that I have in trying to understand this is the feeling that I don't have access to all the data that the FDA is using in the decision process. For example, you talk about discussions with Janssen, and they had done a safety analysis, which obviously you've seen, but I don't think anybody in the community has seen.

Similarly, the actual database that you were able to cull from your search of the Adverse Event Reporting System, I haven't been able to review that and to go over the cases. I know you say it's more than the cases that you base the decision on, but the problem is most of the data other than those cases, from the anesthesiology perspective, involves much larger doses where there's no question I think at these huge doses that there's an issue. And trying to cull down the risk at these low doses requires, in fact, digging through the minutiae of these cases.

So the first part is really just a statement, which is if somehow we could get access to the same data so that we're not just trying to guess what's out there but actually can assist in looking at it, that would be helpful.

A specific question is that you presented a slide where you talked about these very small doses. This was slide 5, by the way, of your presentation. Here what we see is that you have 7 cases at 2.5 or below that were associated with QT prolongation and torsade, and we also have only 4 cases where the time course is really pretty much immediate. As we expect from the kinetics, we see the actual QT prolongation appears to peak in the first minute or 2. So it's a very, very rapid response. Can you tell me how many of the rapid peaks were associated with the lowest doses?

You see what I'm saying? Again, because I don't have access to the data, I'm trying to understand the extent to which a causal relationship, even with the limitations, could be inferred.

DR. CHANG: Let me try and step back and answer a few of your other remarks.

The Janssen analysis is more or less presented. So, in other words, the Janssen analysis was primarily a review of the literature that was presented and a review of

case reports which have been integrated now into our own database.

So the question about the specific cases. I couldn't tell you right off the top of my head which ones were associated with which onset.

I think, as you'll see later too with the presentation of our own study, while the greatest extent of QT prolongation does appear to be in the early part of the study, first of all, as I think you'll hear from Dr. Malik, we don't really know what to make of those early changes. There's a number of factors having to do with trying to correct for hysteresis and so forth that make that early data with respect to QT prolongation really very difficult to interpret.

I think the reason that we didn't try to present in a way that emphasized these time courses is what we were trying to say is that these events really have been occurring at a variety of times. That, again, is supported by the data which seems to show that although there is an apparent peak in the early times, the QT prolongation related to droperidol actually probably goes on for longer than that. A number of the cases that are more interesting, such as Guy's case, for reasons that we don't understand, we are seeing events of torsade that occur fairly remotely from the administration of the drug. So as

you remember, in that particular case, she had an event fairly much immediately after administration, but then the next day she had several more events.

The reason that we chose not to put in the case reports -- and perhaps in retrospect that may have been a mistake -- is several-fold. One is, as I said before, they really are not the sole basis for the decision, and we've spent a lot of energy certainly in the correspondence with the community trying to de-emphasize the notion of trying to pick apart specific case reports.

The point is that at the labeled doses -- and right now the label says basically 2.5 and you can go up as high as you want, that there is no upper dosing limit on the label. And that's because even though we rewrote the label to emphasize the lowest doses, we didn't know where to put a cap. We didn't know how to say, well, 10 should be the limit or 20 should be the limit. We didn't know where to set that. And there really hadn't been a set before.

So, again, while we've focused on those in order to be able to say we have events at all doses going down to the lowest, those probably are not necessarily the cases that deserve the most emphasis because the label really is talking about all doses and up to the sky.

DR. HORLOCKER: So, Dr. Chang, Dr. Shafer had

asked you about the internal analysis from Janssen. Are these the 22 cases from that, or are there additional data?

DR. CHANG: I couldn't tell you how many of these cases came from Janssen, but basically at the time, when we received the analysis from Janssen, we received a number of cases from Janssen as well. Many of those cases were foreign reports, and those reports have been integrated into the data that you're seeing.

DR. HORLOCKER: Dr. Gillett, you're next.

DR. GILLETT: How are patients informed about off-label uses and black box warnings? I have access to only one patient's record. Still again, it wasn't mentioned.

DR. CHANG: As I understand from the legal literature, anyway -- this is not really a regulatory question per se -- because with respect to off-label uses, the FDA recognizes that clinicians should exercise medical judgments and use drugs according to their own medical judgment, we really don't regulate off-label use of drugs. From a legal perspective, as I understand it, the physicians are not under legal obligation to inform patients of off-label use of medications unless in a clinical trial setting.

DR. GILLETT: What about boxes?

DR. CHANG: You're stretching my legal

knowledge. I don't believe that boxes are any special consideration in that regard.

DR. HORLOCKER: Dr. Balser.

DR. BALSER: Yes. Is the FDA within its purview to provide warnings specifically about the use of droperidol below labeled concentrations? Because your comment that you don't have any safety or efficacy data below the labeled doses is not reflected in the black box warning, and the black box warning, because it has said at low doses in the first sentence, what it's done is shift anesthesiology practice from droperidol to other drugs that many of us believe are just as risky for torsade. So it isn't without consequence that there are three or four words in the first sentence of this black box label and the FDA needs to think about that.

DR. CHANG: I think that's a good comment, and certainly we can discuss that later on in the discussion section, exactly what we should be communicating, what is most relevant to communicate. Really what I'm trying to communicate to you now is what the intent was, and the intent was to communicate that we've seen these events at all doses and we don't have a clear safety margin.

DR. MEYER: I just wanted to clarify the question. I agree with Dr. Chang's answer, but just to the question, do we have the purview, it's certainly within our

purview to state the facts of what we've seen in terms of the reported adverse events.

DR. CHANG: One other comment actually related to Dr. Shafer's question. The cases are available through FOI if somebody is motivated and actually there have been some publications in the literature from people who have examined the database. Of course, they were unconvinced, but those are available publicly.

DR. HORLOCKER: We're running a bit late, but there are three more people that I have down on the list. Dr. Eisenach, you're next.

DR. EISENACH: I always thought the FDA had a difficult job and now I think it's impossible, Nancy. So you have something that occurs that you've told us you don't know what the numerator is, and you don't know what the denominator is, and you don't have to show a causal relationship of the drug and the effect. The word that's in the statute says reasonable, and how do you make a reasonable decision? I think as the day goes on, it will be quite interesting. I mean, I drink water every day. I'm going to die. There's clearly a relationship between two common things.

(Laughter.)

DR. EISENACH: But I think without a better understanding by the committee -- and I think Steve's point

is well taken -- of how you estimate the numerator and denominator, it's hard for us to understand what a reasonable solution should be. So maybe you could comment on it now, but I think as the day goes on, we're going to need to sort that out.

DR. CHANG: Yes. We did do a few analyses to try to better understand what the numerator, such as it is, means. One of the things that we did do, for example, is to look at events related to other drugs. We looked, for example, at a number of other commonly used drugs in the perioperative setting that also have been around for a long time. So I think those drugs were midazolam, lidocaine, thiopental, vecuronium. There may have been one or two others. Again, I chose not to present that data here because the numbers are very small, and as I explained before, there are a lot of limitations in trying to draw conclusions about relative risk.

But what I would say is that the incidence of droperidol events did give the appearance of being higher relative to those other drugs when you take into account the relative sales of those drugs. But, again, it's hard to make any conclusive statements about that, especially with such low numbers as we have.

DR. HORLOCKER: Dr. Bril.

DR. BRIL: My question was along that line. I

know you said there was no ability to do comparative studies, but I was wondering in how the use in highly agitated patients and the incidence of torsade would compare to, say, something like Haldol in highly agitated patients. I don't really know that literature whether there are a lot of events of QT prolongation or torsade or arrests with Haldol, and how would the numbers compare? That would seem to be a simple comparison.

DR. KOWEY: There is an incidence of torsade associated with haloperidol and Mellaril. It's the same problem, estimating the relative risk, because it's the same kind of literature that you're looking at here. It's inadequate to the task that you're asking.

DR. HORLOCKER: Dr. Crawford.

DR. CRAWFORD: Thank you.

Dr. Chang, I'd just like a little interpretation of what you would mean or the agency would mean by second-line from our presentation because as I read the second paragraph of the boxed warning, I could interpret the use of the product anywhere from second-line to drug of last resort. So in terms of really interpreting it, could you give us a little more specificity?

DR. CHANG: I don't have the wording exactly in front of me, but the intent was essentially to say that you should try other drugs first. So second-line, not

necessarily last resort.

DR. HORLOCKER: In one of our questions we'll deal with the labeling of that that we'll get into in our 2-hour discussion period this afternoon.

Dr. Katz wants the last question before the coffee break, and as the co-chair, I have to give it to him.

DR. KATZ: Blame me, why don't you.

Just a quick follow-up on the issue of trying to interpret the signal to noise question, which I think clearly is a major challenge here. I was glad to hear that you tried to look at some of the other drugs that have been used for a long time in the perioperative period while, even though it won't be definitive, just to try to get a flavor whether the cases that were seen with droperidol were signal or were noise, which seems like it's not an easy thing to know.

So the way I read the slide was that the number of cases of either QT prolongation or torsade, when using less than or equal to 1.25 milligrams -- well, actually it's up there right now -- would be 4. What were the actual numbers with the other drugs?

DR. CHANG: You really want to know?

(Pause.)

DR. CHANG: I just want to select some specific

slides. The first slide, this is the sales data for droperidol that we have. You can see that, again, the sales have roughly doubled in the time from 1998 to 2001. This is all droperidol, including generics. The y axis is the vials sold.

DR. KATZ: Nancy, it may make your life easier if I focused my question better. How many cases of either QT interval or torsade de pointes, which was one of your search criteria for droperidol, were associated with midazolam, with lidocaine, with thiopental, et cetera.

DR. CHANG: That's where we're going.

(Pause.)

DR. HORLOCKER: Is it necessary to have this slide?

DR. CHANG: I don't know the numbers off the top of my head.

DR. HORLOCKER: We can look for that and go over that after the break.

Let's take a 10-minute break. I'd like to remind you all that the things we discuss here are not to be discussed outside the room. Thank you.

(Recess.)

DR. HORLOCKER: The next presentation will be from Dr. Desai.

DR. DESAI: Good morning, members of the

advisory committee. My name is Mehul Desai and I'm a medical officer in the Division of Cardio-Renal Drug Products at the FDA.

This morning I'd like to present to you some results from a prospective controlled study of QTc prolongation in healthy volunteers. This was a study that was approved and funded by the Food and Drug Administration and was conducted at Indiana University School of Medicine.

The objectives of the study were to determine the effects of relatively low bolus doses of intravenous droperidol relative to placebo on the heart rate corrected QT interval in young, healthy volunteers.

This was intended to be a 4-period, placebo-controlled, blinded, randomized, crossover study of 20 healthy volunteers. The doses of droperidol that were used were 0.625 milligram, 2.5 milligrams, 5 milligrams, and placebo. All doses were administered as an IV bolus over 30 seconds.

We recruited healthy subjects between the ages of 19 and 40 years of age that were on no prescription or over-the-counter medications for at least 2 weeks prior to study initiation. The subjects had normal reported cardiac histories and normal baseline electrocardiograms.

12-lead ECGs were obtained at the prespecified time points shown in bullet 1 of this slide. As you can

see, sampling was heaviest in the first hour after drug administration and tapered off thereafter. Subjects were monitored for a total of 12 hours in a clinical research unit.

The ECGs were read blinded to time, treatment, and subject identity. Originally the QT and RR intervals were measured manually in conjunction with a digitizer board, and heart rate was corrected using Fridericia's method. Subsequently we had the ECGs reanalyzed using digital technology and applied a subject-specific heart rate correction. In addition, the impact of heart rate trending or QT/RR hysteresis was also taken into consideration. Dr. Malik helped us do this latter analysis and he's scheduled to speak after me this morning.

The reason we did this latter analysis was to validate the findings from our original analysis, particularly as there have been limitations cited in the literature regarding use of manual techniques, digitizer boards, and ad hoc correction methods.

This slide summarizes the characteristics of the subjects that were enrolled in the study. As you can see, we enrolled a total of 8 subjects into the study. As you'll recall from one of my earlier slides, we intended to enroll a total of 20 subjects with each of those subjects completing all four study periods. However, we were well

short of that goal for reasons I'll get into in the next slide. The consequence of the small study was that it was under-powered.

We studied a total of 3 male subjects and 5 female subjects. The age range was 19 to 39 years of age. On the right-hand side of the screen, you see these X's. That represents study periods that were completed by each subject. As you can see, 2 subjects completed all four study periods. 2 other subjects completed three of the four study periods. 3 subjects completed two study periods, and 1 subject completed only one study period.

Neuropsychiatric adverse events led to early study termination. The adverse events included restlessness, anxiety, difficulty concentrating, claustrophobia, and these adverse events were moderate to severe in intensity. A few subjects refused to come in for further dosing unless we could assure them they would receive a placebo.

(Laughter.)

DR. DESAI: A couple of subjects left the clinical research unit against medical advice within a few hours of dosing due to intolerable symptoms. And 1 subject was unable to work the following day due to persistent symptoms.

This slide shows the effects of intravenous

bolus doses of droperidol on heart rate. What you see along the y axis is the change in heart rate from pre-dose baseline in beats per minute, and along the x axis, you see the time post droperidol administration in minutes on a logarithmic scale. What we see on this slide is that relatively soon after droperidol is administered, we see that there appears to be an increase in heart rate on droperidol relative to placebo, and that applies to all three of the doses that we studied. However, around 10 minutes and afterwards, we see that the heart rate appears to be returning back to pre-dose baseline levels. Understanding that these heart rate changes are happening will help us in interpreting the results from the next slide I'll show you.

This slide shows the results of the heart rate corrected QT intervals. On the y axis, we see a change in heart rate corrected QT intervals from pre-dose baseline, and along the x axis is the time post drug administration. As you'll recall from the previous slide, heart rate changes are primarily occurring within the first 10 minutes after the drug is administered. Because of this reason, heart rate corrected QT estimates are unreliable, and this is due to the phenomenon of heart rate trending, or QT/RR hysteresis. I won't discuss this concept, but Dr. Malik, who's going to present after me, will go into this concept

in much more detail.

However, as you'll recall from the previous slide, the heart rate changes were beginning to return back to baseline levels at 10 minutes and afterwards. We see that during that time period, there appears to be an increase in the heart rate corrected QT interval relative to placebo for all three doses.

This is better illustrated in this next slide where we see the time average changes in the heart rate corrected QT interval between 10 and 60 minutes after drug administration. We see that on placebo, this time average change from baseline is roughly 0 milliseconds, while that for the three doses of droperidol ranges between 6 and 9 milliseconds. Again, there are significant variability in this data as you can see by the large error bars. And no conclusive statements can be made, but we can say that there appears to be a trend.

It may be reasonable to ask what is the significance of this magnitude of change. Clearly within a single individual, changes of this magnitude may not be important, but it's important to understand that we often average these changes among a group of individuals.

It's also important to recognize that we're seeing this magnitude of change in the absence of maximal metabolic inhibition or in the absence of using high doses

of this drug.

This slide shows the results of the maximal changes in the heart rate corrected QT interval. We see that for placebo these maximal changes in the heart rate corrected QT interval is about 8 to 9 milliseconds, while that for the three doses ranges from about 17 to 27 milliseconds. Again, significant variability in the data and the best we can say is that there appears to be a trend.

So, in conclusion, this study was under-powered secondary to early termination due to the adverse events in the healthy volunteers. However, we feel there is a strong suggestion that relatively low doses of droperidol prolongs the QTc interval, and although we can't make any definitive conclusions, we feel that further studies that characterize this better may be warranted.

Thank you.

DR. HORLOCKER: Any questions or points of clarification? Yes, sir.

DR. RODEN: I love it when people call me sir.

DR. HORLOCKER: I'm still trying to get people to call me sir.

(Laughter.)

DR. RODEN: Yes, sir.

A couple of just comments and questions. One

is the issue of adverse effects in the normal volunteers versus the relative lack of adverse effects in the patients. This is, I think, a relatively well-recognized phenomenon when neuroleptics are studied. It certainly happened with the risperidone profile as well. So I just wonder, and maybe Marek can think about answering this during his unbelievably long talk that's coming up.

(Laughter.)

DR. RODEN: The question is whether the adverse effects themselves might, by inducing autonomic effects or other kinds of adverse effects, affect the QT interval in the normals and yet you would not see a similar response in patients who don't have those kinds of adverse effects. It's an interesting problem to which I don't know if there's an answer.

The second question or comment has to do with the pharmacokinetics. So there's this idea that the adverse effects come and stay, and they stay for a long time like maybe till the next day, and that, after a single intravenous whack of a drug usually suggests generations, slow or otherwise, of an active metabolite, or at least that is what it would suggest to me. Yet, your ECG monitoring occurs every minute for the first 10 minutes, suggesting that you or someone thinks that the real player in this is the parent drug, and I'd like some clarification

of that.

Parenthetically I'd add that whether these effects were obtained at maximal metabolic inhibition or not seems to me to be largely irrelevant after a single intravenous dose of a drug. Maximal metabolic inhibition will be an issue with chronic therapy, not with a drug that's used in this way.

So those are the sort of trial design issues off the top of my head that I think need to be at least thought about when this kind of study gets presented to us. So the PK and the issue of the side effects modulating the QT independent of the drug's intrinsic effects on IKr channels or whatever other channels you want to invoke.

DR. DESAI: Yes, with regard to the side effects, we clearly don't know in that subject who had those persistent symptoms for 24 hours. It seems clearly unlikely it's related to the PK. The PK of the drug is known to be 2 to 3 hours. We don't have a good answer for that.

DR. RODEN: I mean, with a drug that's given the way this drug is given, there's surely a very rapid distribution phase followed by an elimination phase. So that's why I would think that -- unless there's some peculiar redistribution that only members of this committee understand, the idea that the plasma concentrations could

somehow persist very, very late just doesn't make much sense to me after a single dose.

DR. HORLOCKER: Dr. Eisenach? Dr. Bril?

DR. BRIL: I'm just curious. How many of the placebo patients had restlessness and agitation and things like that, or was that strictly related to the droperidol?

DR. DESAI: Yes, that was strictly related to the droperidol. There's no one who got placebo who had any of the symptoms, and patients who had gotten drug and subsequently got placebo clearly knew there was a difference.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: A couple of things. First, in response to "sir's" comment --

DR. RODEN: Just plain Dan.

DR. SHAFER: -- plain Dan's comment, as I'm sure you know, normal volunteers aren't almost by definition.

DR. RODEN: They're more normal than your patients are.

DR. SHAFER: They probably are.

In terms of these adverse events and particularly the person who missed 24 hours, was that related to the dose or did they get four doses and maybe at the lowest dose they missed it because they just weren't

feeling well that day? Do you have dose response for the adverse event data?

DR. DESAI: We tried to look at that. Again, we had small numbers of subjects. Patients clearly felt that these symptoms, even after the lowest dose, patients who got the lowest dose, they felt some symptoms. We couldn't clearly characterize dose response for restlessness.

DR. SHAFER: The person who missed 24 hours, do you know how many doses had they gotten?

DR. DESAI: Yes. She had only gotten one dose and that was a 5 milligram dose. After that, she didn't come in.

DR. SHAFER: People have told me that actually throwing up is more pleasant than droperidol in the absence of other drugs. So it's not too surprising I guess.

The report that we got talked a lot about the outliers from this study and yet what I saw here were mean data. Can you talk about the outliers? Because that seems to be where the anxiety was felt in the course of your research here.

DR. DESAI: With the original analysis that we conducted, we had identified outliers. The issue is that when we reanalyzed this data with Dr. Malik, some of those outliers were occurring early on, within the first 10

minutes, where the heart rate was changing substantially. So it's difficult because of this QT/RR hysteresis, which Dr. Malik will talk about, to really interpret what the true QT interval was in those subjects.

The other issue is that the two outliers that we did note both didn't have placebo periods. But that said, looking at the placebo data that we have on hand from all the subjects, if you look at the variability in that placebo period and try to make some determination of whether those two outliers could have been outliers, we would have probably guessed they would have been. But this is just speculation.

DR. HORLOCKER: We need to move on. I have the names of the other people that would like to question. Let's have Dr. Malik make his presentation and we'll discuss the clinical studies.

DR. KOWEY: I have a comment that's specifically related to this that I'd like to make, please.

DR. HORLOCKER: Okay, final question.

DR. KOWEY: A final comment. For the people on the committee, they need to know that these kinds of studies are very important in trying to define whether a noncardiac drug has a QT effect. The doses that are usually used in these kinds of trials are not on the low end of the dose range. In these kinds of trials, you're

looking for a signal and you use very, very big doses with metabolic inhibition.

So this study, unfortunately, is fairly worthless not only because it didn't achieve the numbers of patients that you needed to detect a signal, but also because you're dealing at the bottom end of the dose range and the sensitivity of the analysis here is very, very poor because you're at the lower end of the dose range. You're seeing much smaller changes than you saw magnitude-wise when larger doses were used, although that wasn't within a clinical trial context.

So before anybody gets carried away with this study -- and this is in direct response to Steve -- this study is just about almost completely worthless in terms of what we're going to decide with this drug. I'm not saying that as a criticism.

What Dan said earlier is the truth. You can't do these studies with these kinds of drugs in normal volunteers and really learn very much. I mean, even at the lower end of the dose range you couldn't do this study, let alone at the upper end of the dose range. So I don't want people to think that this is a study that cardiologists or electrophysiologists give their imprimatur to. We don't. This kind of a study, although it would have been an interesting analysis if you had finished it, with this kind

of numbers is just not going to help us.

I'm sorry to have held you up.

DR. HORLOCKER: Dr. Malik.

DR. MALIK: Good morning. My name is Malik and I'm from St. George's Hospital in London. I will, as Dan Roden just said, bother you with a rather longish talk trying to sort of explain to you where the current thinking is. I have to recognize that in many aspects I will be going into details which are perhaps just relevant because you were asked to recommend about some further studies, about some further investigations, and so on and so forth.

I am very aware of the fact that distinguished colleagues and cardiologists on the panel are as knowledgeable, perhaps even much more knowledgeable than I am, in this field, and that they could make these recommendations as well. Nevertheless, I was asked by the agency to make these sort of summaries of the present thinking.

I will be talking about these topics here. Rather than reading the slides, I will simply try to cover the topics from the basic understanding to some practical suggestions, if you were considering conducting further studies with this drug, what sort of considerations should be taken into your mind.

So, firstly, I would like to address the issue

whether QT interval prolongation is the true problem. Well, it isn't. Nobody dies by QT interval prolongation. QT interval prolongation is really just a surrogate. It's a characterization of drugs that lead to torsade, and QT prolongation is a part of the definition of torsade. So we are simply just looking at one of the surrogates. And I will try to show you how it is linked together.

This is a clinical example of torsade recorded in hospital after actually a suicide attempt on an entity which I won't mention because I don't remember it. You can see here how horrendously prolonged the QT interval was, and indeed then this led to a typical episode of torsade. Even after the standard rhythm was restored, you can still see the quite substantial repolarization abnormalities.

There were a number of studies trying to suggest what actually torsade is, what is the mechanism of torsade, and it appears that we are really talking about a tachycardia triggered by sort of sub-endocardial mechanisms within the ventricle wall where perhaps the center is moving around the wall which makes these typical patterns of the unstable ECG rhythms stable. Also studies in animals showing that it is an extra stimulus which triggers the tachycardia, which is well within our thinking, knowing that after depolarization, there are those abnormalities at the end of action potential, that they lead to torsade

induction, which we occasionally see on these drugs.

What mechanisms are involved? We are talking about modifications of action potentials, and not only that, perhaps also increased heterogeneity of the intraventricular repolarization. And on top of this, this needs to be combined, as I will try to show you some evidence for such a thinking, with some further factors which are making the subjects and the hearts more susceptible to these type of troubles.

This is a slide shown in every talk on torsade, so I felt obliged to show it as well, although perhaps it's not that pertinent to this discussion. Well, to some extent it is. This is the slide showing what the action potential looks like on a normal ventricle myocyte with a list of cardiac channels which contribute. You can see the development of these outward and inward channels which contribute to the precise shape of the action potential. Of these here, you see the delayed potassium rectifier channel which, as you have heard from Dr. Chang, is very much affected by droperidol, as well as every other drug which has been so far implicated in this issue of torsadogenity.

This is not to say that this would be a unique marker and that we could just screen for this and every drug which has this propensity is a bad drug. There are

other mechanisms which can compensate it, which unfortunately are not that well understood. Some of them are, some of them aren't.

In this drug, it appears, reading the literature, there is little known about other possible compensatory mechanisms. Nevertheless, it looks like that they are not present. Also there's not much evidence for that.

Electrocardiogram is simply a pure summation of all these action potentials through the heart, projected on the surface, and that's the ECG, as simple as that. And we are talking about this type of measurement. Why I am showing here a picture of the electrocardiogram is just to remind you that it is standard recording. The width of these little boxes is 40 milliseconds. So just keep that in mind when talking about sort of the precision of the ECG. We'll come to it later on again. This is the level of precision which might be required when sort of reading the ECG and when implementing some recommendations from the labels.

How is it related? These are a couple of slides which I have taken from Dr. Antzelevich which is from dogs or actually from chunks of dogs' hearts. But I believe and everybody believes that this is very relevant to human hearts. This is how actually the T wave is shaped

due to distribution of the durations of action potentials through the heart. If you would think about it, if the action potentials were exactly the same, the same duration everywhere, it would become probably unstable, but more importantly, for our purposes, the T wave would be negative rather than positive and those leads where the QRS complex is positive. So this shape of the T wave is determined by the distribution. It is the distortion not only of the duration but distortion of the distribution of the durations which is important to think about.

This is, for instance, the control situation which you saw on the previous slide and now adding not only a drug which is known to affect the channels but also some predisposing conditions such as hypokalemia. And you can see a very typical example of a bizarre T wave, how it is affected and how this simply leads to repolarization abnormality.

This repolarization abnormalities, then when combined after depolarization and indeed triggering after depolarization, can easily be degenerated into tachycardia, which is the mechanism of torsade, which we are trying to prevent.

So QT or QTc prolongation. I will use these terms sort of interchangeably because trying to use them simply specifically would just make simply my mind too

complicated. That is really just a surrogate, and it looks like a change in repolarization is not always harmful, which means the only information which we can extract from this is that if a drug does not cause QT interval prolongation, the possibility of its causing torsade is so low that it will not be of regulatory concern, with some limitations. This is just experience. It is not a good science.

And there is some but rather limited experience with surrogates which go beyond the QT interval prolongation, and I will present some comments on this at the very end of my talk.

So the question is, actually one of the questions which you are asked, whether one can wait for torsade de pointes appearance in clinical investigations, whether these investigations actually mean something, whether it would be possible to simply suggest a trial. Let's investigate droperidol in a good number of patients and compare it to, say, some other competent drugs or to placebo and simply just make the counts of the appearance. Well, unfortunately, it will not work.

There are no drugs which would cause torsade and drugs which would not cause torsade. It is not black and white. It's a whole spectrum of possibilities, and I have tried to draw this sort of different colored bar

having on one side drugs that cause torsade fairly frequently, again not in everybody. Sir Roden might know better than I do whether there are some chemical entities that would really cause torsade in every human being. I don't think that they exist and whether they have been simply tested in such a clinical setting. Nevertheless, there are drugs which cause it fairly frequently, and fairly frequently means something like every 10th or 30th exposure. Mainly these are drugs designed to be antiarrhythmic and to change the action potential, simply drugs which are specifically made to make such changes.

And on the other side, there are drugs that cause it, as has been documented, but extremely infrequently. There is just one reported literature case, for instance, on torsade on fexofenadine, the antihistamine. That is a fairly safe drug. However, in this particular combination of simply predisposing factors in that particular patient, whether it was the present clinical situation or whether it was sort of the congenital makeup of the combination of these heterogeneities within the heart in that particular subject, it's difficult to say. So this is the whole spectrum.

The present experience with regulatory labeling, simply how the agencies -- not only FDA but how the regulatory agencies in Europe, in Japan, and so on and

so forth -- look at things, it appears that the threshold of what I call a regulatory awareness is somewhere around 1 torsade incident in between, say, 100,000 and 1 million exposures. I am not saying that this regulatory awareness is that this needs to be sort of banned, that these drugs are bad and that these drugs should not be approved. I am saying that simply the regulators need to know about such an incidence and only what is below this incidence, such as, for instance, with fexofenadine, may be taken to be so low that it doesn't make much sense simply to make any regulatory decisions on that.

It appears with droperidol, for instance, not that I would pretend that I have any experience with the drug, that it is much nearer to this end than to this end. Nevertheless, it is probably on the left-hand side from this arrow, I would guess. If I read correctly the French reports, we are talking about an incidence, something like 1 in 50,000.

The incidence of predisposing factors is also not very frequent, and on top of that, episodes of TdP, as I will show you in a moment, can be frequently asymptomatic and may be sort of missed. On top of that, as was already discussed by Dr. Chang, it is fairly difficult, once you have a situation of a clinical setting in which adverse reactions occur, to make a correct results -- simply

continuous monitoring and so on -- to make a proper distinction between torsade and other sort of side effects.

This is an experience from congenital long QT syndrome patients as published some time ago by the group in Rochester. Why I'm showing this is that, firstly, the incidence especially when the QT interval is not horrendously prolonged is not that high. Only when one talks about a fairly prolonged QT interval, the incidence is quite high. However, these are not patients who are given a drug and simply experience changes in cardiac channels for minutes or hours or days on treatment. These are patients simply who are walking with these abnormalities all the time and still we are talking about incidents before the age of 40. So we are not talking about an event that would happen that frequently. So this is a combination that the drug alone -- even those drugs which cause torsade frequently perhaps need to be linked to some either congenital abnormality or some other predisposing factors to trigger the event. We are talking about something which happens rather infrequently.

And moreover, this is again a friend of mine. Dr. Fenichel gave me these couple of slides. This is from a drug study which was conducted under Holter monitoring. This is a typical example of the Holter when the patient came simply after being discharged upon 24 hours and simply

was saying, yes, simply take it over. I had enough. Simply nothing happened to me, of course. This is simply dumb. I was probably on placebo, whatever. I need to take a shower. Simply take this off immediately. And still the next half an hour of this table is like this. And this occurred not in the middle of the night. This occurred simply during the day, and still this was completely asymptomatic. So there are episodes of TdP that can be missed.

So clinical trials addressing a TdP incidence. My distinguished colleagues will remember that one week ago or last week we were at a meeting where we were actually asked by a sponsor whether it would viable with their drug to conduct such a trial and how many patients they would need to randomize, to which Dr. Kowey quite politely said, well, you need to randomize a country.

(Laughter.)

DR. MALIK: Probably not a very big country. Switzerland would do.

(Laughter.)

DR. MALIK: But nothing short of that actually makes sense.

So I'm afraid that those letters sent to FDA saying we had experience with 5,000 cases in our hospital and we observed nothing -- if they observed something, it

would mean that the drug is pretty dangerous and it probably should be withdrawn from the market. But that they did not observe something means unfortunately very little.

Therefore, the only possibility is to investigate surrogates. Unfortunately, the only surrogate which we know and with which we have enough experience is QT interval, although I have to say we also understand that this is a very primitive and very imprecise surrogate.

So since you are asked about sort of suggesting the conduct of further studies, let me talk about some aspects of how to design an appropriate QT study, and I will be talking specifically about three aspects: ECG recording, QT interval measurement, and correction or control for heart rate, which has some implications for the studies on droperidol since you have seen that even in that very small study which the FDA supported led to substantial heart rate changes.

So, first of all, the recording. It is now recognized that the data should be recorded, that we are talking about simultaneous 12-lead recordings, that we should have good recorders, and that we should record them electronically.

Unfortunately, it looks like with drugs that change heart rates rapidly, such as droperidol, the

standard 10-second recordings, which is unfortunately the very standard in electrocardiography, is not enough and that we should have recordings of longer duration. Ideally probably one should conduct studies, with drugs that lead to such a fast heart rate change, under sort of continuous monitoring of 12 leads; if not that, then at least start with a 12-lead monitoring for, say, a couple of hours at the very beginning.

And good quality of the recordings must be maintained. ECG quality is of paramount importance. I have taken this from a drug study unrelated to this compound from a different sponsor, different class, whatever. Of course, if you have ECGs recorded of this kind, nobody will ever be able to say anything. This is useless to have ECGs of this quality. So it needs to be simply taken into account because when the study is performed casually, ECGs with this level of noise can easily be obtained and nobody will be able to do anything.

QT interval measurement is actually a pretty difficult topic. You have heard comments by Dr. Desai about a digitizing board. A digitizing board is believed to be a very precise technology, and it's quite easily to operate collecting on the basis of the electrocardiogram.

Just to show you what I think about it, this is the results of a study that I have conducted sometime ago

in St. George's when we have printed such a spider on a laser printer knowing precisely where the individual border dots of the spider were. And we have asked 100 people to measure it very precisely on a digitizing board following these 15 dots, and everybody was supposed to follow them 15 times and collect 15 times the sequence. These were nurses, cardiac technicians, other technicians, medical students, and so on, simply whoever we can put our hands on. In order to sort of motivate them to a better performance, I promised to pay 100 pounds, about $200, from my own pocket to the person who will be simply most precise with this.

100 quid for nurses and students is actually quite good money in London. So they were precise, and actually those people who were helping me with this were saying perhaps this won't work because simply they are much more careful than the technicians simply when they click on the digitizing board when measuring the ECGs. And still there are good reasons the differences in measuring distance and repeating the dot are different.

This is a distribution of the maximum error which the people made. There are 100 individuals here, and these are the maximum errors which they made in measuring a distance. As you can see, the median of it is slightly more than 1 millimeter, therefore on the standard

digitizing board, about 50 milliseconds.

Repeating at the same dot, the results were simply astonishingly bad. The median of the maximum errors were 3 millimeters which is one-eighth of an inch. Simply it's a lot because there is no feedback.

So digitizing board in my opinion is a technology that really should not be used, and simply just recording paper ECGs and processing them in this way should perhaps be discouraged.

Some people advocated we should use 12-lead ECGs and look at the maximum duration of the QT interval. This is based on good ECG thinking. Nevertheless, what I am showing to you here is a distribution of the maximum along the different 12 leads, and what I'm showing to you in yellow is a summary of about 12,000 ECGs that were measured in our lab. And beyond that are bars showing how the distribution was in four studies that actually constituted these about 12,000 ECGs.

As you can see, it is not very reproducible from study to study because simply the maximum QT interval is too much dependent on noise and simply on inaccuracies in the measurement. It actually looks like that you have, of course, a 3D loop. As the sort of electric field moves, it projects on the surface of the thorax. It looks like that most of the 12 leads and roughly at the very same

time. There are big differences, however, between different leads because some of the leads simply look at the loop in such a way that the end of it is projected into isoretic line and therefore the QT interval is artificially shortened. These are again the same data as I showed on a previous slide, and it looks like that recording just one lead or perhaps even mixing leads one with another is a very bad option.

This is a slide showing what I mentioned before, that when you look at the distribution and when you look at the middle of the distribution such as the median, there are most leads and at roughly the same. Here I'm showing to you a distribution of how many leads end up, what is the percentage of leads ending up within 3 milliseconds of the median or within 1 millisecond of the median, where the median QT interval is the green bar, and as you can see, this is a fairly good possibility. So this could be perhaps advocated.

One should not really measure fewer than 12 because here I'm showing two differences between medians of various striplets and median of all 12, and you can see inaccuracies which are in excess of what we would find tolerable for the precision of the study. So if you are commenting on a new study, the measurement of the ECGs is quite complicated.

Fortunately, it looks like that we do not really need to measure the 12 leads separately, and what I have here is when you take an electrocardiogram superimposed over the 12 leads, you can make the measurement of the QT interval pretty easily. It clearly starts here and it ends here. So you can measure the 12 leads as you see them superimposed, which is probably a technology much faster than measuring separate leads, and that could be perhaps used for future studies. Even when the ECG is this flat, as you can see here, one can sort of expand it, and again, the measurement is pretty straightforward.

Of course, the question is can we actually rely on what is printed by the machine? Well, the straight answer is you can't, which is actually a bit of concern because while I am now sort of talking about design of a study, when you think about the clinical implications for labeling that people will rely on what is printed on the electrocardiogram, not always but fairly frequently or at least simply not infrequently, this can be horrendously wrong.

I'm showing to you two examples in which one is 406 and one is 506. So the difference of 100 milliseconds. It's quite a lot, 100 milliseconds. Still, when you take this bit and superimpose it here, you can clearly see that

simply the duration hasn't changed at all; simply just this ECG is a bit more noisy. And there are good studies showing that while probably when you would sort of sort the imprecisions caused by the standard ECG equipment, the error would be more frequently towards the longer QT interval. Again, there are not very infrequent cases when it is shorter, which potentially might be of concern, and that needs to be also reflected.

There are, however, perhaps new approaches. What the machine does, it simply interpolates it with various simple mathematical waves because the computer processing within the electrocardiograph is not terribly powerful, and these can be easily fooled such as by noise, as you saw in the previous slide.

Fortunately, it appears that there are new approaches, especially in terms of some sort of pattern recognition. For instance, this slide is taken from such a preliminary prospective validation of an automatic technique. This is yet another example, and I have several examples and I can be showing to you example after example. There are automatic techniques that can be sort of used for this purpose, although they require fairly heavy computational involvement on the digital electrocardiograms.

Finally, with drugs that change heart rate,

heart rate correction needs to be taken into consideration. And heart rate correction is a favorite topic of mine. As other people collect stamps or whatever, I collect heart rate correction formulae.

(Laughter.)

DR. MALIK: There are a number of heart rate correction formulae, and they differ quite substantially. These are the standard formulae of corrections. Bazett corrects the QT interval by dividing it by the square root of RR. This alpha is 0.5. This actually has been reported to vary very widely. The extremes by probably sheer coincidence both come from Japan. Kawataki reported that this should actually be 0.25, and Mayeda, it should be 0.604. There are substantial differences in that.

Similarly in the linear formulae there are big differences. Van de Water is from ducks, so we should perhaps discard it. The human data led again to very substantial differences and so on and so forth.

Does it matter? Well, it does matter to a great extent. I will very briefly show you simply how easily the regulatory decisions can be sort of fooled by use of wrong heart rate corrections.

I have used retrospective data as a model. This is data from a post-infarction study from EMIAT. That was that study which compared amiodarone and placebo in

patients surviving acute MI. These are the differences between the patients on and off amiodarone reported by different formulae. As you can see, amiodarone is one of those drugs which prolongs QT interval. So it's not surprising that these formulae all also led to the conclusion that indeed the QT interval is prolonged. Nevertheless, the prolongation is fairly different, ranging from something like 13 to 30-plus.

Much more interesting perhaps is the case when one looks at patients on and off beta blockers. Beta blockers have, of course, a substantial effect on heart rate, and here you can see that three formulae, including Bazett, led to a report that the QT interval is shortened or other formulae led to the report that the QT interval is prolonged, including the Fridericia formula. As I mentioned, this is a new drug and this is coming to the regulators and this would be everything that the regulators would see.

Then knowing that the drug has such a profound effect on heart rate, one would be probably inclined to say, yes, we know that the Bazett formula is problematic when heart rate has changed. Nevertheless, here is such a plateau in the middle of around 7 milliseconds, and 7 milliseconds is what we have seen on therapeutic doses of, say, terfenadine and so on. This would be, again, the

thinking that I will be talking later on. But still this is clearly a positive effect and the drug has an effect on QT interval and it needs to be further investigated. And we would be in trouble with beta blockers.

There is fortunately a possibility of looking at this further on. One could look, for instance, at the real success of each heart rate correction formula, and actually the goal of the correction is to get the QTc data independent of heart rate.

So what I'm showing to you here is 40 different formulae acting on amiodarone data, what is the reported difference between placebo and amiodarone and what was the success of the correction, which I have taken this simply as a correlation coefficient between QTc and RR. As you can see, there are just two formulae which are close to being successful in here which suggests that the prolongation is about 20 milliseconds.

The effect of beta blockers is even more surprising because the line goes through 00. So I just think that those formulae which got the correction right, they also reported that there is actually no effect on beta blockers.

This leads to a sort of suggestion that perhaps we should design a formula for each study. Simply when a study is conducted, we should take the data of the study

and design a formula for heart rate correction in that particular study.

For instance, this is data on and off amiodarone, and I'm showing to you a nonlinear regression through the data, including confidence intervals. This is the data on placebo. This is the data on amiodarone. You can see how the curves are shifted, showing a clear QT interval prolongation. This can be turned into sort of a correction formula and reported in milliseconds.

On beta blockers, it looks like this. Now I have forgotten which line is which, but it doesn't matter because they are the same. Simply there is no change in the QT/RR relationship. The only change you can see is the green dots, the placebo, are here and the red dots, beta blockers, are here. As the heart rate has slowed down, the RR interval prolonged, but the data moved along exactly the same pattern.

There are various possibilities of sort of using interpolations. It is in the handouts. I will go through the details. Here are the possibilities of what sort of modeling one can use to describe these QT/RR patterns and how to turn them into a heart rate correction formula.

There is perhaps more to it, that is, that when we fit this sort of baseline data -- and I'm explaining

this in this detail for you to understand what were the differences in the analysis that was originally submitted to you in the study of droperidol which Dr. Desai mentioned and what were the analyses used in his most recent presentation. When we fit this data, when we simply do the regression modeling, we will balance the relationship between QTc and RR and we will make sure that QTc is independent of RR in the whole population.

The question is whether this will be also the case for each individual subject in the study because when we try to talk about outliers and so on, this is fairly important. Well, the answer is unfortunately it won't because the QT/RR data are highly individual.

This is from a very simple academic study. And I have to say that these readings are coming from a 12-lead Holter read by computer in spite of what I have said about the precision of the reading of the computer. Since this study involves about 1 million ECGs, we simply didn't have any other possibility than to do it by computer, recognizing the imprecisions. These outliers, which you see on those graphs, are probably just rubbish. Nevertheless, this sort of general trend is probably correct.

This is from 6 different individuals which I have taken from a study which involved 50 healthy

volunteers. For instance, you will find that in this block when the RR interval changed between 600 and 800 milliseconds, the QT changed by about 20 milliseconds, while in this young lady, when the same heart rate change occurred, the QT interval was changed by about 70 milliseconds. There is no way that the same formula would fit both these subjects. Simply it can't be. So that is the reason why the individualized approach has been sort of suggested and used for the heart rate correction.

The other reason for that is that these patterns are actually stable in each individual. It looks like that simply we are talking about something like a fingerprint. Simply all of us carries a particular pattern of QT/RR adaptation and we need to extrapolate this in order to make a precise analysis of the QT data.

When one does the QT reading correctly -- I mean simply when all the precision is used -- you will end up with patterns like this. When the width of the pattern is approximately 10 to 15 milliseconds, which is the variability of the QT interval which goes beyond heart rate, other parameters varying the heart rate, such as what Dr. Roden mentioned, simply these adverse reactions. And I will come to that comment in a moment. If we were just looking at heart rate and not controlling for anything else, it looks like we won't be able to take the precision

even further beyond these 10 milliseconds.

This is more to it. The patterns are differently curved. Those people who advocate using just one common mathematical formula and simply just balancing the same formula for all individuals do not have it entirely right because in some people the sort of pattern is more curved than in others, and this needs to be reflected in order to precise, and so on and so forth. So simply the conduct of these is not that easy and not that straightforward.

What is perhaps important to realize is that -- this is yet another analysis from this study of 50 healthy volunteers. What I'm showing to you is if one would use just this mathematical formula which is this type of Bazett formula and if one would balance this correction parameter, these are the correlation coefficients between the QTc and RR for the given levels of the parameter, and these are the optimum corrections, that is, the optimum factors for each individual. Bazett is out of it, and Bazett is the formula which is most frequently used perhaps because it is easy to remember and perhaps because it got stuck in our thinking before everything became known.

What is of concern is that if you would sort of advocate monitoring and if you would use what is sort of calculated by the computer, leaving alone the trouble that

the computer can have it wrong, Bazett would lead to shorter QTc intervals at slow heart rates. And slow heart rates are of possible concern. So if you think about reformulating the label, which presently exists for droperidol, I think that this particular danger might be anticipated in clinical practice and perhaps lowering the limits of sort of active ability of the drug might be one of the possible solutions.

There are other approaches advocated such as, for instance, controlling for heart rate rather than correcting for heart rate. I do not like these approaches personally because I have listed here some of the, in my opinion, dire inefficiencies of those approaches, and you will find it in the handouts.

Perhaps I should also, since we are talking about first design of studies, mention some of the frequent pitfalls of these studies.

QT interval measurement, as I anticipated, is frequently a very big problem. This is from a study of a different sponsor who had paper ECGs analyzed by a central laboratory, and this laboratory had a SOB requiring the operator to tick the complexes which were measured for the QT interval and this is from the results.

This is not very old. This happened last year. Still it included patterns like this when nobody could

possibly see a T wave. Patterns like this. Nothing could be really measured.

They had another study. It was on this harmonica type of thermal paper, which when it goes over this sort of this flip, it misses some of it. And you will see here is a gap in the ECGs. Simply the ECG was missed because there was this fault of the paper. The fault of the paper was also here, precisely where they measured the end of the T wave. They measured a T wave following an ectopic, which is known to be horrendously wrong. They even measured the T wave which was truncated at the end of the electrocardiogram. So the precision of the reading -- we are talking about life and death decisions and still the agency is simply flooded with data of this kind. I have to acknowledge that simply this is known, and that at the present, the agency requires the data to be submitted electronically. We all hope that this will help very much.

I don't have an example of the slide, but only about two weeks ago I was given some electronic data to look at, and I saw exactly the same rubbish in them. So it is of concern and it needs to be addressed very carefully when talking about future investigations.

The other problem is with these fixed corrections, and I will just quickly run through such a modeling mental experiment. This is from data which you

actually have already seen. This is one of the individual data that I showed on one of the previous slides. If one would correct them correctly, using some of the individual approach, simply fitting exactly the curve that would go through this pattern carefully, this is what one would get, the QTc data. If one correlates them with Bazett, this is what one gets; with Fridericia, this is what one gets.

Let's now assume that this is sort of data where we are starting from and let's assume that this subject is given a drug which slows heart rate and also prolongs the QT interval. I have made this simple. I have just added 20 milliseconds to the data and using it as a mental experiment. If one corrects it sort of individually, the difference in the QT or QTc is obvious. If one would then would say, fine, these are, say, six values here and six values here, which we have collected in the study, and if this is corrected with Bazett formula, we will completely miss it and we will find that -- this is actually with Bazett because simply we have over-corrected it so much -- this is actually longer than this. So the signal would be completely missed. So this is yet another possible pitfall in studies. The heart rate correction with drugs that change heart rate needs to be taken into consideration very, very seriously.

Finally, as has been already discussed, the QT

interval and QT/RR hysteresis needs to be discussed. This is a schematic slide coming from a study of atrial pacing, showing that if one changes the RR interval abruptly, the QT interval does not change abruptly. It takes about 2 minutes for the QT interval to adapt to the, say, 90 percent of the change, and likewise when one goes back.

Surprisingly the pattern of this adaption of QT interval is quite different from the pattern of the monophasic action potential that one can record simply directly on heart surface. This is probably because of the changes in the distribution and so on. And this needs to be again taken into consideration when you have abrupt heart rate changes.

I'm showing to you here an example of an electrocardiogram where obviously the heart rate has accelerated during those 10 seconds of the recording. This is not respiratory arrhythmia because for respiratory arrhythmia the wave would be too long. We are not whales. We have breathing habits more fast than this. So this clearly happened, something. And it is very difficult to control for it.

When I'm talking to my students, I'm saying that, for instance, ducks are a very poor model of the human being because ducks usually don't have a mortgage.

(Laughter.)

DR. MALIK: It is sufficient for the volunteer once the nurse comes and simply says I will put electrodes on you and so on and he said, electrodes. Oh, my God, I forgot to pay the gas bill or the electricity bill, and simply I will get a pen out. And the heart rate goes simply through the window. And you can't control for that. So this needs to be very carefully monitored and looked at because this could lead to very substantial imprecision.

Here, for instance, if one would use this, this QT interval hasn't changed at all through the recording, and here if one would use this interval for correcting the QT interval by Bazett, one would end up with a value of 371 milliseconds. At this site it would be 433, more than a 60 millisecond difference. So this needs to be looked at.

There is perhaps such a modeling study which looked at this, and what I'm showing to you are 10-second averages of data taken in healthy volunteers after they have been subjected to postural change. This is an abrupt change from supine to unsupported sitting. Unsupported sitting leads to activation of the spine and therefore the heart rate goes up. And this an individually corrected QTc interval that we recorded in the study. Here is the change and the QTc interval jumped up and went down again and then simply stabilized a bit shorter than that.

Here I could perhaps answer Dan's question.

Dan, I believe that this QTc shortening is due to sympathetic overdrive. I think that those effects that Mehul described would also probably be more sympathetic rather than vagally driven, and they would therefore lead artifactually to QTc shortening. Of course, it's fairly speculative, but I would probably believe that this would not mimic a QTc prolongation, although in that study -- and I will come to what Peter very rightly said about the doses used -- it would probably lead to simply not to those effects that were seen there.

Likewise, if one does from sitting to standing, again, you can see some QTc prolongation. This is absolutely artifactual, and it is an effect of this sort of missed correction of QT interval.

This is an example of an ECG which was recorded after the supine to sitting change, and as you can see, this is a fairly systematic heart rate accelerations through the electrocardiogram that can actually be measured. These are the RR intervals obtained in the 10-second ECG reading, and this is a regression line through them. We can take the slope of the regression line as a measure of this trending of the RR interval and to measure how stable the RR interval is within that 10-second ECG. Again, simply if the ECG has respiratory arrhythmia because the wave of respiration is much faster than those 10

seconds, we will not see this trend due to respiration only.

Here I am showing to you the same slides as I showed before, now with the raw RR/QT data and this data of the trending. As you can see in this change from supine to sitting, the heart rate went up quite substantially, RR shortened but went back again, and the QT interval did not follow this because simply it didn't have the time to follow it and adapted fairly slowly to this new level of heart rate. So clearly this pattern here needs to be avoided because that pattern leads to inappropriate bits of the data in QT and RR.

This is the heart rate trending, and as you can see, here it is going to levels above 10 or minus 10 milliseconds per RR interval, and this can be taken as a cutoff simply to distinguish ECGs that are and are not polluted with this program. Of course, it is very approximate, but once you have only 10-second data, this is perhaps the best one can do.

This is the same from the other change.

Indeed, in the data that Dr. Desai and his colleagues recorded in this study on droperidol, there were changes like this. For instance, this is in one of the subjects, 40 minutes after the administration of a 2.5 milligram dose. This was a very obvious heart rate

trending. And still, if you take these two complexes and superimpose them, you will find that the QT hasn't changed at all.

This is another example down the other side in a different subject, again on the same dose, probably because the dose was so frequent. You have a clear heart rate deceleration. Again, if you take these two patterns and superimpose them, the QT interval hasn't changed because simply it doesn't change that quickly.

Perhaps I could use this as a comment. If one would use this with this bin approach that has been advocated at an advisory committee in May, one would put this interval into this bin and this interval into this bin. The data will be, in my opinion, completely wrong. So this needs to be taken into consideration.

The only thing that was possible to do, because we did not have longish ECGs, was to simply look at effects which this trending has simply removing the ECGs that show this trending from the data set and looking whether the results would change. And I have to say they don't. This is a copy of the slide that was shown to you by Dr. Desai including the individual changes and individually corrected QTc when including the data with trending. And this is what happens when excluding the data with trending. I do recognize how primitive this is and also the limitations

this has, but it still shows that this sort of window around here from 10 minutes onwards is there.

You will also note that this is a bit dropped. This is simply very difficult to comment on. I do not believe that the QT interval could change within 1 minute that rapidly because simply it will take some time. And to conduct a study looking at very fast effects of the drug is possible, but it is quite complicated, and we can come to the end of the discussion.

Again, these are similarly the average effects then to 60 milliseconds that you saw previously, and this is what happens to them when one removes the data with heart rate trending. Again, as you can see, the general pattern is preserved.

Finally, one of the crucial topics, how to interpret signals from the QT-definite studies. Here I would like to second what Peter said. The data of studies at low doses are very difficult to interpret, and they are highly problematic.

Here I'm showing to you data, which I found sort of scattered in the literature, of QTc prolongation on various drugs, including placebo. The placebo is from a study that I have analyzed and that showed a fairly systematic change on placebo simply from one day to another, highly statistically significant perhaps because

of some autonomic conditioning. The patients were frightened when they came to the unit or what.

Here you have terfenadine, one of the bad players, and standard therapeutic dose. This is nondistinguishable from drugs that are sort of believed to be rather safe. One needs to investigate high doses or in cases when it is appropriate, metabolic multiplication. Simply load the system as much as one can in order to decipher whether the drug has a propensity to QT interval prolongation or not.

Here I am, for instance, showing to you the typical slide of terfenadine when administered together with ketoconazole. This is from the study of metabolism, how the levels of the drug change enormously. Here I am comparing terfenadine with placebo and two other antihistamines, the metabolism of which is also blocked by ketoconazole. The placebo is ketoconazole alone. I'm showing to you how in that case simply the good players and the bad player are very substantially distinguished.

So the interpretation of definite studies -- even when you have very small prolongation at a low dose -- how do you put it? Every drug that has been implicated in QT interval prolongation and torsade induction has been shown, when simply one pushed the dose or metabolic multiplication or whatever, when one tried very hard simply

to make the model as sensitive as possible and simply to make the prolongation as big as possible, then it was shown to prolong the QT interval by about 50 milliseconds.

So drugs can only be proposed to be safe, in quotes, when one either tries very hard and pushes very hard and one does not achieve a prolongation, say, 25 to 30 milliseconds. Small QTc interval prolongation at low doses such as therapeutic doses which are not multiplied which are not overdosed offer very low or no meaning for assurance in terms of the safety.

Standard doses do not generally cause TdP in broad population and the tachycardia occurs only in drugs that are overdosed or multiplied or in subjects who have a special sensitivity to it. And Dr. Roden understands this better than I do, but I think that in some respects this has perhaps even types of or characters of allergic reactions. In susceptible patients, it can happen on pretty small doses, and it can, therefore, happen even later on. It can happen simply when the drug has been not almost but simply washed out pretty sufficiently, and suddenly simply some other mechanism occurs which simply then combines it together.

So I have put here that in my opinion, removing a warning from a label of a drug that has been shown to have a propensity to TdP induction is about as appropriate

as removing seat belts from an airplane. Please don't misunderstand me. I am not trying to be patronizing or I'm not trying to make this ridiculous. Not at all. This is, I think, a pretty fitting example.

I fly a lot. My air miles account is in millions, and still I don't remember an example where I needed a seat belt. On the contrary, I repeatedly -- I think twice -- stuck my thumb into that stupid buckle which British Airways has and simply made a blister. So I could actually write to civil aviation authority and say, look, seat belts in my opinion are not needed because I have never seen a case of needing a seat belt, and at the same time, there is an appreciatable health risk related to seat belts and they are expensive. And buckling it up simply takes time and so on and so forth. Why don't you remove the seat belts from the airplanes?

What has been said here about droperidol tells me that there are probably still some airplanes without seat belts, but what sort of seat belts do we need to wear and whether two-point seat belts are appropriate, whether you need four seat belts or whether you need simply some air bags on planes. It's a very tough regulatory decision, and I will not pretend that I envy the position of the employees of FDA who are frequently in a very difficult position. But I don't think that removing a label from a

drug that has been shown to cause torsade -- and I don't think that there can be any dispute about droperidol causing this from time to time -- that this should be removed.

Finally, perhaps very quickly, are there any surrogates beyond QT interval, knowing that QT interval is such a primitive marker? There is very little experience I have to say, and what I will present to you I am presenting with a bit of hesitation because my knowledge in this field is very limited, probably like everybody else's. So please keep this in mind what I will say further on.

There are clearly drugs with which the QT interval prolongation is not that bad. The same QT interval prolongation can be simply bad and perhaps even good and can be indifferent, and it depends on the different combinations of the drugs. As I said, only very preliminary attempts exist to discern these possibilities.

One of these possibilities how to discern it is measuring the irregularity of the repolarization. What one actually does from the standard 12-lead electrocardiogram, we can reconstruct the loop of the ECGs, simply the movement through the heart, and then we can look at what is the reminder of it, what are the signals that cannot be explained by single dipolar movement, what are the signals that can be distinguished as simply coming from beyond the

loop and therefore coming from different islands of tissue in the heart. As we understand it, perhaps these islands of the tissue with different electrophysiologic properties are those responsible for torsade induction. This can be done.

There are still in this technology numerous limitations and numerous technical problems. I have listed some of these. They are in your handouts. Nevertheless, there are already clinical studies conducted. For instance, what I'm showing to you here is from a study of cardiac patients in whom these residua of the T wave were measured, and it was found that those patients -- it was a very long follow-up of 15 years. The data existed. Simply they were recorded before a long time ago in VA in Washington and here. When we measured the residua, we found out that patients who have increased these residua -- it was just about the median of the population -- had a poorer prognosis. Similar observation now exists in the general population. It was the strong heart study conducted in American Indians, again showing that these residua do predict adverse outcome.

I'm showing to you now a relative residua, which is yet another expression of it. They have properties that would sort of make the mosaic of knowledge consistent. For instance, these residua are higher in

women than in men, and we know that women are more prone to torsade. So simply this again made sense.

My experience, apart from droperidol, with this residua is related to two drugs and two drugs only. Nevertheless, it looks like that some possible pattern may be emerging.

One drug on which I was able to investigate this residua was moxifloxacin which I would characterize that the QT interval prolongation on moxi is probably in that category indifferent. If I have it right -- and the data were provided to me by my European friends -- there are now about slightly less than 20 million exposures to the drug, and of these 18 reported cases of torsade I have to say in patients with other sort of factors contributing to the torsade. So there is incidence of approximately 1 torsade per 1 million exposures, which is probably the border of where the regulators should get concerned, and this is what I would call indifferent. While moxifloxacin prolongs QT interval, the residua are not changed.

My other experience with residua is on ebastine which is an antihistamine widely used in Europe, Japan, but not here. The data were provided to me by the manufacturer. There are 70 million exposures of the drug from the sales. There are 2 questionable cases of torsade. The QT interval prolongation occurs only on very high

pushed doses. I think that the incidence of 1 torsade per about 35 million of exposures appears to be probably below the background. So here, with quotes, I would say that here the QT interval prolongation at the higher doses is potentially beneficial because it looks like that simply the drug is actually slightly antiarrhythmic.

The residua are decreased. This is from a study in women showing a statistically significant decrease. I have to say that when ketoconazole was added to the drug and when the concentration was pushed up, it was still simply numerically more decreased than on placebo, but the difference was no longer statistically significant.

When one, in a different study, looked at it again -- these are the relative residua and absolute -- because I didn't have it. When looked at the relationship between the concentration and the residua, they were clearly decreasing. This includes the placebo part which is everything here hidden on the level of which I used sort of to model the below laboratory precision. Still, simply it looks like that the drug decreases the residua.

And then I looked at the residua on droperidol where the incidence, as we have heard, is about 1 in 50,000. This is from the analysis of the data that Dr. Desai has recorded and which Mehul presented to you before,

and you can clearly see a slight but still increase of the residua on droperidol. When one looks at the maximum changes, this is what we get. Mind you, these were just 3 subjects. Simply it would not be appropriate to talk about any bell-shaped relationship. These are the changes within the first 10 minutes. These are the changes within the 10 minutes to 2 hours. They are clearly different. Mind you, the residua might depend on heart rate differently. This has not been taken into consideration here. There are still some dire limitations to this approach.

Nevertheless, it looks like with all these question marks that I put here that perhaps there might be some surrogates beyond the QT interval and that one could, indeed, distinguish by the changes in residua the bad, indifferent, and good QT interval prolongation.

Thank you very much.

DR. HORLOCKER: We'll take one or two questions. Dr. Shafer.

DR. SHAFER: Actually two quick questions. First, is it possible that some of the QT prolongation that's been reported in clinical studies early on with droperidol are an artifact of the heart rate increase and thus making it hard to interpret those studies?

And secondly, it seems like the right study design going forward would be to bring subjects in and

establish their QT versus heart rate relationship prior to getting dose. In which case, how would you be sure that the subjects -- how would you stimulate them? It sounds like exercise might cause artifacts. Sitting them up would cause artifacts. How would you ensure that the heart rate covered the span of interesting heart rates in that pre-dosing development of the RR/QT relationship?

DR. MALIK: The answer to the first question is yes, indeed. I would have my substantial doubts about the QT interval prolongation that was reported previously. For instance, some of it was not even versus baseline. Some of it was versus unrelated volunteers which, of course, at that time simply nothing better was known, but under the circumstances of the present knowledge, I would have very big doubts about the data that were presented before.

Perhaps one could take from it that there is probably a propensity to the prolongation of QT interval as was actually confirmed in this little study, but nothing else can be said.

There is a very good point. On the second one, I don't think that one should use exercise or any sort of provocation. I would rather have the patients, because the heart rate varies through the day, quite sufficiently, and those changes that I showed to you were simply when the participants of the study were taken for 24 hours into the

unit and simply left on their own with a monitor attached. So this is perhaps the best way forward to establish the sort of unprovoked QT/RR relationship because the heart rate simply changes on its own due to psychosomatic or whatever actors and due to circadian pattern. This also gives you then the possibility of comparing like with like, comparing the data which occur at the baseline at the same time of the day with the data that occur on the drug at the same time of the day. So it really requires simply one extra day rather than simply a couple of hours. I do understand that this is more complicated, but in the presence, I think, of the understanding of the QT/RR relationship, I don't see any other solution.

DR. HORLOCKER: Dr. Roden.

DR. RODEN: Marek, two questions. One is how do you envision a study with a drug like this where the dose cannot be pushed. So you'd love to see what happens at 50 milligrams or 100 milligrams just to get a handle on whether that QT signal is actually real or not. So you made a big point that that should be done, but it's not clear to me that that will be tolerated either with pushing doses or with metabolic inhibition.

And then the other question is the T wave residua data. Those are pretty provocative and interesting. Do you have positive controls like with

sotalol or dofetalide or some drug that is known to cause torsade so that we know what the T wave residua do there?

DR. MALIK: To the second question first, I don't. This is everything I have. And I do understand. Simply that is the reason why I put so many question marks and so on and so forth. At present, we are collecting data on terfenadine, but the studies on the residua are not that easy to conduct. One has to be very, very careful.

I would probably answer the first question I think that really without pushing the dose high, simply no meaningful conclusion of the study, as Peter said, will ever be possible. However, I think that one has to make a distinction between simply general population of patients in whom it would be quite difficult to conduct because you would have simply the underlying cardiac diseases and underlying ECG abnormalities, but if one would select carefully the patient population who would tolerate these doses for simply clinical reasons and who would at the same time have a stable electrocardiogram, that in my opinion would perhaps be the best compromise.

DR. HORLOCKER: The final question from Dr. Eisenach.

DR. EISENACH: I wonder if you could comment a bit more about the difference between the spontaneous torsade incidence and that which the regulatory agency is

interested in. It sounded like they were almost the same number. You said 35 per million was background and 1 million is --

DR. MALIK: Again, Dr. Roden will have a better understanding about this. It's my understanding that the background incidence in -- we are talking about exposures here in a short time. If one would sort of do it with placebo, my more guess than a -- because simply the incidence is of -- if one would get this on a placebo treatment over, I don't know, a month or so, I guess that the incidence would be around 1 in 5 million to 10 million. Is that right? It's a guess.

DR. HORLOCKER: Dr. Schultheis has said that his presentation is 15 rather than 45 minutes. So if you can swear that that's an accurate number, we'll go ahead and have his presentation before lunch in an effort to try to stay on track.

DR. SCHULTHEIS: I'm Lex Schultheis. I'm a medical officer and anesthesiologist in the Division of Anesthetic, Critical Care, and Addiction Drug Products. I'm going to review some study proposals that we might consider to help understand these issues better.

A challenge to the scientific advisory committee is to weigh the value of performing additional studies to assess the risk of dysrhythmias that may be

related to droperidol and consider alternative designs, outcomes, and the potential resources that might be required.

We've had a lot of commentary so far on the types of studies, so I tried not to duplicate too much of this but tried to just summarize what we know and where we might go from here.

What do we know about droperidol and QTc prolongation? We believe that droperidol seems to prolong the QTc in a dose-dependent fashion. We only have very rough information about that at this time. And there's an indication also that there may be outlier responders.

What additional data can we gather that would improve the safe use of droperidol for postoperative nausea and vomiting?

We'd like to know the incidence of serious cardiac dysrhythmias related to droperidol. We don't have that information at this point. As Dr. Chang pointed out, we don't have the numerator, we don't have the denominator.

We'd like to be able identify particular populations who may be at increased risk.

And finally, we'd like to have more precise, quantitative dose-response information of QTc prolongation associated with droperidol.

Further, we'd like to know how droperidol

interacts with many of the other drugs that are given in the perioperative environment that may affect its dysrhythmic properties.

And we'd like to improve our knowledge of the type of patient assessments that would be needed to ensure the safest possible use of this drug.

I'll present three approaches that we could consider to gather more data. This is not intended to be comprehensive. Clearly the goal is to not restrict your thinking to these types of approaches but to use them as examples.

One approach is to compile a registry of serious dysrhythmias comparing patients who received droperidol to patients who did not receive droperidol for postoperative nausea and vomiting. A very large study comparing many patients that are treated or prophylaxed for postoperative nausea and vomiting.

A second approach is to use a randomized trial using QTc prolongation as a surrogate in a patient population that would normally receive droperidol or similar drugs comparing treatment/prophylaxis and evaluate the effect on QTc.

And finally, we could consider an expanded definite or thorough QT study in volunteers. This would include dose-ranging effects, randomization, and would be

placebo-controlled.

In the notion of a registry for patients managed for postoperative nausea and vomiting, the one feature that we would get out of this is an estimate of the incidence of serious dysrhythmias. Now, this would have to be a very large study, ranging from tens of thousands of patients using the data that Dr. Chang suggested to maybe even the population of a small country. It would include all patients managed for postoperative nausea and vomiting regardless of the agent used. The goal is to capture all serious dysrhythmias in a standardized fashion. This would be complicated in and by itself. Then we would attempt to relate the serious dysrhythmias to droperidol and have sufficient numbers so we could make some kind of a statistical assessment.

The advantage of a registry is that it would examine the incidence of serious dysrhythmias, not biomarkers. After all, we're really interested in the clinical features that affect patients. It would engage a wide spectrum of patients, including those with various comorbidities.

The disadvantage to a registry is that it's not randomized. Of course, if we did randomize it, then it would become a large, simple clinical trial, but it would have many of the same features of a registry.

Randomization would just add another level of complexity to this.

It includes a high level of patient variability so that it might make it difficult to interpret how to evaluate the patient in front of you based on the data that was collected.

It is a data acquisition and management nightmare, very complicated and difficult to collect all the data in a standardized manner.

It has the potential to miss significant QT prolongation that may occur without adverse events. So we're really only looking at adverse events here and we would ignore the near misses.

A second alternative is the randomized trial design. This is randomized and blinded and would engage droperidol versus controls. Certainly placebos would be a preferred control, but we might have to include active agents or dose controls to achieve sensitivity of our assay to make sure that we were actually capturing the QTc intervals that we thought would be important and to verify that.

It could engage treatment or prophylaxis or both.

And it might include an enriched population to reflect actual use, and I'll get to that in the next

slides.

The main outcome would be QTc prolongation. We could collect data on serious dysrhythmias, but it's unlikely that this would be particularly significant data because it is a smaller scale study than our registry design.

In the randomized trial, there are distinctions here. Patients that are at particular risk for postoperative nausea and vomiting may not be the patients that are at particular risk for prolonged QTc. However, there may be some overlap within these two populations, and these are the patients that we would be particularly interested in. This is how we would try to enrich the study.

For example, patients managed with droperidol, young age group, female outpatients undergoing gynecological surgery have a high incidence of nausea and vomiting. They're treated prophylactically or they're treated in the PACU for symptoms. When I was a resident, we used to routinely treat patients undergoing eye surgery, cataract surgery with droperidol. That's not done so commonly anymore because there are advances in the approaches to the same kind of surgery. But there may be some subset here that we could still consider.

There are a number of factors that increase the

QTc and the likelihood of torsade: female gender, elderly age group, various electrolyte imbalances, the presence of cardiac disease, congestive failure, coronary disease, metabolic inhibition, CNS dysfunction or even physiology such as postural changes, and congenital long QT syndrome. What we would hope to do is overlap somehow the patient population that would be normally managed with droperidol with a patient population that may have increased risk factors for QTc prolongation.

What are the advantages to a randomized trial?

Well, randomization. It's an important feature to reduce bias.

Second, we might be able to construct a clinically relevant population and really address the issues that matter to doctors.

And finally, it's a manageable size of data set. It's something that we do and the patient population would be something that we could manage with more conventional techniques.

There are disadvantages.

Recruitment may be difficult. Patients who have a history of nausea and vomiting don't like to be told that they might be getting placebo. It might be hard to pull patients into that study.

Also, since we're interested in evaluating the

sensitivity of our assay, we may have to include active controls that have a higher risk of QTc prolongation. So there may be more risk to patients who would participate.

This still involves collecting a lot of data and it's likely that we will miss some of the data for some of the patients. So our data set is unlikely to be perfectly complete, and that's going to reduce our ability to interpret it.

And because it is a limited population, we expect that we will miss some rare events.

That brings us back to the definite QTc study or the thorough QTc study design. We have a number of options.

We can expand the crossover volunteer study along the lines that Dr. Desai presented. Now, our focus of interest, of course, is on postoperative nausea and vomiting doses, low doses of droperidol. We may have to use the highest possible doses that patients will tolerate in order to achieve the sensitivity that we need in our assay.

We may be able to consider a controlled heart rate study in patients who have atrial pacing. That would certainly simplify some of the analysis, but it has disadvantages that Dr. Malik has just presented so I won't repeat them again.

And our outcome measures are primarily QTc and the dose response associated with that.

The real advantage to a definite or thorough QTc study is complete control over randomization and dosing and complete ECG data. As we've just heard, it is very difficult to analyze the ECGs in a precise, sensitive way, and this study design offers the advantage of capturing all the data and doing it properly.

There are some disadvantages. There's little to no benefit to the participants despite the potential risk of giving them drugs that prolong QTc. Because it's a small population, there's a reduced chance of actually detecting some of the outliers that we'd like to capture, and because these studies are typically conducted in volunteers, it may be difficult to apply the results to clinical practice where there are comorbidities and co-administered medications.

Other steps that we need to consider to reduce the risk to particularly vulnerable patients. Eventually we need to estimate the interaction of droperidol with other drugs that may affect QTc prolongation, and I'll come back to this in a moment.

We need to determine the type of patient assessment that's really needed to ensure the safest possible use of droperidol. That's in terms of patient

selections, a screening process, and the type of monitoring that is both practical and sensitive enough to protect the patients.

Some of the other QTc prolonging drugs that we routinely encounter in the perioperative environment: anesthetic vapors, other drugs used to treat postoperative nausea and vomiting. Many anesthesiologists don't give just one drug. They give a combination. I've been in hospitals recently where a number of drugs have been drawn up in the same syringe and administered, off-label application. Antidysrhythmics, many other drugs can prolong QTc and can be used in the perioperative interval.

So what can we do to reduce the risk when we treat patients with droperidol? We may be able to improve the patient selection process based on comorbidities or other risk factors so we can pre-identify patients that we think might benefit from droperidol and exclude those that we think might be at particular risk.

We can improve our understanding of the role of the ECG as a pre-administration screen and monitor. How effective is this? Now, of course, as anesthesiologists, we routinely monitor patients in the operating room and in the postoperative period with ECG, but if it's a very insensitive monitor that only picks up dysrhythmias, we're not going to be able to even assay QTc prolongation and

have the advantage of an early warning system.

And then finally, we need to accurately define the risk period after administration of the drug.

In summary, these designs that we've just reviewed here are very limited. So we're going to invite the scientific advisory committee to comment on the value of any additional studies to understanding the potential risks of cardiac dysrhythmias that may be related to droperidol. Again, we encourage you to think about alternatives and to weigh the value of performing additional work in relation to the resources that it would consume to do this work.

We also suggest that any elucidation of the relationship of the QTc prolongation to droperidol should consider the agency white paper, the working document, on the study of QTc prolonging drugs. It's on our website.

That's all I have.

DR. HORLOCKER: What I'd like to do is have Drs. Malik, Schultheis, and also Desai share the podium. We've heard different presentations on the overall cardiac events and I know there have been a lot of questions left unanswered within the advisory committee. So we'll take 15 minutes of free-for-all.

DR. RODEN: So I have two more suggestions to put on the table in terms of data gathering. I guess I'd

preface my comments by saying that it's pretty clear that there are two camps around this room and they both painted themselves into corners. One way out of this dilemma is to get more data. When all else fails, get more data.

So the two other pieces of data that I think could be considered as part of the shopping list are, number one, more in vitro electrophysiology, and there are models that are relatively sensitive to torsade risk as opposed to QT risk. And if those studies were mounted, I think despite what the agency says, they should include other antiemetics as controls, as well as droperidol. That's one thought.

The other thought is that it is remarkable to me that we're discussing a drug whose pharmacokinetics are completely uncharacterized. What if I told you that this drug is a CYP 2D6 substrate and there's an active metabolite that is generated or a CYP 2C19 substrate and there's a marked drug accumulation with late effects in poor metabolizers? You have to know that, and if you don't know that, then you're really swimming completely in the dark in studies of metabolic inhibition. You don't even know what metabolic inhibitor to use. So I think that the conversation needs to take that into consideration as well.

I don't know who gets to do those studies, by the way, but somebody does.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: Two questions. First, to what extent do these rare events happen only in susceptible individuals? First off, we know that there's one genetic predisposition which is long QT syndrome, and do we actually know that those individuals are in fact more sensitive to drug-induced torsade?

And secondly, is there any evidence for silent mutations that don't show up as long QT intervals which nevertheless predispose subjects to torsade? Because if our concern is based on case reports in subjects which have a polymorphism that has a very, very low incidence, then we may be very hard-pressed to establish something that is useful in a clinical study of manageable size.

DR. RODEN: Steve, since that's how I spend my life, let me just address that. The answer to the question of whether there are patients out there who are silent mutation carriers -- another way of saying it is whether there are patients out there with subclinical long QT syndrome that becomes clinical under provocative stress. The answer to that is definitely yes. Our group and a number of other groups have reported such mutations.

The other issue is predisposing polymorphisms. The fact is that as we understand more about genomic medicine, everybody has predisposing polymorphisms to

everything and you're never going to be able to get rid of a drug, whether it's a QT-prolonging drug or an anemia-causing drug by saying, well, there are predisposing polymorphisms to adverse drug reactions in the community.

The specific QT stuff is that there are a couple of polymorphisms that have been implicated in exaggerated QT responses, and there's one particularly interesting one which has a minor allele frequency of about 15 percent, so not inconsiderable, only in African Americans.

So you're opening Pandora's box that I don't think you want to open right this instant because we just don't know enough about the genetic determinants. There are clearly some people who have unrecognized congenital long QT syndrome that will misbehave on exposure to a drug.

DR. HORLOCKER: Dr. Katz.

DR. KATZ: It seems to me that the question is what added risk comes from using droperidol in terms of these outcomes of torsade de pointes, the clinical outcome of interest? So what is the risk of that outcome conferred by using droperidol out there in the community in comparison to using other agents for postoperative nausea and vomiting?

If that's really the question, then what I'm trying to understand is what is the value of doing these

intensive studies where QT prolongation or some other surrogate measure is the ultimate outcome. It seems to me to be almost a technical issue to come up with some sort of study design where you could show that droperidol prolongs some surrogate measure. But if the linkage between that surrogate measure and predicting these outcomes out there in the real world is either unknown or very tenuously known at best, why is that a useful activity and why wouldn't it make more sense to essentially abandon those activities and focus more on an epidemiologic approach where you would understand from the actual cases of torsade de pointes to what extent droperidol versus other antiemetics is a risk factor, drug interactions, patient clinical status and try to learn about real risk factors in real patients with the real outcome of interest?

DR. HORLOCKER: Any or all of you can answer that question.

DR. SCHULTHEIS: One issue is whether we would be successful if we tried to estimate that risk in comparison. It would be a very difficult study to do. And yes, in the best of all possible worlds, we'd have a clinical indicator, but it just seems like the likelihood that we'd be successful is very small.

DR. KATZ: If measuring what we're really interested in is difficult, I'm not sure how that problem

is solved by getting a very good measurement of something that's not relevant to what we're interested in.

DR. SCHULTHEIS: Well, I don't think we've said that it's not relevant. One of you may want to take that. It's the best we have.

DR. MALIK: It's, of course, a very tough question. Actually I am far from convinced that a further study, unless we are simply talking about a study which would cost millions and millions and which would be really very difficult to conduct, that it would advance our knowledge sufficiently simply beyond the present sort of wishy-washy background.

I think that at the present three things are known about the drug.

Firstly, it is a quite potent blocker of one of the channels that has been repeatedly implicated.

Secondly, there is some appreciatable incidence of torsade on the drug, as perhaps suggestions not from this country but simply from across the ocean suggest.

And thirdly, it has been shown, with all the difficulties there are in interpreting the data from the literature and in conjunction with the study that Dr. Desai conducted, there is some propensity of the drug to attack the QT interval. If we would push the dose high, with all the difficulties which Dr. Roden mentioned and so on and so

forth, whether we would reach the levels of 80, 70 milliseconds which would clearly tell us that something is very wrong, whether this is needed at this moment, when a 30-year experience exists with the drug, or not I don't know. I would rather think that perhaps sort of rethinking -- in my opinion there is clearly something wrong with the drug. The drug is not sort of risk-free.

Maybe a general suggestion of how to modify the label -- and again, I wouldn't like to be critical of the agency because I do understand the very difficult position they are in. Maybe, in my opinion, simply some tailoring of the restriction of the label and what is now presently written in that box might be appropriate. For instance, in my opinion if one would, say, take an electrocardiogram in a patient and one would see that the ECG -- and I would like to hear what my colleagues would say about it. If the ECG is pretty normal, then I don't think that one needs to worry about simply having this as a second-line treatment. I think that in a patient who has a pretty normal electrocardiogram to start with, one would be unlikely to cause troubles unless one would push the dose horrendously high, which I understand -- this is far beyond my knowledge -- that the levels aren't that high.

So I think that from the last presentation that you very clearly summarized, I think that I would somehow

concentrate on the limitations, and I think that in order to gain further advance, you are very right, this is an impossible position. Unfortunately, while we call for evidence-based medicine here, to gather the evidence is so difficult and so complicated that perhaps we have to be guided by the mixture of evidence and general understanding which might be indeed wrong and we might be perhaps criticized simply 10 years in line. But simply at the moment, unless you take -- I don't know -- not Switzerland, but Kansas plus -- I don't know -- I'm terribly sorry -- which country is next to it -- and randomize all of that, you won't know.

DR. HORLOCKER: Dr. Bril.

DR. BRIL: My question is somewhat along that line. I was interested in your presentation, Dr. Malik, where you showed that patients can have asymptomatic torsade. So my question really is, is every episode of torsade bad? And if the QT prolongation predicts an increased frequency of torsade, do we know if it predicts an increased frequency of the bad symptomatic torsade or just episodes of torsade? If you monitored all of us in the room for 24 hours, would some of us have torsade that's asymptomatic? You did talk about the background incidence. I thought from years ago I used to remember we could have bits of ventricular tachycardia asymptomatically. Maybe

that's old thinking now and old knowledge. But I'm just wondering if we do want to use the surrogate, how many really bad torsades do we have?

DR. MALIK: That's, of course, again a very good question. Torsade, while perhaps one may argue that it might be in some cases indifferent, it's certainly not good to have it because of the electrical stability and so on and so forth. The understanding which we have, especially from animal studies, suggest that it can deteriorate to fibrillation pretty easily because of the sort of random nature of the tachycardia. It is true that it is very frequently self-terminating. Nevertheless, the symptoms of every tachycardia, such as either monomorphic VT or torsade, depends on the hemodynamic implications. Once the tachycardia affects the ventricle performance in terms of pumping the blood, then we are getting the symptoms.

You are quite right that there are healthy volunteers who frequently -- I mean simply every month or so, perhaps not that frequently -- have a short monomorphic ventricular tachycardia. There were studies on the normal heart VT patients on possible interventions and so on and so forth. The conclusion of these studies was that the best thing is to do nothing. Whether the same applies to these asymptomatic torsades is not known because

asymptomatic torsades and asymptomatic tachycardias are simply tachycardias which we do not know about.

I would doubt that these tachycardias are very frequent. I think that simply one needs to have some provoking factors and so on and so forth, and I would be surprised if this were as frequent as the normal heart VTs, which again are not very frequent. And the background incidence, because of all of this, is very difficult to know and is based on guesses, as you have seen from the discussion.

DR. HORLOCKER: We only have time for two more questions. They'll be from Dr. Rose and Dr. Kowey. Dr. Rose?

DR. ROSE: Dr. Desai, this question is for you. I was very fascinated by this study that you didn't, unfortunately, get a chance to complete. I was curious as to the time course of the different doses that the various patients had. What was the time between the different doses that the patients received?

DR. DESAI: So you're asking what was the time period between the study periods?

DR. ROSE: Yes, that's correct. In other words, my thinking is was there any buildup of the dose in the patient. I think I remembering hearing that you had studies to show the concentration of the drug in their

blood, but that could also be different than the concentration in the brain. I was wondering, especially those people who had all four of those doses that included the placebo, what was the time between each of those doses.

DR. DESAI: Sure. The time period that we had between the study periods was between 3 and 6 days. So from what we know of the PK of this drug, the terminal half-life being 2 to 3 hours, we thought that was sufficiently long enough.

DR. ROSE: And as a follow-up, I know you give informed consent to study patients. Did they have informed consent relating only to the possible arrhythmias, or were they warned about the possibility of dysphoria, nightmares, sedation, et cetera?

DR. DESAI: Yes, that's a good question. In our informed consent, we made them aware of both risks because, as Dr. Roden was mentioning, the side effects of this drug are characterized and they're also in the label, some of these dysphoric side effects. So we clearly made the subjects aware of those risks as well.

DR. HORLOCKER: Dr. Kowey.

DR. KOWEY: Marek, I'm going to respond to something that you said earlier, and I want to agree with you and let the committee know that among the choices that we were given for the clinical trials in that last

presentation, there is no clinical trial that will exonerate this drug. There is almost no way that I can think of, whether it's epidemiologically or whatever, that's feasible that can be done to lead to a conclusion that would allow you, based on that information, to remove a black box warning.

So we're going to talk about trial design this afternoon. The trials about QT interval are not about this issue. This drug prolongs the QT interval to some extent. It causes some incidence of torsade. We know that. And having known that, it is going to be impossible to design a trial that takes away that concern.

What Dan said is probably closest to the truth, which is the only chance you have of finding out more about this drug that might exonerate it or partially exonerate it, is in the preclinical arena, not in the clinical arena.

So I think that the discussion -- among those three choices you gave us, I don't like any of them. They're all terrible. They're terrible because they're not feasible. And even if you did the study in patients, I don't know how you would ever come to the conclusion, based on all of the variables in that patient population, that you could use this drug without any worry about it. It's just impossible.

It's not a question. I guess it was a comment.

I apologize.

DR. HORLOCKER: Dr. Fleming, a final comment before lunch.

DR. FLEMING: Well, I'd like to follow up with a thought following Dr. Katz's question and then I had a question.

I'm very sympathetic to the thought of really not having to rely on surrogates. The reality, though, is from the numbers that I'm hearing, that I'm understanding, if we were looking at quinidine, we could, with just a couple hundred patients, establish the association with torsade that is real. My understanding is what is expected here is that we're trying to sort out with droperidol the difference between what might be 1 in 50,000 to a background rate of one-tenth that, and that would take on the order of a half million to a million people, which I guess is Peter's point of not being feasible.

Just to pursue the feasibility of Dr. Schultheis' first proposal -- and that was one, as I understood, that was in postop nausea and vomiting using serious dysrhythmias as the measure -- could you give me a sense of what you're expecting? What would you want to be ruling out there? What is the background rate there that you'd want to rule out?

DR. SCHULTHEIS: There are a host of numbers in

the literature, and I'm not sure we can give you a number that's precise that's going to tell you that at this point. Dysrhythmias are common in the perioperative environment, but the kind of torsade event is very uncommon.

DR. FLEMING: Well, my understanding was exactly that point. What you're going to try to do is go to a broader measure by not just limiting yourself to torsade, but looking at all serious dysrhythmias.

DR. SCHULTHEIS: Right.

DR. FLEMING: And what I want to try to get a sense of to think about over the break here is what would that rate be as background versus what is the increase in that rate that you'd want to rule out or that you expect could be real with droperidol.

DR. SCHULTHEIS: And again, it would depend on the patient population that you were examining. Patients that were in an enriched population, the number would be very small. If you were take all comers, it might be considerably higher. You might see it on a daily basis in a busy hospital. But cardiac patients, for example, patients undergoing major surgery, will have dysrhythmias.

DR. FLEMING: I think you talked about a postop nausea and vomiting. I assume there was kind of an all-comers in that category.

DR. SCHULTHEIS: Well, actually there are

certain procedures that are associated with a much higher incidence of postoperative nausea and vomiting and require more aggressive treatment, and those are outpatients, young people, for example. Sicker patients, who may remain intubated and in a monitored setting for a considerably longer period of time, wouldn't necessarily be treated. So I think we'd have to establish, first of all, the population of patients that we're interested in and then maybe work to numbers on that.

DR. HORLOCKER: With that, we'll adjourn for lunch. We'll reconvene here at 1:15 for the public hearing.

(Whereupon, at 12:35 p.m., the committee was recessed, to reconvene at 1:15 p.m., this same day.)

AFTERNOON SESSION

(1:25 p.m.)

DR. HORLOCKER: I'd like to begin the open public hearing please.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages the speakers here, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I'd also like to remind the advisory committee members that interaction with speakers at the public hearing is for clarification only and we do not actually query the speakers.

With that, the chair recognizes Dr. Cullen.

DR. CULLEN: Good afternoon. I'm Dr. Bruce Cullen. I'm a practicing anesthesiologist in Seattle, Washington. I am also a professor in the Department of Anesthesiology at the University of Washington, and I'm here today representing the American Society of Anesthesiologists. I'm the Vice President for Scientific Affairs for that organization. That organization consists of 38,000 anesthesiologists in the United States.

Personally I've used droperidol for 30 years. In fact, it was interesting to hear that it was developed and released in the '60s. That's exactly when I was doing my residency, and so I'm very familiar with Innovar and droperidol.

Over my career I've used droperidol commonly. The only complications I've seen with droperidol have been the dysphoric reactions, which are real, and the hypotension is probably due to the alpha blockade, but I've never personally experienced complications in terms of dysrhythmias. I've also been on academic departments for my entire career where we have weekly quality assurance

sessions, and at those sessions I've never heard a cardiac complication from droperidol discussed.

On the other hand, it's very interesting that the short time that ondansetron has been available -- in my departmental experience, in fact, with one of my own patients, I had a young woman, aged 30, with no cardiac symptoms who was given ondansetron, developed severe signs and EKG evidence of cardiac ischemia which was pretty directly related with the intravenous administration of ondansetron, an alternative for droperidol in terms of treatment of nausea and vomiting.

So two cases in my institution associated with ondansetron, nothing in my career related to droperidol.

So it was quite a shock to me and to all my colleague anesthesiologists throughout the country when we saw that the FDA came forth with this warning on the use of droperidol.

I will clearly state I have no conflict of interest here. I have no association with any commercial entity involved with the manufacture or distribution or sales of droperidol. And my funding for attendance of this trip was by the American Society of Anesthesiologists.

The purpose of my presentation today is to advocate that the FDA remove this black box warning for droperidol when administered at low doses such as those

used for treatment of postoperative nausea and vomiting, which we refer to as PONV.

Alternately, perhaps the FDA should undertake an analysis of the large numbers of cases reported in the literature where droperidol was shown to be safe and effective at low doses for the treatment of postoperative nausea and vomiting.

Just as an aside, listening to the discussion this morning, I too think that doing a prospective study would be unproductive.

The American Society of Anesthesiologists has submitted a position paper to the FDA committee which outlines the arguments and our concerns. It goes without saying that large numbers of anesthesiologists are quite disturbed by the action that the FDA took. I'm going to only emphasize a few points in this presentation. The remainder are in that position paper that was submitted.

It's my contention and our society's leadership's contention that droperidol is a safe and effective therapy for treatment of postoperative nausea and vomiting. This problem is common, probably the most common complication of anesthesia. It also can be a very costly complication from anesthesia, and that is, patients have to remain in the postoperative period for treatment of their nausea when otherwise they could have been discharged and

sent home. It is not just a little emesis here and there. Some patients can be severely debilitated and it can be a complication for them.

Also, it can complicate surgery. If the patient is having ocular surgery or they have a wound dehiscence or some other disruption as a result of the retching and vomiting. It can be very difficult to treat. I know that I frequently get calls to the recovery room saying, Dr. Cullen, so and so is having a severe problem with vomiting and we can't send the patient home. They're very uncomfortable. What can we do? My choices are limited. It's been very difficult now that droperidol has been effectively eliminated from that armamentarium.

The doses of droperidol effective for treatment of postoperative nausea and vomiting are usually on the order of a milligram or less. The evidence that droperidol is unsafe at these low doses, in terms of its potential for serious dysrhythmias, I think and many of my colleagues think is nearly nonexistent, and I think it's kind of been described here as well.

There are case reports of dysrhythmias with droperidol, but the ones reported with the low doses have so many concomitant problems, it's difficult to sort them out.

The FDA warning has effectively removed

droperidol for use as a treatment for postoperative nausea and vomiting. The reason is because this warning mandates continuous ECG monitoring before, during, and after use of the drug. Yes, anesthesiologists typically monitor ECG intraoperatively and yes, it's monitored postoperatively in the recovery room, but it's not typically monitored for 2 or 3 hours after administration of the drug. So this has effectively eliminated our use of the drug.

And also the malpractice concerns have effectively eliminated our use of this drug. Anesthesiologists now fear that if they give that drug and the patient has any complication, whether it's related to droperidol or not, if it comes out in the courtroom or in the testimony or whatever that you gave droperidol and didn't monitor the patient appropriately, no matter what the complication is, you're kind of hanging yourself out to dry. So most anesthesiologists have just quit using the drug.

Many hospitals, pharmacies, and physicians have removed droperidol from their formularies for similar concerns. They just don't want to take the risk associated with it.

The alternative drugs to droperidol for treatment of postoperative nausea are more costly than droperidol and may, in fact, be of greater risk to

patients. There's ondansetron and the other serotonin antagonists which are known to prolong the QT interval. I've already mentioned my personal experience of seeing two cardiac complications associated with ondansetron. Are we sure that that is in fact a safer alternative than droperidol?

Another drug is metoclopramide, a gastrokinetic agent. I didn't have a chance to ask somebody, but I'm curious of whether it's in the same class as cisapride. Does anybody know? Are they different drugs?

DR. RODEN: They're different.

DR. CULLEN: They're different drugs?

But anyway, what's the safety of that drug?

And then the newest player on the market for treatment of postoperative nausea is dexamethasone of all things. So here we are giving steroids to patients now because of the lack of effective alternate therapies for droperidol.

So as a practicing anesthesiologist with 30 years of experience, as an academic anesthesiologist and scientist who's reviewed the literature on droperidol, and as a spokesperson for the American Society of Anesthesiologists, the nation's anesthesiologists, I, my anesthesiologist colleagues across the country, and importantly our patients who are suffering from nausea and

vomiting strongly urge that the FDA remove this black box warning for droperidol, at least for the small doses used for the treatment of nausea and vomiting.

Thank you for the opportunity to speak. Any questions?

DR. HORLOCKER: Any points of clarification?

(No response.)

DR. HORLOCKER: Thank you, Dr. Cullen.

Dr. Gan.

DR. GAN: Thank you very much and good afternoon, ladies and gentlemen. I'm delighted to be here and given the opportunity to speak on behalf of the Society of Ambulatory Anesthesia.

I'll just go back. My name is T.J. Gan. I'm an associate professor of anesthesiology at Duke. I'm the Director of Clinical Research there. I'm a practicing anesthesiologist, but today my capacity is representing the membership of the Society of Ambulatory Anesthesia, an organization that represents ambulatory anesthesiologists across the country.

In fact, SAMBA does not even pay my expenses, and I have no other financial association with any manufacturers of droperidol or distributor of droperidol. I actually paid my own funds to come here, and the reason that I do that is because I feel that our patients are

denied an effective, cost efficient drug for treatment and prophylaxis of postoperative nausea and vomiting.

I have two objectives. First of all, I'd like to show you some data to show the efficacy and cost effectiveness of droperidol. And I'm going to show you what is the implications of the FDA black box warning on our patients that we take care of every day.

So, first of all, let us look at does anyone care about postoperative nausea and vomiting. What do our patients think about it? Alex McCara from Stanford did two separate studies to find out the most unpleasant experience that patients experience after surgery, both from the patient perspective and also from the anesthesiologist's or physician's perspective. And you can see that nausea and vomiting are among the top five of the most unpleasant experiences following surgery, especially patients undergoing minor ambulatory procedures. Often these are fairly minor. They don't have a lot of complications postoperatively, but what kept them in the hospital or delayed discharge is because of their persistent nausea and vomiting.

Several years ago, we wanted to see what is it of value to our patients, how much would they pay if we asked them to pay for an effective antiemetic. So we did a study in a group of patients in the recovery room, those

who had surgery. Those who did not experience the symptoms say on average they would pay about $60 for an effective antiemetic. And those who developed nausea went up to about $70. And those who were actively throwing up said give me an effective dose. I'm willing to pay you 100 bucks for it. Now, although the amount is not important, it clearly shows that patients disliked having the symptoms and are even willing to pay out of pocket to try to treat that symptom and avoid the symptoms, which probably you and I would do the same as well.

Now, I put up this slide for two reasons, first of all, just to remind you that antiemetics work in what we believe in this area called the chemoreceptor trigger zone where there are four different receptors. And droperidol is one of the dopamine receptor antagonists and works on one of these four receptors in the chemoreceptor trigger zone.

The reason I put up this slide is to remind you that postoperative nausea and vomiting are multifactorial. One single drug would not be 100 percent effective, and therefore the concept of using a combination of drugs, which I'll show you some data a little bit later on.

Now, how effective is droperidol? I put up this table just to show you a comparison of droperidol with some of the other well-recognized, well-used antiemetics.

This is the concept of number needed to treat -- and I'm sure many of you are very familiar -- which is the number of patients they need to treat to get an additional success which would otherwise develop the symptoms had you not given the treatment. As this table shows, droperidol compares very favorably with some of the other antiemetics that we use routinely, for example, the 5-HT3 antagonists. Propofol is an anesthetic, scopolamine, as well as dexamethasone.

Now, there have been more than 70 studies, randomized, controlled studies, comparing droperidol with other antiemetic agents. And I don't have the time to show you all the studies, but I wanted to pick up one big study which represents the results of most of the studies.

This is a study that was conducted. We reported it several years ago. 2,000 patients prophylactic treatment either with droperidol .625, droperidol 1.25, or ondansetron 4 milligrams compared to placebo. So these are high-risk women undergoing high-risk procedure with previous history of nausea and vomiting. So on any account, they're high-risk patients.

If you look at the incidence of complete response, which is no nausea or no vomiting, compare these four groups. Placebo patients, about 47-50 percent; droperidol .625 went up to 60; 1.25, 72; and ondansetron,

62 percent no nausea and no vomiting. Happy patients. At 0 to 2 hours and obviously 0 to 24 hours, the incidence of complete response went down, but still droperidol fares equally well with the other drug ondansetron. In fact, the 1.25, if anything, stands out a little bit better compared to the .625 milligram of droperidol when used as prophylaxis.

Let us look more specifically about nausea. As you know, there are two entities in PONV, nausea and vomiting. In fact, they are very separate although some would like to sort of lump it together. Because if you look at it, some drugs seem to be better at controlling nausea and others seem to be better at controlling vomiting. Just a point in fact, if you look at the absence of nausea -- so these are patients who are given, in the same study, droperidol .625, 1.25; ondansetron 4; or placebo -- you find that the droperidol 1.25 was actually more effective in controlling nausea compared to the lower dose of droperidol, as well as ondansetron. So droperidol seems to be particularly effective in controlling nausea.

Now, when you look at the use of rescue antiemetics -- so these are patients who failed and needed to be rescued. And again, you find that the three treatment groups were better than placebo, and again droperidol 1.25 stands out the most effective.

So this is one of the largest studies, 2,000 patients, 500 patients per group, and the result is representative of most studies.

Just to illustrate that fact, this is a group from Germany that did a meta-analysis of over 76 trials, basically looking at this concept of number needed to treat. Now, this maybe looks a little bit complicated. let me just take you through. The gist of it is to look at the number needed to treat on the y axis, so the smaller number is the top which is most effective. As you go down, the number needed to treat becomes more and therefore less effective.

Now, on the x axis, these are early, which is 0 to 6 hours. These are late incidents, 0 to 24 hours. On the x axis, range from .25 to .3, 1 to 1.25, and 1.25 to 2.5. As you can see, there's a little bit of a dose response in that the maximum efficacious dose seems to about 1.25. And the square represents incidents of nausea. The circle represents incidents of vomiting. And the size of those squares and circles represent the size of the study. So if you look at the bigger square, it represents more valid data, again suggesting that 1.25 is the maximum efficacious dose both for early as well as late postoperative nausea and vomiting.

What about in pediatrics? Now, in pediatrics,

as you know, nausea is difficult to assess, and therefore we will need typically to assess vomiting in studies. And this again, in that similar meta-analysis where they looked at early as well as late vomiting as indicated by the circle. In the pediatric population, the maximum efficacious dose, about 75 micrograms per kilo both for the early as well as late prevention of postoperative nausea and vomiting.

Now, a little bit earlier when I showed you that slide with four different receptors, suggesting that PONV is multifactorial. One single drug, typically you will get an efficacy of complete response of about 60-65 percent at most. Now, as an anesthesiologist I want to try and assure my patient that you have a much better chance of not developing the symptoms. So if you want to go beyond that in the 80, even 90 percent complete response rate, then there's a lot of evidence to suggest that you need to use combination antiemetics. And there have been numerous combinations studied, but one of the most popular combinations is using droperidol as one of these drugs as well as some of the other drugs, including 5-HT3 antagonists. In fact, 5-HT3 antagonists plus droperidol are a very extremely effective combination.

And I just want to show you a study that was recently published that looked at combining ondansetron and

droperidol. You have a complete response rate of 80 percent. Now I can at least tell my patient that if I give you these two drugs in combination, your chance of not throwing up is 80 percent rather than the typical 50 to 60 percent with a single drug. Therefore, I think droperidol is also very useful not only as a single drug, but as a combination drug.

Now, just move out of the operating room. I reviewed the literature, and there are several articles that looked at the use of droperidol in the emergency department, and this is just one of them. Obviously, it's difficult to do any prospective studies.

So the study I'm going to show you -- there are two studies, a retrospective analysis, and this group of investigators looked at about 2,500 patients who were treated in the emergency room. The mean dose of droperidol that was used was about 4 milligrams. And these are the indications where droperidol was used: agitation either from ingestion of drugs or alcohol, about 54 percent; agitation as a result of trauma, about 30 percent; and a variety of other reasons, pain, vomiting, headache, as well as psychosis.

Now, in that retrospective analysis of 2,500 patients, they found 6 serious adverse events. They found 2 respiratory depressions, 3 post-droperidol seizures, 1

cardiac arrest, and this cardiac arrest occurred almost about 10-12 hours after the ingestion of droperidol. So these are the serious adverse events. So these are retrospective. There's no cause-effect relationship ascertained. And there are certainly a number of minor adverse events: transient hypotension, which we know the drug can cause, as well as 28 patients with extrapyramidal side effects, which again we recognize the drug can cause that.

Another retrospective analysis of at least 12,000 patients again in the emergency room over the past 10 years where they used droperidol to treat severely agitated patients, and this group of investigators came to the conclusion that droperidol is in fact an extremely effective and safe method for treating severely agitated and violent patients. There was no pattern of sudden death analogous to those provided by the FDA warning about thioridazine.

Let's just look at cost effectiveness. In our practice, obviously it's because of the constraint about health care costs, we are always very sensitive about the drugs that we use. Is it cost effective? In fact, this is really where evidence-based medicine comes in. What is the cost effectiveness of droperidol in comparison to other antiemetics?

This was the same study that I showed you earlier, but instead of looking at the efficacy, this study looked at the cost effectiveness. In fact, this study was originally done for the specific purpose of looking at the cost effectiveness comparing ondansetron and droperidol versus placebo. So these are high-risk women undergoing high-risk procedures with previous history of nausea and vomiting that most anesthesiologists will give a prophylactic antiemetic.

Now, when we look specifically at the cost associated with nausea and vomiting -- so these are direct costs of the drug, the rescue antiemetic cost because of failure of the drug, the cost of treating side effects because every drug that one gives, there are always side effects, and also the cost of prolonged stay in the recovery room and unanticipated hospital admission as a result of persistent, uncontrolled nausea and vomiting. So if you look at this PONV, the cost to prevent a further PONV-free patient, as well as the cost to prevent a PONV-free and side effects-free patient, obviously because each drug that you give is associated with side effects. Now, this study suggests that certainly in these high-risk patients it is cost effective to treat them or prophylax them with an antiemetic. And if you look at droperidol 1.25 -- again, that is the optimal dose, it's associated

with the least cost. In fact, it's the most cost effective compared to droperidol .625, as well as ondansetron 4 milligrams. So it is certainly a cost effective drug for prevention of PONV.

Just to give you an overview of the direct cost, acquisition cost of the various antiemetics that we use every day in practice, ranging from 5-HT3 such as ondansetron, dolasetron, perphenazine, as well as the prochloperazine, and if you look at the droperidol costs per 5 milligram dose, it's about just under 50 cents compared to some of the more expensive 5-HT3 antagonists.

Now, about a year ago, a group of experts within the field came together to look at the literature specifically about, in addition to other aspects of treating and managing postoperative nausea and vomiting -- also looked at droperidol. And what this group of experts concluded, based on the evidence as published, that if it were not for the black box warning, droperidol would have been the panel's overwhelming first choice for postoperative nausea and vomiting prophylaxis. So this is taking into account all the data there is in the literature.

Now, I have no doubts -- and again, it's been expressed by the panel this morning -- high doses of droperidol can and do cause prolongation of QT intervals.

We do have a lot of data, and this is just one of them that looked at .1, .175, and .25 milligrams per kilo. So taking the lowest dose of .1, it's still about 6-7 milligrams, but we don't give that dose in the perioperative period. As I showed you earlier, the most optimal dose is 1.25 milligrams of droperidol, and really there's no reason to repeat that dose if it is within 6 to 8 hours following the administration. So the highest dose that we would use in the perioperative period is 1.25 milligrams, and there's no reason to go higher.

You have been shown this list about what are drugs in the perioperative period that can prolong or have the potential to prolong QT intervals. This is not an exhaustive list and this is certainly drugs that we commonly use in the perioperative period, inhalational agents, 5-HT3 antagonists, numerous reports, tricyclic antidepressants. Metoclopramide can cause QT prolongation. Thiopental, succinylcholine, the reversal agents. So a lot of drugs can potentially cause QT prolongation.

Now, through the Freedom of Information Act, we were able to get some of the cases, the Medwatch forms that were submitted to the FDA and which the FDA based their decision on the black box warning. And we wanted to know what is the implication or what is the impact of those cases that are using small doses of droperidol. Out of

those over 300 cases, there are about 10-11 cases where droperidol 1.25 milligrams or below were used. And we published this in Anesthesia and Analgesia in May this year, the detail, whatever we can get from the Medwatch forms. And this is really to show you that these are typical scenarios. Certainly these 3 patients, .625 milligram of droperidol was given, and these were the cardiovascular effects ranging from acute QT prolongation, V tach, as well as V fib, either prolongation of the hospital stay or death.

As you can see, in many of these cases, there are other concomitant drugs being given. I highlighted in yellow. Some of these drugs in yellow is the list I showed you earlier that also have potential to cause prolongation of QT intervals. So it's very difficult with this Medwatch form to have a cause-effect relationship and often just like if I give a drug, if I see a reaction, then I write up the report, and if you give several drugs and you write out the drugs that you have given . And there are a lot of other confounding factors of other drugs that potentially can prolong QT intervals.

Some of the cases. Again, you can see that certainly in many of these cases, there are other drugs which can potentially cause it as well.

Obviously, all this came out from the United

Kingdom following the Lancet paper, as you all know. Now, the Medicines Control Agency in the UK -- this is before the FDA black box warning that action was taken by the manufacturer or the company to actually discontinue the production of droperidol following the appearance of that article in the Lancet. And because of discontinuance of the oral formulation, the company felt that the injectable form would no longer be commercially viable.

In fact, if you go to the website and look at what is the response of the Medicines Control Agency over in the UK, with regard to the perioperative use of droperidol, in one of the questions and answers page, there's a question on can droperidol continue to be used in anesthesia or as an antiemetic, and the answer from the Medicines Control Agency is yes. The acute use of droperidol can continue as long as supplies are available because of the fact that the manufacturer withdrew production of droperidol. So there it seems to take a slightly different viewpoint of the low dose droperidol.

Now, I just put up this slide just to show you that over the last couple of years or so certainly there's a lot of correspondence to the journals, as well as editorials, and really just to express that from a practicing anesthesiologist's point of view what does this drug mean without having the black box warning. And

certainly at my hospital, it's still on the formulary, but we would not use it as a first-line treatment and we only reserve it only for those failure patients.

Now, as has been previously pointed out, we are in a litigious society. If you care to type in droperidol, if you go to the website and go to Google and type in droperidol, the top choice that it will take you to is not the FDA website, is not the company's website, it is the lawyers' website, and it says that if you or a family member have received droperidol and have an ill effect, feel free to call us. We will take care of it. So that is the society that we are in and because of that, droperidol use will not be what it used to be with the black box warning.

So, in summary, I just want to say that I think droperidol in my view is an effective antiemetic, and I showed you the data. And in my view 1.25 milligrams is the optimal dose. There's no need to use a higher dose. The 1.25 milligrams is cost effective, and I believe that 1.25 milligrams is certainly safe.

Thank you very much for your attention. I'd be happy to answer any questions.

DR. HORLOCKER: Points of clarification.

DR. DWORKIN: I was a little unclear on your statistics. In your earlier slides, I wasn't sure of

whether there was actually a statistically significant difference between droperidol 1.25 and the lower dose of droperidol and ondansetron or whether the significance of the difference with placebo was just more. So did you compare the different active drugs or were you just comparing the active drugs with placebo?

DR. GAN: Yes. Thank you for the question.

As far as a complete response and the use of rescue antiemetic, there was no statistically significant difference between the .625 and the 1.25. As far as the absence of nausea, the 1.25 was significantly better than the .625 milligram dose.

DR. GILLETT: What sort of warning do you give patients in the consent document using droperidol?

DR. GAN: We don't have a separate consent specifically for droperidol. Personally I use it when I have tried different antiemetics, maybe one, maybe two or three, and it still failed and the patient is still heaving and having nausea in the recovery room, and that is when I would use droperidol given the current climate. But we do not specifically have any consent preoperatively to inform patients about droperidol.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: Do you think that the anesthesia community would have their needs met if this low dose of

droperidol was specifically carved out of the black box warning? So the black box warning could remain as is but as Nancy suggested earlier, making it very clear that the black box warning --

DR. HORLOCKER: Dr. Shafer, that's not a point of clarification. That's something more that we do for our discussion here.

DR. SHAFER: Except that he's representing the anesthesia community and the question is does his --

DR. HORLOCKER: No, but we don't intercede with public hearing speakers in that fashion.

DR. SHAFER: Oh, okay.

DR. GAN: My answer is yes.

(Laughter.)

DR. HORLOCKER: Strike that from the record.

Dr. Chang.

DR. CHANG: I just want to emphasize again droperidol is approved at doses of 2.5 milligrams and above only. The agency has not reviewed data to demonstrate safety and effectiveness of less than 2.5 milligrams. If we carved out doses greater than 1.25 milligrams, that would solve our problem. We wouldn't have a drug anymore on the market.

DR. HORLOCKER: Dr. Fleming, did you have --

DR. FLEMING: No.

DR. HORLOCKER: We have one more speaker. Dr. Alam.

DR. GAN: Thank you.

DR. ALAM: Thanks for inviting me. I'm Abu Alam, Vice President of Research and Development at Akorn.

Most of what I wanted to talk about has already been discussed. So I'm going to give you some chronology, some questions that I personally have, and some of the comments that you might have that I could answer.

What inspired me, about 4 weeks ago my 14-year-old son had an ACL tear on his soccer field. Two weeks later, we met a bunch of physicians, friends of ours, and they said he has to get one of those ligaments from the back from a hamstring transplanted for his knee so that he can play soccer and tennis and so forth.

So we went for the surgery. Two weeks ago, his surgery was done. I asked the anesthesiologist what would he get for containment of PONV, and she said she had an ACL tear also two years ago and she got droperidol at that time. And she has been practicing for 15 years at a surgery center outside Chicago, and now she's resorting to only the 5-HT3. And in this case, she only had the choice of ondansetron and as a backup metoclopramide. I said what happened to Inapsine, or droperidol? She says, no, it's a black box warning. As Dr. Gan mentioned, you know, this

country is very litigatory, and anything that you do that's outside the constraints, you could be up for a legal action.

So I asked the anesthesiologist would she give him droperidol, even the generic version, because our version Inapsine is still off the market. And she said she couldn't.

After my son came out of the surgery, I said, how did it go? He said, Daddy, I vomited. And then I asked the anesthesiologist, what is the incidence of vomiting with Zofran and Reglan? She said 1 out of 3 patients vomit. And I said, what was the incidence for droperidol, or Inapsine? She said she had 90 percent efficacy. And that's what inspired me to be here today.

The question before us is -- we used to make or we still make droperidol. We used to make for Janssen. As you know, many of the drug inventions are done in Europe or other countries. This drug was invented back in the '60s. The patent was issued then. The U.S. became the second country where droperidol was marketed. All the preclinical tox, chemistry, preclinical pharmacology, clinical studies were done in Europe by Janssen, the inventor of this drug. We used to manufacture for Janssen, since 1982, these two drugs, Inapsine and Sublimaze, which is fentanyl.

After that, we bought two other drugs from

Janssen because we were manufacturing those drugs in Illinois. And Janssen used to market these products for anesthesia. So when this thing came, we purchased the NDA in 1996-1997 era because, as you know, this drug has been generic since 1986. There is no incentive for Janssen or for any drug pharma to do any more studies or even market these kind of products. We are a small company, so we took it over. We used to manufacture the product. We kept the trade name and we continued to manufacture this product since 1997 on our own label, but the trade name remains the same.

Lo and behold, with the Lancet article by Riley in 2000, April, there was a big commotion. It's like a wave on a football field; it just kept on going. First, UK Medicines questioned the company to see if Janssen would like to keep the product on the marketplace or would there be any action. Janssen looked at the economics of this drug and said, hey, the three or four areas of our market all comprise the oral tablet and the oral solution. The injection is a very, very small market globally.

We do not have the license to market this product globally. We only have the license for the U.S. and the trade name for the U.S.

So I contacted Janssen, because they contacted me first, from Akorn. They said, we are going to

discontinue manufacturing this product because, not benefit to risk, but economics to risk. This drug is not going to be financially feasible for us to continue the supply of the raw drug to Akorn moving forward.

So, all of a sudden, we manufacture the finished dosage form in the United States. As you may know sitting here, most of the droperidol, the two generic brands, which I'm not going to name -- the drug is not manufactured in the United States. They're manufactured overseas. We just make the finished dosage form in ampules.

So I said to Janssen, I said, look, you cannot just all of a sudden stop supplying us raw material. We'll be out of this product. They says, it doesn't pay for us to keep our manufacturing of the raw material with the U.S. FDA regulation of GMP. So they say, it's a situation we have to face. So we said, okay.

So we went for an alternate vendor for the raw material and we selected a European vendor for this product. We're still working with FDA for the clearance of that alternate vendor. So if you see droperidol, you don't see the branded product anywhere in the United States for the last two years because we have discontinued manufacturing. We're still working, trying to get that thing resolved.

Secondly, when this thing happened, we inquired of Janssen if they would supply us for a couple of years so that we can stay on the market, but Janssen said, no, they're going to go ahead and license out the European and worldwide rights to another company, which they did. A company in Paris, France called OTL Pharma has now licensed this product and they have been manufacturing. Janssen still manufactures not with the U.S. standards, still manufactures with the European standards, provides to this company, and they sell to six countries without a black box warning.

The dosage, as Dr. Gan mentioned -- they have acquiesced the dose to .625 to 1.25 milligrams, the highest being 2.5 milligrams. They have removed the tablet. They have removed the oral solution because it's no longer going to go into the psych clinic or chronic use where it could be used in home situations. So they are still manufacturing this product.

As of yesterday before I came, I contacted them again in France. They said they do not have any torsade. They have no records of any QT prolongation.

And thanks to the speaker earlier, we know the error factors that are involved in measurement of these terms. Once these numbers come on the board, everybody thinks that these are absolute numbers. They are not. You

could have a variation of 20-30 milliseconds just by looking at the EKG chart, and you don't have to be a cardiologist to figure that out.

So what happened was in this whole scenario we have been in touch with OTL Pharma, and as of yesterday, they told us that they have this drug approved as a compassionate product in three other countries. Six countries they have it approved, and three countries like Germany, Italy, and another country in Europe, they have it approved as a compassionate product.

So I said, okay. I'm coming to this meeting. I'll give them an update what happens down the road in the United States.

But again, going back, when we started talking about this in our own company, we had a call around February 2001 from Dr. McCormick's office. At that time, she was head of the department for anesthesia. She said, what would Akorn do on droperidol. I said, we're not doing anything. Our market sector and the drug being used in the kind of surgery centers and in hospitals -- we don't recognize any issues based upon what we have seen in the United States. And then there were a lot of multi, multi conversations between Akorn and the Food and Drug in that respect. What do we do in the United States, whether to keep this product on the market, whether to withdraw, or

whether to go with a black box warning.

So finally back in the October-November time frame in 2001, the company and FDA agreed on a black box warning which you see now. The language -- we went back and forth between FDA and Akorn and finally what you see is the final version that FDA and we agreed on.

But as speakers before me mentioned and my own son, we know that the use of this drug is open for huge liability.

And I was going to ask the FDA speaker earlier -- and I tried to raise my hand -- how did the IRB approve a protocol where a normal volunteer could go into a torsade at 5 milligrams. And those are the questions that I have. How can an IRB approve a drug to study in the United States when we recognize that a patient or a subject could be exposed to a drug where you could have a torsade? So that was one question I had for the FDA speaker.

The things that I had -- and you have a copy of what I wrote to Dr. Rappaport right after my son's surgery.

When FDA and we talked about this and FDA asked us to do a prospective clinical trial to show that the lower dose, as we said in Europe is approved, where the drug was invented in the first place -- FDA wanted Akorn to come up with a prospective, randomized trial rather than taking the peer reviewed and summarizing those data for an

NDA supplement. So we said we cannot afford to do a study. First of all, there's no financial incentive for a drug company, small like we are. And too, as we saw, that 1 out of half a million people can show a torsade because QT is a surrogate marker. So we had a lot of conversations.

One of the articles that was given to us -- and we knew about this article, we heard about -- was the Lischke article that was published back in 1994. I took the data myself. I did not do a lot of mathematical manipulation of the data. I took the data, the IV data, and that one minute you had the highest QT prolongation by the way he measured it for all the three arms. And there were 10 patients in the first two arms and the highest dose was 20 patients. So I just did just a simple least squares regression fit of the data, and I made the number available to the Food and Drug, and my calculations, at a 2.5 milligrams or below the data for a 70 kilogram person, calculating based upon milligram per kilogram body weight, came around about 7.5-8. By different mathematical calculation, you can get different numbers.

And as speakers before me said, 25 to 30 milliseconds is within the normal limits or not to be very concerned. I know recently Levitra got approved where the milliseconds in case of Levitra, the advisory panel came out -- I think I quote the exact numbers, and it's in my

write-up. And my calculation came within those parameters. So I said the chances of having QT prolongation, although it's a surrogate marker, with the dose that FDA and we agreed, the 2.5 milligrams, was acceptable.

The question comes up -- and all these reports -- and I talked to the FDA speaker earlier -- is that 22 cases that FDA cited, how many of those cases were from the United States? Because, as you know, the Europeans used this for oral, chronic. There were concomitant medications, including alcohol. I think very few of those cases were from the United States in the first place. So I think it's good to know exactly how the data was interpreted.

Now, going back, if you look at what Dr. Gan showed, Habib's paper that took all the Medwatch reports and then did an analysis and came out that 1.25 milligrams and below has no cause and effect due to droperidol. And that's what we have been struggling to see if -- and I noticed one of committee members asked that if the U.S. can use some practical sense here and keep droperidol in the marketplace because we all believe sitting here and myself that it's a safe dose. It's a safe product and it is very good not only for nausea but also for vomiting. As a matter of fact, for nausea, as Dr. Gan mentioned, it is probably one of the best drugs that we have on this

combination.

Is there any way that we could use the similar profile of the European dosing and also what we know in our U.S. peer-reviewed articles, to take that database without doing further clinical studies and just use that database to file a supplement for the lower dose for postop nausea and vomiting?

But I know FDA's challenge is to do a prospective clinical trial, and our thing is we cannot afford to do that as a drug company because there is no financial incentive for Akorn.

The one thing that we would do is if we agree on a protocol like a phase IV that the committee agrees that if financially doable and answers the questions, then we might entertain that. But up to now, we were looking for a prospective clinical trial which is beyond our means to do that. And speakers before us told us that how much from a financial burden and number of population that we have to go through to take care of the prospective clinical trial.

I have got a couple of other small items here that I think most of you have gotten my paper or position paper that I wrote.

I think one thing T.J. or Dr. Gan mentioned about the cost to the American society. Based upon my

quick calculation and based upon the number of people that used to use droperidol and the cost differential between the 5-HT3 and droperidol, last year the country took a burden $100 million either paid by the insurance, Federal Government, or the individuals. $100 million. That is the minimum calculation. That's why I think for everything we do -- I mean, science is science, and then we have to also look at practical things that face us not only in science but in medicine.

One of the questions that came up -- I'm going a little bit off and on -- on our analysis was the purity of this drug. Currently United States Pharmacopoeia sets the specifications for generic companies, not for the inventor. In this case, since we bought this drug from Janssen, we are sort of a pseudo-inventor now or we own the branded product. The current specifications for one of the key intermediates is 1.5 percent. It's butyrophenone, a very similar structure to droperidol. So FDA requested that we either prove that this 1.5 percent impurity does not cause cardiac arrest or torsade or we have to reduce the impurity level beyond what is acceptable to the generic two companies.

We looked at the literature. There was nothing discussed about the toxicity of this impurity. I was just thinking. To make this impurity -- and I was wondering

where would we do a study where an IRB would approve an impurity that could cost a patient's health. Then we finally had good negotiations with the FDA and the new supplier and we were able to reduce this impurity by a factor of 3. So we are down to half a percent, which was good. Between FDA and us, we worked out very good terms.

But my question to the body also is the generics that are on the marketplace, although they are used as second-line, they are still held to that high impurity, and my question is why should they be held to that kind of impurity when we know that we can do better.

So with those questions and those thoughts, I have no other comments. I would rather ask the advisory committee and the FDA to look at, really, the dose from .625 to 1.25, using the peer-reviewed articles as a way to take the black box warning and if we need to do a study that we are able to sponsor or somebody can help us sponsor, we can do that as a phase IV. That's from the company point of view.

DR. HORLOCKER: Dr. Alam, do you want to disclose any financial relationships?

DR. ALAM: I do not have any financial relationship with anybody outside the company. I'm a corporate officer. I work for Akorn and that's the only company I work for. I have no other obligations.

DR. HORLOCKER: Any points of clarification, committee members? Dr. Eisenach.

DR. EISENACH: This is as much a question for Nancy as anyone. I'm trying to sort out what the numerator and denominator are for this. You suggested that the denominator included European cases as well. I wondered if Nancy could comment. We know approximately how many units were sold in the U.S. How many units were sold in Europe over that time if that was the case?

DR. CHANG: We don't have sales figures for Europe.

The postmarketing database does include foreign cases. It is a report of all the cases that we received, including the foreign cases.

DR. EISENACH: And just to get a rough idea, what proportion were foreign cases? Because we only know the denominator for one of these parts.

DR. CHANG: It's what?

DR. POLLOCK: (Inaudible.)

DR. CHANG: 9 domestic. The remainder were foreign.

DR. HORLOCKER: Could we disclose the source of that information? Somebody from the audience just shouting numbers.

DR. CHANG: I'm sorry. That's Marty Pollock

from our Office of Drug Safety at FDA.

DR. HORLOCKER: Thank you. I need to know the reliability of numbers on which we're basing decisions.

Dr. Roden.

DR. RODEN: I'm not sure I want to say this but I will. I'm not a drug company executive, but you don't have to be a drug company executive to figure this out, just to paraphrase you. I find it truly offensive that you can come up here and lecture us and then have the luxury of sitting down without having to defend your position. You were invited to be a participant in this panel meeting and elected not to. It seems to me that by taking advantage of this public forum, you have the opportunity to stand up and say whatever outrageous thing you want and then sit down without us having the opportunity to review your presentation and your data beforehand.

DR. EISENACH: Is that a point of clarification you're requesting? I'm just wondering. Terry, you cut someone off earlier when they were asking opinions.

DR. HORLOCKER: I guess we could direct the statement to the committee rather than to the speaker.

DR. RODEN: Or I could direct it to FDA. The frustrating thing for me -- and I'm not part of the anesthesiology community here. I'm just sort of an interested outside observer -- is that people are

passionate about an issue for which no one seems to want to provide or no one seems to have good data. But everybody has a passionate opinion. And it's very difficult to have a reasoned debate in the absence of any willingness to go forward and in the absence of any willingness to participate in that debate. So I'm expressing my frustration. I'm sorry.

DR. HORLOCKER: Any other points of clarification? Dr. Rappaport.

DR. RAPPAPORT: I guess I was thinking of saying something along the lines of Dr. Roden, and I'm glad I don't have to.

The other point is that there are a lot of things in this letter that was passed out, along with the presentation, that are inconsistent with our understanding of what the interactions have been between the company and the FDA. And I don't want to pick it apart. I don't think it's appropriate. But I just wanted to make that comment.

DR. HORLOCKER: Dr. Bril.

DR. BRIL: One clarification that could help, just a factual clarification to help my thinking about the severity of risk with droperidol. Is it in fact true that droperidol is available in France now for postoperative nausea and vomiting? Is this a fact that there's another company that is providing it and that it's approved by the

regulatory agency there since a lot of the concern started with a series of French patients who had cardiac arrest? Do we know that?

DR. ALAM: The answer is yes.

DR. HORLOCKER: We're talking amongst ourselves.

DR. RAPPAPORT: The agency doesn't have an answer to that question at this time. We can certainly look into it.

DR. HORLOCKER: I think we'll have a short 15-minute break and then we will start our discussion of the questions. Thank you.

(Recess.)

DR. HORLOCKER: I'd like everybody to turn to the questions that the FDA has submitted to us. Before we actually answer these, Dr. Chang, could you present the data that I think it was Dr. Katz asked for earlier regarding the QT prolongation with other anesthetic-related drugs?

DR. CHANG: Yes. Before I start describing this data, I want to say one more time -- I know I've already said it -- I truly would not put a whole lot of weight on this data. There is so much uncertainty about numerators and denominators when we're talking about postmarketing data. With the sort of numbers that we're

seeing, we're not in a place where we can make any real conclusions about this. I chose not to put this in my presentation for a reason.

So, again, we're looking at for a span of 5 years, 1998 to 2002, the total sales figures in the United States for droperidol. Once again, we see a doubling from about 5 million vials to about 10 millions in 2001, and in 2002 after the boxed warning was in place, you can see there was a drop in sales.

This was an attempt to kind of get a sense of what the background rate might be. The particular drugs that were chosen were chosen because they represented different drug classes because they were all older drugs that have been around for a long time and they're all felt to be drugs that are used commonly in the perioperative setting.

You can see droperidol is again the rectangular boxes. The top bar there is lidocaine, and lidocaine probably has perhaps as much as a 10-fold higher sales than droperidol. Midazolam comes next and probably has at least a 5-fold difference, and fentanyl after that which perhaps has maybe a 4-fold difference compared to droperidol. The other two drugs, vecuronium and pentothal, had lower sales figures than droperidol, on the order of half or less.

These are some of the antiemetic agents. The

top bar is promethazine. The next bar is metoclopramide. The next bar is ondansetron, and again droperidol is there at the bottom. What we see here is that the top-selling drug promethazine has perhaps a 3- or 4-fold higher sales than droperidol. Metoclopramide, perhaps 2-fold and ondansetron is actually very similar.

I know the slide is a little bit difficult to read but these are cases of QT prolongation and/or torsade. The columns are not mutually exclusive. So, in other words, the 5 cases reported for droperidol for QT prolongation alone may have also been associated with a ventricular arrhythmia.

The highlights are for places where we have events. The drugs that are not listed here, of all the drugs that I presented earlier, did not have events, and so they're not listed here.

As you can see, again, I'm sorry this is a little bit difficult to read, but the rows here are droperidol on the top, midazolam, then promethazine, ondansetron, isoflurane, midazolam with lidocaine, and ondansetron with metoclopramide, or ondansetron with promethazine. So, in other words, the last two columns are where we saw a combination of drugs being used.

Remember again the sales figures that were shown earlier which suggested that the drugs that you're

seeing here, midazolam in particular, had a much higher sales figure compared to droperidol.

So I think there is perhaps a suggestion that droperidol may have a higher incidence of events that rise above the background, but again, I don't think we can put a whole lot of weight on this.

Another way that we tried to kind of get a sense of what the relevance of these events are is we looked at the top terms reported for droperidol. That is, if you take all of the adverse events reported for droperidol, everything, and look at what the actual adverse events were that were reported, there is a total of 776 terms reported for droperidol. These are the top 5. As you can see, the number 1 term which comprises 67 reports was cardiac arrest. After that, we have a number of probably neuropsychiatric effects.

I should say too I just want to acknowledge what I'm showing here and what was shown in the earlier presentation represents a lot of work that was done by our Office of Drug Safety. It doesn't look like a whole lot on the slides, but this really does comprise a lot of work on the part of that group.

DR. HORLOCKER: Thank you, Dr. Chang.

All right, with this, let's go to the discussion. The first two questions are related to how we

could study this issue further, and although I don't want to totally bias the committee, I think we've seen enough data that suggests that this is a relatively rare event when we get to the torsade de pointes, although we know that there is a dose-dependent prolongation of the QT with droperidol that happens even at the low doses. And we don't have a lot of the pharmacology data. There are also serious side effects that sort of limit how well we can study this in volunteers.

Does anybody have a really good idea of how we could study this in either a clinical or a volunteer or a laboratory model? It seems like kind of insurmountable odds to me, but I'm among geniuses.

(Laughter.)

DR. HORLOCKER: Sir.

DR. KOWEY: Then I'm not going to talk.

(Laughter.)

DR. KOWEY: First of all, the statement that there is a dose-related increase in QT interval I would not necessarily swallow because almost all the drugs we ever study have a dose-related effect on QT interval or a concentration-related effect on QT interval. But we haven't really seen any data that extend from low to high in a comprehensive way that we usually see it.

As I said earlier, what we're used to seeing

are studies where the doses are pushed. Metabolic inhibition is used. We see large concentrations of the drug, and we observe an effect. Then we can construct a dose-response or concentration-response relationship. We don't have that here.

As I said earlier, the precision of the QT interval measurement is such that in order to be able to study the drug at a relatively low dose would require great precision in the investigation. It would require a fairly large number of observations over the course of the concentration curve, and it would be a challenging experiment. But it's possible. You could do it. If the magnitude of that effect were similar to what we've seen for other drugs that had a similar effect on repolarization like alfuzosin, for example, or Levitra, which are the drugs that we recently looked at, then we would have some assurance that at the lower end of the dose, at low concentrations, which are the doses that everybody is talking about here, we would be able to use this drug with comparative safety.

It's a shame you didn't get that study done, because the study that was designed actually had great promise for the correct way to do this. So what I guess people around the table have to try to tell us is, is it possible to do that kind of a study with better tolerance

so that we can get information in the appropriate population?

DR. HORLOCKER: Dr. Katz.

DR. KATZ: Being a skeptic about surrogate markers, I would want to put forth to the group a somewhat different idea which is to just do a case-control study. Generally when you have any rare outcome, the only way to collect up enough cases to learn anything meaningful is with a case-control study where you collect up all the cases of torsade that you can find, if that is indeed the outcome of interest, and then match those to matching individuals who did not develop torsade. Then you can get answers about what the odds ratios are for developing that outcome based on various predictors, including whether or not you were on droperidol, whether or not you were on any comparators. You can model out so you can get adjusted odds ratios, controlling for severity of disease and concomitant medications and that sort of thing. If the question before the group is what study designs will give you information about what is the relative risk of developing this outcome if you're given droperidol and then how that compares to other comparators, if that's the question, then I think that's the study.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: I'd like to ask Dr. Gan -- no.

I think a couple things can be done in an integrated form that might be very informative. Evidently, in talking to my cardiology colleagues over here, there is in fact a cardiac wedge model which is a model where torsade is in fact the endpoint. We're not using a surrogate. From that model, we could potentially establish a concentration-response curve for the actual thing that we're interested in, which is torsade. This is a piece of information that to me is as missing as the kinetics, which is what does the concentration-response curve look like. We could get that in the wedge heart model and then we could do the, I'd say, very high resolution study in humans which would really be used to calibrate the wedge heart model against human pharmacology to be sure that the dose-response curve that you saw there in fact matched the dose-response curve, to the extent that it was possible to measure the dose-response curve.

I would also think, as Dr. Roden pointed out, we have to have good kinetics. We have to know what the metabolites are.

There's a number of things we can talk about for the human study. It won't surprise some of the people around the table to know I would propose using targeted control drug delivery where you are able to hold a concentration steady, allow the QTc/RR hysteresis loop to

basically come to equilibrium so that there's no hysteresis, give you a period of steady state where you can get multiple measurements of QTc while the plasma levels are being held steady. And also you don't have to start off by whacking somebody with 5 milligrams which may predispose you to problems. You can also put in good controls. You could put in, for example, a butorphanol control because it's very dysphoric and sort of get some sense of how much does dysphoria itself lend to these problems.

So I think with a thoughtful design, a good quality human study could at least get you close to something within the clinical range, although by the time you're down at 1 milligram, you may not have any signal at all. But that part you could then fill in from the wedge heart study.

Sorry it was a long answer, but I wanted to give you the whole program.

DR. HORLOCKER: Dr. Rappaport or Dr. Meyer, could you comment on the FDA's ability to fund or organize such a study?

DR. MEYER: I think it would, unfortunately, be fairly limited. We do have some research funds available, but the ability to do that kind of program I think would be, unfortunately, fairly limited as far as the FDA being

the sole sponsor of it.

DR. HORLOCKER: Dr. Roden, did you have a question?

DR. RODEN: So just in comment to the last comment, maybe you guys can think about partnering with the ASA and SAMBA and perhaps even the manufacturer to split the cost of something like this if it's of interest to all those stakeholders.

I'm not sure what a case-control study will accomplish. I think you'll collect a bunch of cases of torsade on droperidol and a bunch of controls that don't have torsade on droperidol, and no matter how you slice or dice that, you'll be able to identify risk factors, which we think we know about already, but I'm totally open to hearing about new ones. But I'm not sure how a case-control would get at that. That's comment number one.

Comment number two is I think that the pharmacodynamics of a response -- I mean, what you really want to know is response to a bolus, not response to a controlled, steady state infusion. I think you can't make the a priori assumption that the pharmacodynamics will be the same. Those are things that have to be worked out or thought of before a design gets settled on. I don't think we want to settle on the minutiae of a study design here today.

So those two comments are criticisms of previous speakers.

But I would also urge that the FDA take a look at the efficacy data. You're never going to have an efficacy trial the way you want it with this drug. I mean, that's pretty clear. But it sounds like there's an awful lot of data in the literature. Now, I'm a skeptic of what appears in the literature because the way things are presented are not necessarily the way the protocol was originally written. But there seem to me to be no chance that you're going to get an FDA-approved protocol executed in this country, and every chance that there is lots and lots of data out there that would lend itself to analysis by some really disinterested third party, a department of biostatistics somewhere that has no dog in this hunt, so to speak.

So those are the thoughts. I think that the FDA really ought to be looking at the lower doses if that's what the entire practice is. I know that's not a tasteful kind of comment, but it enters into this discussion because this discussion is a risk versus benefit discussion. You're uncertain about the benefit. Everybody else around the table seems convinced, and so I think there are ways of settling that.

DR. HORLOCKER: So if we stick to the first two

questions about which additional data do we need to know about the risk, which I'd like to do, because I think we're going to spend most of this discussion on how can we safely use this drug or what things do we need to know that we can safely use this drug.

Dr. Holmboe, you had a comment.

DR. HOLMBOE: I just also want to make a plug from a patient point of view. I think that, obviously, we need to know a lot more about the pharmacokinetic data, and I think some of the studies that have been described are very important. But I agree with Dr. Katz that we do need to try to uncover the other risk factors. I'm not comfortable in simply saying, yes, I think I know what the risk factors are, as my colleague down the end of the table said. I think we've been burned many times in the past when we've uncovered things that were unexpected. Despite the limitations of case-control studies, they are a good way to look at rare events and at least try to get some idea, from a crude perspective, about what those risk factors might be.

Other possibilities include observational study designs. Again, despite the limitations, I think we do need to have a better understanding of what the potential risk factors are that would make droperidol unsafe, whether it be concomitant medications or conditions. I think we've

all seen today that many of these patients had either a lot of other drugs on board or other comorbidities, and as other people have shown, those comorbidities can actually have substantial impact on how people handle drugs.

So I think that it would be worth trying to think about using some of those clinically based studies to try to get at some of those issues. Again, we can argue about the study design, but given we're talking about a rare clinical event, things like observational trials and case-control studies, if done properly, can provide useful information.

DR. KOWEY: I just completely disagree with that, with all due respect. We've been down this road only a million times with noncardiac drugs and QT effects, and I can tell you that the QT interval is not a wonderful measurement, but it is a measurement. I don't like surrogates either, but it is the clinical surrogate we have. We've spent a tremendous amount of time trying to come up with designs that refine the measurement, and Dr. Malik did a very good job of reviewing those designs. Why on earth would we want to throw that all away and say let's go try some completely different experiment to try to figure out what the repolarization effect of this drug is?

I agree, by the way, with Steven that preclinical assessments here -- if we had limitless ability

to do experiments, we need to do some preclinical experiments to understand this a lot better. And the wedge is a wonderful model to do that. That would be optimal.

But if you only have a study to do and you need to know something about the QT effects and the potential for torsade, we have a way of doing it. It's been done. It was done for alfuzosin. It was done for Levitra. It's been done for lots of other drugs. If you're going to do it, that's what you got to do. I mean, that's the road map.

The draft guidance that you guys all have in your packages here from different organizations, Canada, UK, here in the United States, have all given this information out in a way that I think is very cohesive.

So I just think going off into case-control territory at this point in time with this kind of a question I think is not going to work.

DR. HORLOCKER: That initial study went up to 5 milligrams and we had to stop it because of the neuropsychiatric events. If you're going to redo that, what would the dose range be that you would utilize? Because this is going to be one of those things where you said you really want to go supratherapeutic, and yet we can't because of the side effects and complications.

DR. KOWEY: Exactly. So what you need to do is

give the doses that you think you can get people to tolerate, and if it's a dose that's 1.25 or 2.5, at least that's information that you can get. As I said, if you do it in a relatively large number of patients, relatively large for these kinds of trials, and you do it very precisely, you can come up with a point estimate of the QT interval prolongation. And we know that that correlates at least in some way with the chances that people are going to have a problem down the road.

DR. HORLOCKER: Dr. Rose.

DR. ROSE: Thank you. I have a few comments to make, keep in mind that I am absolutely not a researcher and my interest is purely clinical.

I think that the research that was done, the study that had to be stopped because of the dysphoric response, though it was wonderful and it's a shame that it wasn't able to be completed, is a very unrealistic study because there would be very few times that I can imagine that we would be using droperidol in a patient who has had no other drugs given to them. They wouldn't be needing the droperidol because they wouldn't have had the effects for which droperidol was being used to counteract the nausea and the vomiting. So I think it's a little unrealistic. Therefore, I think the idea of using case studies becomes more realistic and more real life. That's one point.

Also, I think that although all day long we've been talking about the negative side effect of QT prolongation with droperidol, we also need to talk about dysphoria as a negative side effect. It seems like that's been the elephant in the middle of the room that everybody has been ignoring. Those of us who do administer clinical anesthesia, many of us will use the drug only very, very, very sparingly because of this dysphoric response, but we use it as a rescue drug knowing that there may be dysphoria. And when I use it for a patient, I always inform them, before I administer it to them, that they may have this response. That study that was stopped actually had the information about the dysphoria, but it wasn't one of the side effects that was going to be looked for.

Also, we have many drugs, as we've been told all day long, that have QT effects, and yet those drugs are being used. Somehow they got through the FDA. Somehow they are on formularies and are being used. But though I'm not a researcher, I don't understand why we're not making a big deal about those drugs and we are about droperidol.

DR. HORLOCKER: Dr. Chang, do you want to comment on that?

DR. CHANG: As I said in my opening remarks, this has been an evolving issue both from a regulatory perspective and from a scientific perspective. We didn't

even have torsade and QT prolongation in the adverse events lexicons until the 1980s. This was not even appreciated as a problem prior to that time. So, yes, we do have a large number of drugs that are already on the market that have been in one report or another associated with QT prolongation.

As an agency, we don't have the tools or the resources to make comparative risk assessments at this time. We've, really unfortunately, been forced to look at these on a case-by-case basis when problems have arisen that have forced us to take a closer look at particular drugs. It's certainly not the optimal situation, but that's unfortunately the regulatory reality.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: I'm relatively convinced from what I've heard people say that it would be possible to come up with an assessment of the risk in the average individual for low-dose droperidol. My guess would be that that would actually be a number that would be somewhat reassuring to us.

What I'm not so convinced about is the issue of the genetic polymorphisms, the possibility that in doing this we would be looking at the wrong population of patients and that there is a population of patients out there. A question I have for people around the table --

Dan touched on this earlier. To what extent can we study those patients thought to be at a genetic predisposition for this so we're sure about the risk in that group?

To me it's not acceptable to just say, well, there are some people who are going to die from this drug and we're either going to take it off the market, but we don't know who they are, we can't identify who's going to have this problem, because we could potentially lose every drug on the market. We could lose all of our options that way. How can we try to assess the patients who are at genetic risk?

DR. HORLOCKER: Actually I'd like to have Dr. Malik address that because he said something that was very interesting during his presentation and I want him to clarify this. You said that if somebody had an electrocardiogram that was normal prior to administration of one of these drugs, that the chance of them having a significant event was very low. And that would be very relevant to all of us both clinically and possibly negate the need to do a true study in the clinical or volunteer population.

DR. MALIK: Thank you for the question. I will be grateful to my distinguished cardiac colleagues on the panel if they would check what I am saying.

Indeed, I do believe that if a patient is

having a pretty normal electrocardiogram, including a short QT interval duration, please -- I should first make a comment to this effect. When I said during my talk that QT interval is just a surrogate, a lose surrogate, I did not really mean that this is not useful, that this is not a good measure. It is very useful to measure it, although we may have some imprecision and so on.

So in this respect, I do formally believe that if a patient has a normal electrocardiogram with a QT interval which will be reasonably short -- and I will come to this in a moment -- then the drug can be given without much risk. What I mean by reasonably short QT interval is -- of course, I do appreciate that in clinical practice the QT interval will be probably read by a machine. It will be corrected for rate by a machine. And considering these sort of possible introduction of errors in this, I think that if, for instance, the limits were set to be 420 for males and 440 for females, that then the drug would be given in a rather safe environment. You will never achieve a situation that the drug will never cause torsade in anybody, but once you push this towards the limit, 1 in 5 million and so on, you are outside the arena which is of regulatory concerns.

440 and 420, as I said, in my opinion based on the readings of the electrocardiograms and so on, will pick

up approximately, I should think, between 10 and maybe 15 percent of subjects. So you will be not imposing a limitation that would be too substantial. So I think -- and I would like to hear conformation from my distinguished colleagues -- that in such a scenario the drug could be used safely.

DR. KOWEY: Marek, I don't disagree with what you said. Are you assuming in your hypothesis that the magnitude of the QT effect of the agent you're prescribing is what? Is less than what? Less than 10 milliseconds?

DR. MALIK: That's a very good point. I think that if you increase anybody's QT interval by 10 percent, unless we are talking about a patient who already has a long QT syndrome and has hypokalemia and so on, then 10 milliseconds will probably not cause harm at all.

DR. KOWEY: So what you were predicating your argument upon is some information, proven information, about the magnitude of the QT effect that the agent has.

And to answer Steve's question directly, when we study drugs that have a QT effect that is in single digits, so that we do the study that we've been talking about that's in the guidance and we do the study and it's less than 10 milliseconds, the chances of developing torsade, assuming that within the population of patients there are unknowable individuals who will have a genetic

predisposition, nothing real awful happens. It's at the end of Dr. Malik's spectrum, which I thought was very useful. Whereas, when the numbers are over 10, over 20, over 30, the risk increases.

So I completely agree that if you were to have an cardiogram in someone that was reasonably normal, within the limits of what we call normal, and the drug didn't have a double-digit effect on the QT interval and you knew that from a relatively well-done, small study in normal volunteers, that the chances of someone having a problem with that drug would be almost zero. Almost zero, maybe even zero.

DR. MALIK: I would perhaps go even further than that. I would say that if you would use those limits that I have just now proposed, I agree simply from rather thin error because I'm thinking about combination of normality and reading imprecision and the potential correction imprecision. I think that even if you would have drug which would cause the prolongation which would be substantial in, say, double digits, not very high double digits, 40-50 milliseconds, in that particular individual, that you will still not hit the very dangerous zone of bizarrely prolonged QT interval that would lead to torsade. Even in such a scenario, the incidence of torsade will probably lower. I don't know whether you would agree with

that.

DR. KOWEY: I think that's uncharted territory because we don't have a lot of examples where that's the case. Antiarrhythmic drugs, for example, that prolong the QT interval by 40 or 50 or 60 milliseconds clearly have a risk of torsade which is higher than what we would accept in this patient population. So it does appear to be a gradated risk. We just don't have a real good way of giving you precise numbers.

DR. RODEN: So, Peter, let me clarify. If you had a drug that produced a maximum change in real QT effect of 10 milliseconds, that's one category. Some of the numbers that Dr. Chang --

DR. SHAFER: At the therapeutic dose or --

DR. RODEN: No. That's the thrust of my question. Some of the numbers that Dr. Chang showed us were 50-millisecond changes in reasonably poorly controlled, small-number studies. So if droperidol could be pushed -- the notion of pushing the dose is a really important one that I don't think has gotten enough play and that is that under ordinary conditions Marek showed you that terfenadine doesn't do much, but it does a little bit. And then the question is if a drug does a little bit, are there populations out there that might exhibit a whole lot more than a little bit of change. And the two kinds of

populations you need to think about are, number one, people predisposed for PK reasons, and that's the terfenadine story in its entirety. And number two, are there people predisposed because of serum potassium that they have or the particular genetic makeup that they have? And that's a much harder thing to get your hands around. So that's why you need to look at whether there's a real change with the drug and if there is, then the next question is are there people who are going to get much larger changes.

I would just add that I don't think it's ever possible to get rid of a really rare side effect. I think if the job of this committee is to identify conditions under which no patient would ever, ever have a chance of torsade, we can all go home now.

DR. HORLOCKER: Dr. Fleming.

DR. FLEMING: I'd like to just probe a bit on what our options might be along the lines, I think, somewhat related to what Dr. Roden was just referring to. But just in terms of a general answer to this question, I strongly endorse earlier comments that additional PK analyses will be extremely important for our improved understanding.

I also share the concerns that many have with relying on surrogate endpoints. In any instance in which it's at all achievable to obtain reliable insights from

direct clinical endpoints, whether it's for efficacy or safety, we are well served to do the very best we can to pursue trials of that nature. But I'm also persuaded in having been part of discussions of many other advisory committees on QT prolongation that we are left, unfortunately I think, with a need for a fairly heavy reliance on this surrogate of QT.

I was persuaded also by Dr. Malik's presentation when he pointed out that small QTc interval prolongation at low doses doesn't offer meaningful assurance because, in essence, his message was that arrhythmias are going to occur because the drug is overdosed, it's metabolically multiplied, or there are other predisposing factors. So his conclusion was that we need, if it's going to be torsade-safe, to be assured that QT interval prolongation is less than 25 to 30 milliseconds under the worst possible conditions. So I'm left with the thought, how do we get that?

Just as a quick aside, I share Dr. Roden's concern about our inability to really interact in the sponsor's open session comments where at least among the comments was the indication that we're the same as Levitra. Having been among those serving on the Cardio-Renal Advisory Committee on May 29th for Levitra, it certainly was a very complex discussion. Without getting into

whether or not the data are consistent, in fact, I have a great deal of uncertainty as to whether the sponsor's indication that we're in the same realm is true. I'll tell you one thing. We had more data. We did have clinical trial data that provided a lot more insight, and we need to have better insight about what the actual effect is on QTc.

I'm not sure about the answer about the best way to get it. We've had discussions about the perioperative nausea and vomiting setting. Might the agitated patient setting enable us also an option to be able to look at QTc effects at higher doses since the doses delivered are higher in that manner?

I'd be inclined in any event to be trying to do these studies in patients and trying to deliver what is a clinically acceptable dosing level but at the highest level that would be clinically acceptable in order to follow the principle that Dr. Malik indicated, which is try to understand what is the effect in those patients where you're really pushing the dose to the maximal ethical level.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: But just to respond to that, wouldn't you welcome a volunteer trial given that the volunteer trial provides you the ability to get baseline RR versus QT relationships prior to the study, the opportunity

to very precisely control your dosing to have considerable periods where the patients are at steady state so you can measure your drug effect? I'll never argue for less data, but wouldn't you feel informed by a very carefully done volunteer trial to tease apart the concentration-response relationship?

DR. FLEMING: That's a valid point. As I said, when I prefaced my last comments, I'm not sure what the best way to do this would be. I'm a little bit uneasy, though, about whether in a volunteer trial we can get doses as high as what we might be able to deliver in a clinical setting. So that's the tradeoff.

I'm coming back again to Dr. Malik's point. What I'd like to know is what is the effect on QTc at whatever we can maximally achieve. He called it worst possible conditions, and I think that would, for ethical reasons, be in a clinical setting as opposed to a volunteer setting.

DR. HORLOCKER: Dr. Bril.

DR. BRIL: I have some comments about the QTc as a surrogate. From my background in research, I'm not against surrogate measures at all. It just seems to me that there is a lot of data already on the QTc. We know it's prolonged with droperidol. We know it's prolonged at multiple doses, low and high. We know it's prolonged to

similar levels that other drugs that we use all the time prolong the QTc. We know, from what we've just been shown, that there are 69 cases of cardiac arrest.

Surely you can go back and do something like a numbers needed to harm. You could estimate how many patients have received droperidol since it was approved 30 years ago and see does that QTc prolongation that has been documented for droperidol imply that 1 out of so many people should have torsade and a cardiac arrest or does droperidol in some patients produce a QTc prolongation that is different than the effect of the QTc prolongation in another patient. If it's just the QTc prolongation that interferes with repolarization and conduction and leads to torsade, then everybody who's QTc is prolonged to the same degree should have the same kind of effect.

I'm also a little concerned, from Dr. Malik's talk. The 40 milliseconds is one of those little boxes on the EKG paper tracing. To see a quarter of that box by the eye alone -- I know digital methods are used, but I saw those repolarization curves and there's a lot of little wiggle at the end of that T wave. So that also limits your surrogate.

So those are my issues. That's why I think getting a good estimate in the real patients with multi-pharmacy is necessary. So I would support a case-control

process at this point because we know what happens to the QTc. It goes up.

I'm not saying that some of the metabolic studies shouldn't be done. Those would be useful. Those would be interesting. Those would confirm what we know to some degree with the QTc prolongation, but they won't eliminate it. I'm not sure they'll make it any safer. We have to have some way of knowing the patients who go on and have the torsade and the arrest.

My question to the cardiologists at the break -- and I'm happy to have this -- is that whenever I refer one of my patients for surgery, I say, you could die from the anesthetic. Right? I mean, there's a risk of death from any anesthetic. We all know that patients carry that risk of bleeding, infection, and all that from surgery, but just the anesthetic. So now in all those patients who've died suddenly with anesthetics, have they looked at their ECGs retrospectively and said they had a long QT or they had a short PR or they had something that predisposed them to abrupt death? We have a lot of information that we should know about.

DR. HORLOCKER: What I'd like to do is just summarize what we've got for the first two questions because I think we might come up with additional suggestions for the FDA as we go over the way that we can

change or modify the labeling at this time.

It sounds like there's really no consensus among the group that we think that there should be both laboratory studies that try to document perhaps even the true endpoint, the torsades, and then correlate that with pharmacologic data in humans whether it's volunteer or clinical studies. And Dr. Shafer has volunteered to pay for all this.

(Laughter.)

DR. SHAFER: I'll have to talk to Visa to see if they'll support this, but yes.

(Laughter.)

DR. HORLOCKER: It is definitely going to take some time and effort and resources to perform these studies. So what I think we also need to address are the issues of can we give this drug safely and under what conditions at this point in time while we're waiting for these data to come back.

So what I'd like to do is move on to question number 3, and we'll come back to 1 and 2 at the end, especially if we have time. But I'd like to get all these questions addressed.

So the third question is, based on the available clinical and preclinical data and the settings and circumstances, how should the labeling reflect safe

use? The current labeling is under tab number 7 in your handout. Does everybody have a copy of the labeling?

DR. KOWEY: I'll take a first crack at this. This is one of the weirdest advisory committee meetings I've ever been at. I've never been at an advisory committee where there were fewer data. I can say that very comfortably.

The only time that I've ever been at an advisory committee like this was when amiodarone had to be approved based on basically a paper NDA because there was no clinical data, and we had a whole bunch of people in the United States on the drug, and the company that was shipping it to us said, we're not sending to it you anymore. And one of the American manufacturers said, well, you know what? We'll market it but we don't want to do any studies. We just want you to approve it. And we did based on a paper NDA. It was the last weird advisory committee I was at, and that was back in the mid-1980s. It's been a long time. It's been almost 20 years.

We don't have sufficient preclinical or clinical data to label the drug for safe use because what we're being told is that the drug is being used at a dose that FDA has not reviewed either for safety or for efficacy. So however we answer this question is a hallucination based on data that people are telling us

today that we don't have anywhere in black and white. We don't have it in a book. I've not reviewed it. Nobody around the table has reviewed it. The FDA has not reviewed it. So I think --

VOICE: They can.

DR. KOWEY: They can but they haven't. So number 3 is give us something to do and we'll do it, but based on the information we have right now, we don't have a way of doing it.

DR. HORLOCKER: Dr. Rappaport, could you discuss how you could go ahead and work on these lower clinical doses that we've been using for the last two decades?

DR. RAPPAPORT: We don't have the data either. That's the problem. In general, except in very unusual cases -- and we can talk about those if we want to -- we need to have the data submitted to us to review. Now, what the basis for that data is -- there are many ways that could be done. Generally it's done with clinical studies, but it can also be done from reports of clinical studies in the literature if those reports are adequate. The problem right now is we just don't have any data. None has been submitted to us by anybody.

DR. HORLOCKER: So what you've heard from the clinicians around the table that there have been a number

of clinical trials, as well as meta-analyses of the efficacy -- I mean, I think all of us agree that there are no documented safety -- if these were all put together in a large review, is there probably sufficient data available to label this for the lower doses?

DR. RAPPAPORT: We're always hesitant to say yes or no to question like that because what we do is review the data and then make that decision. That's why we are given the time to really do a thorough review. I can say that what we hear sounds promising. There does sound like there may be data out there. Dr. Chang can speak maybe to preliminary review of the data out there that her group has been looking at. But to do the scrupulous review that we do in order to approve a new drug or a new indication for an old drug, we have to have it in house and have the time to look at it.

DR. HORLOCKER: Dr. Eisenach.

DR. EISENACH: Well, I used to be on this committee and this committee deals with weird issues all the time.

(Laughter.)

DR. EISENACH: In part, it reflects the specialty. So you're talking about pushing a drug to the maximum ethically advised dose and seeing what it does to QT intervals. Well, I guarantee you if I give you four

times the appropriate dose of pentothal, I will kill you. If I give you three times the appropriate dose of the volatile anesthetics, I will kill you. We deal with drugs with very narrow therapeutic margins. So we understand the idea that a drug can be extremely dangerous in certain concentrations, but used on a routine basis in other concentrations.

I'm sorry. I'm going back to the first two questions because the philosophy that the two cardiologists are presenting is very different than the one I've heard and that we use daily in anesthesia. I deal with spinal anesthetics, and this advisory committee met regarding 5 percent lidocaine which is a spinal anesthetic that's been available for over 30 years -- over 50 years. Excuse me -- which at the marketed concentration can produce permanent neurotoxicity and paralysis under unusual circumstances, but at about 50 percent above the marketed concentration can routinely produce paralysis. So we're right on the cusp of toxicity there. So again, we don't have a problem with using lower concentrations and studying that.

So my question goes back to this idea of is there a safe QT prolongation, 10 milliseconds or whatever, at the therapeutic dose, not pushing it to higher doses. I want to get your response because it sounded to me like if you hit 40 or 50 milliseconds at any huge dose, then it

really needs a black box warning on it for anesthesia purposes as well.

DR. KOWEY: There have ben cases where drugs were not able to be pushed much higher than their normal therapeutic concentration and the QT effects studied just the way you described because there was a narrow toxic-to-therapeutic ratio. And I think that's perfectly reasonable if that's the case with this drug.

If you say that that's true, then I accept your word for it. I don't know that that's the case. I don't know that there's any way that maybe you can get more of this drug into somebody without placing them at real hazard. But that's what it's all predicated on. If you can't do it, you can't do it. Get what you can get.

DR. EISENACH: No, but you can do it because the fentanyl combination product, we were giving 20 times this dose. Now, we were giving it as part of anesthesia.

But my question goes back to if we're clinically going to be using this drug at doses under 2 milligrams and we did a study that showed that those doses prolonged the QT less than 10 milliseconds, would that be useful information, or if we were able to give 5 milligrams and it produced 50 milliseconds, does that preclude us from using the lower doses?

DR. KOWEY: The conventional wisdom has been --

and Dan said it earlier -- is that you attempt to examine the drug at a higher concentration on the premise that there are some individuals who are going to be at risk if you hit a higher number on the QT interval because of all the issues that Dan brought up. In that situation, I think that's really the data that the advisory committee would need to look at and then make a decision based on relative value versus that QT prolongation. And we use drugs that prolong the QT interval more than 50 and 60 milliseconds because they have great value.

See, if this committee meeting were occurring after you had those data, then you'd be able to make an informed decision about benefit-risk. As things stand now, you don't know the risk really. I think we have some idea of the benefit, although we haven't looked at the data properly. So that's where we stand.

DR. EISENACH: Yes. But that was my question. So it would be worthwhile to get those data.

DR. KOWEY: Yes.

DR. EISENACH: In other words, if you had those data, one of the outcomes might be that we might discuss the possibility of a different recommendation for lower doses. We would also need efficacy data, either paper or otherwise, it sounds like.

DR. KOWEY: I think that's right on the head.

DR. HORLOCKER: Dr. Dworkin.

DR. DWORKIN: I have a question for Dr. Chang. Unfortunately, I wasn't able to be at your talk this morning. I did review your slides. And it's about the label. In your slide it says the boxed warning is not about doses of droperidol less than 2.5 milligrams. And I was unclear about that because when I read the label, what the label says is that the maximum recommended initial dose of Inapsine is 2.5 milligrams, and the word "maximum" in the label to me suggests that less than 2.5 milligrams as an initial dose is within the label.

Now, I'm not trying to split hairs here. The reason I think a dose of less than 2.5, the question of whether that's within the label or not in the label is based on conversations I had this week with my colleagues in anesthesia who, when we thought about the black box warning not being within the label, seemed less perturbed by the black box warning.

So what it seems to me it hinges on here is the interpretation of the word "maximum" in the label. If the word "maximum" in the label means that less than 2.5 is within the label, then my colleagues are perturbed. If your slide is a more accurate reading of the label, which is at lower doses are not within the label, then it seems to me there might be a way to finesse this whole issue

which would be for the agency to publicize that doses of .625 or 1.25 are not within the label and therefore the black box warning doesn't apply.

I hope that was clear. I didn't sleep well last night.

(Laughter.)

DR. CHANG: First of all, I'll address the wording of the label. The old label recommended a range of starting doses. I believe it was 2.5 to 10 or something like that as the initial starting dose. The rewrite that said a maximum 2.5 milligrams starting dose was meant to emphasize don't use 10, use the lowest labeled dose. It was not an indication that lower doses were appropriate because we simply don't have that data.

DR. DWORKIN: So the word "maximum" I just want to clarify.

DR. CHANG: It was the maximum starting dose.

DR. DWORKIN: My colleagues are going to ask me tomorrow. You're saying that the agency's interpretation of the label is that it is not applicable to doses lower than 2.5 and therefore the black box warning is not applicable to doses lower than 2.5?

DR. CHANG: The boxed warning is information that is being conveyed to practitioners, our best recommendations, on how to use the drug according to the

drug label, when used according to the labeling. When used according to the labeling, which is doses of 2.5 milligrams and above, those are our best recommendations.

DR. HORLOCKER: Dr. Fleming.

DR. FLEMING: You had started the discussion about what steps we might recommend as it relates to understanding efficacy at lower doses, and just in that context, a couple of comments.

The first is if in fact that is to be entertained such that there could potentially be a revision to the label to allow for lower doses, I would first endorse the concept that this scientific information that we've heard exists but we haven't been able to review because it hasn't been submitted to us through the FDA should, in fact, be submitted to the FDA. A lot of past experiences have shown that a lot of things show up under the scrutiny of an intense FDA review, and so I do think if there's going to be regulatory action taken on these studies, it will be important for them to be reviewed by FDA.

In the open session, there was some data shown about the endpoint of absence of nausea, and one of my colleagues was, in fact, probing about what was statistically significant in that. I just jotted down the percentages. On placebo, it was 23 percent. On the .625

it was 29, and at the 1.25, it was 42 percent, which if we take these numbers literally means the increased fraction in those that are now rendered free of nausea by the 1.25 dose. Only a third of that increase is achieved by the .625 dose. That's a fairly modest increase. It just leaves me with the sense that this is not a slam dunk issue. This is an issue that really will deserve very careful regulatory and scientific scrutiny.

And so if that is the intention, my last comment is I would hope that that scrutiny is done in a comprehensive way as opposed to an ad hoc retrospective choice of those studies that we like based on what results they're going to provide. Ideally it would be prospective because in a prospective validation one is, in fact, free of this post hoc or ad hoc choice of which studies are being used to establish efficacy. Given that we've heard that there are a whole lot of potential sources of this information, I would either argue when this is done, it would be done in a prospectively planned trial or it would be done in a comprehensive retrospective manner so that we're not getting a biased assessment based on selection of certain trials.

DR. HORLOCKER: I'd like to just summarize number 3. I think Dr. Fleming did an excellent job. Does anybody have anything to add to that about how we should

evaluate this for changing the label to reflect the safe practice? Jim.

DR. GILLETT: I'm concerned because the patients are left out of this, they're out of the loop. They're not being talked to by the physicians about this in any way. I talked to the physicians. They're totally dedicated to the use of droperidol and want to continue using it. Patients don't know anything about it.

You ask this question what needs to be on that label, and I think that at least some concern should be shown for the fact that the patients are suffering with inferior medications if the black box continues to be there. At the same time, they're in this Alice in Wonderland phase of all the uses being below the label. I mean, what is this? Why is this going on? Why is not FDA sticking to its practices? So I find the patients are kind of left out of this.

DR. HORLOCKER: Dr. Rose.

DR. ROSE: There are some items that I note here in looking at this current labeling. One of them is that on the second page of the labeling towards the top it states: Inapsine is not recommended for any use other than for the treatment of perioperative nausea and vomiting in patients for whom other treatments are ineffective or inappropriate. I know clinically speaking that

anesthesiologists rarely use the on-label doses for nausea and vomiting. So here we are stuck with a labeling that says you should only use this drug for nausea and vomiting, and you notice that there were no psychiatrists giving any testimony today. They are the doctors who had been using the drug also in addition to anesthesiologists. So we're supposed to use it only for nausea and vomiting. Yet, we can use it in the effective doses for nausea and vomiting.

Then if you go to the last page of the labeling immediately under dosage and administration, the bold printing, it says in bold printing: Dosage should be individualized. Well, what are we physicians for other than doing the right thing for the patient and appropriately individualizing the doses?

Now, below there it says, the maximum recommended dose of Inapsine is 2.5 milligrams IM or slow IV. It doesn't say the maximum and the only dose, the minimum dose is 2.5. It says the maximum dose. So if we're going to combine, the dosage should be individualized and then say the maximum dose is 2.5, what are we left with as anesthesiologists? Having to give 2.5 when all we need is 0.625? The way I read it right now, the labeling tells me I can use it in 0.625 milligram doses.

DR. HORLOCKER: Dr. Wlody, you've been waiting patiently. Thank you.

DR. WLODY: This is sort of a procedural question. We asked Dr. Rappaport about providing these clinical studies to the FDA in order to approach the idea of the lower doses. I just want to know who has standing to give that information to the FDA. Is that only the producer of the drug or do other stakeholders have standing to give that information?

DR. RAPPAPORT: Other stakeholders, any legitimate organization that was willing to take on the full responsibility for making sure that the application was filed with the usual regulatory standards and that the scientific material was complete would be considered.

DR. HORLOCKER: I have a question for the FDA. I'm sorry.

DR. RAPPAPORT: Sorry. Nancy did have a good point. The other problem that you're going to run into if you're not the drug manufacturer is that you have to have an agreement on the chemistry, manufacturing, and controls so that you could supply that as part of the application. But that's certainly something that could be arranged.

DR. HORLOCKER: Obviously, you sense the frustration in that there's a disparity in the way we use this drug clinically and the labeling. It's going to take an NDA or something to actually justify the efficacy of the smaller doses. I think all of us agree with that.

However, if we get back to the black box, I think Dr. Malik gave us good data to support the use of a 12-lead electrocardiogram prior to administration of this drug.

The other thing that's very onerous to practicing clinicians is the 2- to 3-hour monitoring time interval. This really does seriously prolong people's time in the PACU and/or hospitalization. So I guess based on what we've heard today, is there any way that we could decrease that monitoring? Is that absolutely necessary given that most of these events occurred over a very short time frame, usually within 10 minutes? Do we need to monitor the people 2 to 3 hours afterwards? Just shortening that time interval would significantly improve the ability to deliver this drug.

DR. RODEN: When somebody shows us pharmacokinetic data, then you can answer the question. Otherwise, you can't answer the question. Or pharmacodynamic data of some kind.

DR. HORLOCKER: How was the 2- to 3-hour time interval selected to begin with? I think Dr. Chang said it was one half-life.

DR. CHANG: It was a few factors. Again, what we see from the published literature, the elimination half-life appears to be on the order of 2 to 3 hours. If we

take the most conservative approach which is to say monitor for 2 to 3 half-lives, that seemed to be clinically impracticable. So 2 to 3 seemed to be a compromise that might somehow be clinically practicable. And in addition to that, what data we have with respect to the sedation effects of droperidol is that the sedation effects of droperidol appear to last for about 2 to 4 hours. So that was the basis for choosing 2 to 3 hours.

If I could, again with respect to the earlier question about lower doses, I just want to emphasize again the agency does not regulate off-label use of drugs. Physicians, when a drug is marketed, have the prerogative to use drugs in the way that they see fit. We at the agency were faced with a very difficult situation of a drug that we had only approved at doses of 2.5 milligrams and above.

I wasn't being facetious. If we start talking about getting rid of doses 2.5 milligrams and above, we don't have a drug. Because we do not have data at doses below 2.5 milligrams, we cannot endorse that. We only discussed doses of 2.5 milligrams and above, and that was the action that we were forced to take. We simply can't comment on those doses, and if we limit the discussion to those lower doses, there's nothing to discuss.

DR. HORLOCKER: I think we'll move on to number

4 then. Until you receive those data, there is no way that we can modify the label in any way from the sense of both the black box and the indications and dosage. Is that correct?

DR. CHANG: Until we receive the data, we can't comment on doses lower than 2.5 milligrams.

DR. HORLOCKER: All right.

Then question number 4. In addition to the QT data, what else should the agency consider in making a risk-benefit assessment for droperidol used in the setting of surgical and diagnostic procedures? Dr. McLeskey.

DR. McLESKEY: Thank you, Madam Chairperson. This is sort of in follow-up to what Carol said earlier and what we were just discussing. I'm actually going to ask for the wisdom of the agency on this.

But one of the things that we have done in the past is through the so-called paper NDA process, when repackaging or reworking old drugs that have been grandfathered and they then come under reconsideration by the FDA, sometimes we take an opportunity then to actually look at the label, look at the indications in light of current usage and justify a change in the label on the basis of published data rather than necessarily the kinds of studies and so forth that we're alluding to today.

I'm kind of asking for the wisdom of the agency

here. Would this be an opportunity where, because maybe the practice of clinicians -- as I look around the room, every anesthesiologist at this table, myself included, has used this product in a dose that's below that of the label. Is the kind of situation that the agency would potentially look favorably on reviewing in that kind of a format, a change in the label in that kind of a format before we go forward with the QT interval assessment first of all?

DR. KOWEY: Charlie, can I ask you a question, just a clarification of your question? The thing you talked about the very end -- I was with you until the very end and then you said absent the QT interval data. I think the published literature is maybe up to the task of telling us something about efficacy and at the doses that you're talking about. But I don't think the published literature is going to be able to tell us much about what this drug is going to do in terms of its torsade risk at the doses that you're recommending because no matter how many papers you come up with, the n is not going to be big enough.

DR. McLESKEY: Fair enough.

DR. KOWEY: So absent the QT data, how can they do that?

DR. McLESKEY: Fair enough, but Nancy said that if we go below the 2.5 milligram dose, we don't have a drug. We don't have a label. We don't have anything to

consider. So I was trying to scratch my head and see how could we reconsider this drug at a dose that's clinically used and then go forward from that point and address the issue you've raised.

DR. RAPPAPORT: I think there are possible ways of doing this. We would consider looking at the efficacy data certainly that's available in the literature if it was submitted to us appropriately. The question is whether we can adequately assess the risk side. That's a matter for the review once we have whatever this committee seems to be recommending to us as the best way to go forward in assessing that risk. If there is no way to assess that risk, we have to live with what we have right now and make the risk assessment based on what we presented to you today which is pretty limited.

DR. McLESKEY: May I follow up?

DR. HORLOCKER: Yes.

DR. McLESKEY: Sort of the logic behind that would be that if the agency would then consider relooking at a label with a lower dose, then in order to show some exaggeration in that dose and show the QT effects and so forth, we potentially could discover those then at a lower delivered dose to volunteers. So that was sort of the logic I was going for. If we could get a label at a lower dose, maybe the obtainable data in volunteers in a simpler

study would then be possible.

DR. HORLOCKER: Dr. Bril.

DR. BRIL: My question was a little along the same lines, having been involved with another substance that went forward for review for non-labeled indications. The trouble with the literature studies that show efficacy is that the studies are run in a way that the data for safety is not usually collected in a manner that the regulatory agencies require to demonstrate safety sufficiently. I'm wondering if for older drugs like this or for other agents where there may be extensive off-label use and extensive evidence for efficacy, yet the safety isn't up to the standards that have been required, for those particular trials safety has already been done because these agents have been licensed for other indications. So there's a lot of safety data that has been collected according to agency requirements. I mean, it's not as if there isn't any of that.

But now there's a new indication and the efficacy studies are all published and accepted and the scientific community accepts them, in fact, to the degree that some individuals in the scientific community would not do a placebo-controlled trial with those drugs anymore because of the feeling it would be not ethical.

So the bottom line of my question and comment

is, are there discussions within the agency that perhaps the safety profiles could be evaluated, I mean, could incorporate what has been published or submitted for safety for those agents before and the requirements for safety demonstration could be somewhat different than for, say, a new drug? If you were going to change the label, do you have to have the same degree of safety acquisition and reporting in the studies? Because most of those studies would just fail on that point alone.

DR. MEYER: Let me attempt to answer that and also make some comments with regard to your comments.

First of all, I think you're correct that the literature reports, even if they're very well-done studies, may not have collected the safety data in the way we would want from a regulatory standpoint. But more often the case, even if it is, it's not very well reported. If you look at the safety discussions in a lot of these efficacy studies, they're generally a paragraph and they're very, very high level, like 30,000-foot altitude discussions of safety.

With regard to what we might be willing to extrapolate with safety, I think there is a lot of use with this drug which means there's a lot of anecdote. But if you look back, as Dr. Chang had stated earlier, considering when this drug was developed and approved, the actual basis

for approval by modern standards is quite scant. I think it would be hard from our standpoint to think that lower doses would be less safe, but I think the critical question here is are they more safe, particularly with regard to the torsades question. I think the natural assumption would be that they may be, but I don't think we would have the kind of data from the literature to say that. So while it is possible that we might entertain including lower doses in the labeling based on a literature-based submission to us, I'm not sure where that would leave us with regard to what we could say with the relative safety of those doses.

DR. HORLOCKER: Dr. Eisenach.

DR. EISENACH: I think what Charlie raised is really a key question and in order to move forward, I'd just like to clarify it again, that the agency would consider for efficacy purposes only -- and then we're continuing to discuss the safety -- a well-done literature review if it were presented in an appropriate format.

DR. MEYER: I think we'd certainly consider it. As Dr. Rappaport said earlier, I think we're always loathe to make promises about what the outcome of the review would be, but I think in the circumstance of a drug that's otherwise approved, relatively well-characterized in some respects, and for which there's a lot of experience, I think the potential path forward for a well-done

literature-based submission to support the efficacy of these lower doses is reasonable.

DR. HORLOCKER: Dr. Fleming.

DR. FLEMING: I may be just reiterating what I said before, but I would advise the agency to be very cautious about doing this. You're talking about a substantially lower dose, which of course we're hanging our hat on as the promise for having a better safety profile. I don't know all the data, of course, and many on this panel know the data at the lower doses much better than I do.

But in general principle, one needs to be extremely cautious about looking at this data very carefully, and regulatory review generally provides much greater insight into the reliability of these data than you would detect from literature publications. And literature publications also have substantial selection bias as to what studies get published, et cetera.

So again, I would advise the agency to be very cautious. If the data are crystal clear and there's just enormous consistency and just overwhelming efficacy -- although I gave the one example of the data in the open session and it didn't look so crystal clear to me in that one specific data set. But I would in general advise that there's a lot of wisdom to proceeding with with a

prospective or a very careful, adequately comprehensive review of the literature where the agency is convinced that the data, if they're going to go on a literature review, truly provides the essence of what they would have been able to see if they had done a full regulatory review.

DR. HORLOCKER: So I think we've moved on to question 5. I'll ask you for your comment in second, Dr. Shafer.

So essentially what we're saying is we need the substantial evidence in either a prospective study or an extensive literature review to demonstrate the efficacy and then the previously mentioned laboratory and clinical studies documenting safety before we could change the label substantially. Is that correct?

DR. CHANG: Yes.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: I have a comment and a question.

The comment is it truly breaks my heart to hear anything is based on the terminal half-life for an anesthetic drug. With the exception of esters where the terminal half-life is actually meaningful, these drugs are all described by multi-compartment kinetics. Dan, you're going to say we don't really know the kinetics, but we do know it's a three-compartment model. This British study shows that the first half-life is in the area of about a

minute and the other is about 10 minutes. So we do know it has a very rapid initial distribution phase and the levels after probably about 10-15 minutes are probably an order of magnitude less than they are just acutely.

DR. RODEN: So why do people stay dystonic for hours?

DR. SHAFER: First, it's not clear that they do at the kind of doses we're talking about. That's my issue. A lot of this long dystonia is like the 5 and 10 milligram dose where even after you make that turn, you are still above that threshold.

I'm concerned about the three half-lives just as a point of what evidence because for anesthetic drugs -- for anything -- except for the esters, the terminal half-life is actually not a clinically relevant number. It's looking usually at very subtherapeutic doses when you're talking about clinical doses of the drugs and particularly the small doses.

The other question that I have that's relative to the prior question and to question 5 is what mechanism does the agency have to incent -- and perhaps you wouldn't want to answer this question, which is fine -- a company to actually provide these data. I'm sure there's sort of a hammer, but is there anything that the agency can do to actually give a company a positive incentive to do these

things?

DR. RODEN: A carrot.

DR. SHAFER: A carrot, yes, thank you. Is there a carrot?

DR. MEYER: The carrot, I suppose, might be that if one were to conduct a clinical study in support of a lower dose, one would get exclusivity for doing that. The unfortunate thing for a literature-based submission is you would not get an exclusivity period for that.

DR. HORLOCKER: Dr. Gillett.

DR. GILLETT: To get back to the risk issue, why didn't FDA have a meeting on this? My understanding is that this was just an action taken by the FDA without it being evaluated by the panel. Is that correct?

DR. CHANG: Yes.

DR. GILLETT: And today we hear data that suggests that this risk is there, but we have no numerator, we have no denominator, we're not even sure which cases are included. Would you have been able to argue this case for putting this black box on here before this group when you did it 2 years ago, or did you do that? That's not my impression. My impression is you just did it.

DR. CHANG: In retrospect, it may have been something we would have considered. But as I tried to communicate during my talk, there was a very high level of

concern at the time, and because of that high level of concern, there was a true sense of urgency to convene a committee and to have these sort of discussions.

DR. GILLETT: The reason I raise that is the level of risk that you're talking about here is a level at which you approve drugs routinely that have carcinogenic effects or other adverse effects, side effects that are more serious or at least as serious, leading to lethal consequences. So I didn't understand where the risk was here so urgently that you had to take this unilateral action.

DR. MEYER: I'd like to address that. I think Dr. Chang made a reference to the relevant sections of the CFR that do not require a showing of causality. In fact, what drives, in the regulations, the choice of a black box warning, or a boxed warning more correctly, is actually the nature of the adverse event not the risk of it. In fact, you referred to carcinogenicity. We rarely have even hints of human carcinogenicity certainly when we're approving drugs. We have animal carcinogenicity data, but we don't have human data. We had fatal cases of torsade de pointes in association with the use of this drug with pharmacologic -- I was about to say probability, but pharmacologic logic behind it in terms of knowing that there are in vitro data that suggested that this does block the relevant channels,

and in fact human data to show that on a meaningful surrogate of QTc prolongation, that it does that. So we had all those things together.

From my standpoint, I think we would have felt very comfortable, had timing allowed, bringing that discussion to this kind of forum. From my standpoint, I think we would have made the same decision.

DR. GILLETT: But that puts you in the position of being the prosecuting attorney that can indict a ham sandwich in a sense.

DR. KOWEY: But remember that there are other alternatives with taking the drug off the market, which is not an unprecedented move for drugs that cause this side effect. There have been a number of drugs that have been removed from the market because they did exactly what this drug does. Yes, we all would have liked perhaps that there would have been more discussion. I think the FDA said that this morning, but the fact is that they kept the drug on the market and compromised with this warning which, by the way, is a warning that's on a lot of drugs that are used clinically.

Cardiologists use tons of drugs that have black box warnings, and we don't have formularies taking them off of our list, but we live with the black box warning. I'm a little surprised myself that there's been this amazing

reaction to the fact that this drug has a black box warning, that some formularies have taken it off. I amazed to hear that. I didn't realize that.

DR. HORLOCKER: Dr. Katz.

DR. KATZ: This is just a question about the incentive issue which seems to me to be, from a pragmatic point of view, an important one. Maybe, Dr. Meyer, you can address this.

This hypothetical pathway that you outlined of the sponsor perhaps performing a pivotal trial and then supplementing that with a paper review for the potential carrot of getting exclusivity. Is that more of sort of a hypothetical thing or is there actually a reasonable path that they could follow towards that end of exclusivity?

DR. MEYER: It's fairly complicated because it's more than hypothetical in terms of them getting exclusivity, but considering there are generics on the market, what that exclusivity would actually mean to them, unless the other doses -- the exclusivity would just be for the doses supported by that application. Unless the other doses were disallowed -- and I would suggest they would have to provide the data to say those doses were unsafe -- then the generics would still be able to market, and even though they would not have the specific labeling for these doses, there would nothing to preclude the use of those

products at these doses. So, in essence, it amounts to being hypothetical, but it's not clearly the case.

DR. KATZ: So just to continue to see if there's any way to make this from a hypothetical incentive to a real incentive, is there any pathway whereby the relative safety of the lower doses compared to the higher doses -- information about that could be supplied to the FDA, given that the FDA just applied some of it to us, to make an argument that other generic drugs should be taken off the market?

DR. MEYER: I would say that that is a possibility, but I think there would have to be substantial data to show that in fact these doses are safer than the other doses and the other doses, the currently recommended doses, are not safe for marketing. So it's a fairly high hurdle, but it's possible certainly.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: We're actually, as I understand, talking about question 5, and at the risk of getting off topic, I'd like to address it.

Question 5 is should 2.5 and above be taken off. As an anesthesiologist, I would say yes because I don't believe I have a use for higher on-label doses for nausea and vomiting. I can tell you that when patients start swinging at nurses just because this drug is

available still to me at the VA, this is the first thing that I reach for. Seriously, for a patient who is physically violent, this drug is a great chemical restraint, but that's an off-label use and that's actually not in discussion here. So I'd be very comfortable with the 2.5 taken off.

The one question I'd put forward is should the agency also talk to the psychiatric community because I've read their editorials and they're very unhappy about this. I would propose that they're going to have a much harder argument to make for using these high doses in unmonitored patients in the emergency room where there are lots of other things going on. To me that seems like a harder argument to go for the safety of high doses.

But as an anesthesiologist, my answer to question 5 would be yes.

DR. HORLOCKER: But we still have to get the substantial evidence before we can even get to that point.

DR. SHAFER: Right.

DR. HORLOCKER: Yes.

DR. BITETTI: I have a question. It seems as if one of the major sticking points for anesthesiologists using this drug now at very low doses is the requirement of the preoperative EKG and the 2 to 3 hours of monitoring afterwards. Is there evidence? Dr. Shafer, you alluded to

the fact that perhaps pharmacokinetics and pharmacodynamic evidence is such that that monitoring period really may not be justified. Because I think if we could get rid of that in the label currently, even for higher doses, people might be more comfortable using it in the perioperative setting for postoperative nausea and vomiting and we wouldn't have to address every single study out there and so forth because that's what's preventing people from using it, is that monitoring requirement.

DR. SHAFER: Can I answer? I think that one could do a very simple PK/PD simulation, and I would take the existing study that I mentioned. There is only one PK study, amazingly, on droperidol. It's not great. Actually put that in with Haldol, which will probably have very similar kinetics. It's a very similar molecule. See how well they line up to inform this, and based upon that, try to look at how long are the concentrations, anything in a reasonable range. And I would be very surprised if that was longer than about 15 minutes.

DR. HORLOCKER: How do you determine what a reasonable range is, though? That's the whole problem about what is the dose at which the QT prolongation occurs.

DR. SHAFER: Again, we don't have this concentration-response curve. The first thing I wrote after Peter was what does the concentration-response curve

look like. We don't have that.

But my feeling, on the other hand, is by the time the drug level has dropped an order of magnitude, given that we're already an order of magnitude where the studies were that saw rather minimal changes, we're now two orders of magnitude -- you know, that's 1 percent -- I'd like to know how fast that happens because it seems to me there's very little rationale, if you want to continue it beyond there, not to continue it infinitely.

DR. HORLOCKER: Dr. Roden.

DR. RODEN: I agree with that and I must say that the way the anesthesiology community uses drugs is quite different from the way every other community uses drugs. So any extrapolation from the chronic cardio-renal world or the chronic pulmonary world to this world may be highly inappropriate.

Having said that, I think that a PK study should include intensive ECG monitoring if Marek is still here, with the notion of trying to figure out perhaps something near and dear to your heart and that is, which compartment actually corresponds to the ECG effect compartment. It may be that it distributes very, very quickly and it's distributing right into the myocardium where it stays around for a while. So I think before answering that question, you really have to have a little

more data. We did hear about slow CNS uptake or somebody speculated that that might be going on. So I think you have to, when all else fails, get more data.

DR. SHAFER: The initial data that I saw showed a peak at 1 minute which would suggest that actually it will not correspond to any physical compartment. But interestingly, the problem is now I don't trust that data because now I know that the change in heart rate, which was also seen, could fully explain those findings. So it has to be very well done, as you say.

DR. HORLOCKER: So would the two of you be in agreement, though, that we still need those data before we could remove the 2- to 3-hour monitoring limitation or can we do that now saying that there are no data to support the 2- to 3-hour.

DR. RODEN: Well, the agency gets to decide the answer to that question I guess. But my sense is that you ought to leave it until you have some reason to change it. It's entirely rational that it will change, but you have to have the data to support that.

DR. HORLOCKER: I'd like to move on to the final question then which is are there other modes of risk communication that should be considered in addition to those that have already been implemented. Actually either Dr. Chang or Dr. Rappaport, could you very quickly

summarize what you have done for the risk communication just so everybody at the table knows all the steps you've taken?

DR. CHANG: We have changed the label. A Dear Healthcare Provider letter has been issued and that's also part of the packet. The FDA talk paper was issued and is still on the FDA website, and that's also part of the packet. And as I said, we really have endeavored to continue in a dialogue with the community through various publications that are widely read by the anesthesia community and actually in one of the ER publications as well. That's really been the scope of it to date.

DR. HORLOCKER: Any comments or additional ways that they could increase the communication from the committee members? You're unquestionably silent. Go ahead.

DR. CRAWFORD: I just wondered would it be appropriate for the agency or not to collaborate perhaps with a sister agency like HRQ or perhaps with a professional society as part of education to encourage the development of clinical guidelines or some other manner of looking at the issue more comprehensively.

DR. HORLOCKER: Dr. Dworkin.

DR. DWORKIN: Yes. I might be off base here but it seems to me, as I was saying earlier, that it might

be worthwhile considering the next time you publish a letter or an editorial in Anesthesiology or Anesthesia and Analgesia to clarify that the black box warning applies to the labeled dosage because at least based on my sample of anesthesiologists in my department, that is not understood, and it was reassuring to them. It might be helpful to get that word out about what's off-label, what's on-label, what the black box applies to, what it doesn't apply to.

DR. CHANG: That has been done.

DR. DWORKIN: It needs to be done again because they didn't get the message.

DR. KAHANA: I'm off-label all the time as a pediatric anesthesiologist, and I have to tell you that it's not reassuring to me at all. So I'm not sure who's reassured. From a litigious point of view, I'm certainly not reassured because every time I use a drug off-label, the possibility exists that I'm going to be challenged on that off-label issue. So I think the question is whether it's safe or is that litigious move protected. And I don't know that we know it's safe.

So I think maybe the agency should communicate better that in fact there are no safety statistics, none, on the low doses that we all believe are safe because none of us have related in our practice giving this drug to an event that's an cardiovascular event. On the other hand,

cardiovascular events are relatively common, and so maybe I have seen cardiovascular events and I've given plenty of droperidol. Perhaps I just haven't put the two of them together in the appropriate scenario. So I would be reassured if the agency actually was much more direct about clarifying their position on the black box, but also clarifying the fact that there are no data on small doses.

Being off-label is an interesting position. I think the only thing that protects pediatric anesthesiologists from being off-label is there's so little on-label that it's very easy to defend, but that's not so true for the adult world. So I'd be a little more concerned if I was giving a small dose to an adult patient where the black box was clearly warning of an event that's relatively rare but, nonetheless, we don't know that it's any more or less rare at 2.5 milligrams than we do at .625 milligram. It seems relatively rare across the board.

DR. HORLOCKER: Dr. Shafer.

DR. SHAFER: I would submit that many people in the clinical anesthesia community feel very isolated from the FDA. They don't understand what the FDA does. They don't understand how FDA arrives at decisions. And not that they're being critical. They just flat out don't understand. It might be that a regular communication from the FDA could be established with one of the major journals

in which there was sort of "from the FDA" section that helped to demystify the FDA and formed a basis for ongoing dialogue with the anesthesia community. So I would promote that, as you perhaps know.

DR. HORLOCKER: Dr. Chang wants to comment. She's been volunteered.

DR. CHANG: I fully agree. I think that that is a very important thing for the agency to be doing. Unfortunately, I've talked about resources before. We have a real resource issue.

DR. SHAFER: Maybe in this public forum, we can encourage the FDA to find resources.

DR. CHANG: Write to your Congressman please.

DR. SHAFER: A good suggestion.

DR. EISENACH: There's a real history of that here, of course, with Bob Bedford having done that with Anesthesiology under Larry Saidman's editorship where there was "from the FDA" right at the beginning of Anesthesiology for a few years.

DR. RODEN: I was going to say that, Nancy, you shouldn't have answered until I got my chance to say something because when I was on the cardio-renal panel at FDA, we instituted a "from the FDA cardio-renal panel" thing that was actually written by committee members, not by the FDA. So Steve is the one who volunteered himself,

not you.

(Laughter.)

DR. RODEN: And that serves as a relatively effective forum for a brief outline or discussion of the kinds of events that happened today. That has very little in the way of down sides. It's another entry to your CV, Steve.

DR. SHAFER: Nancy and I are both smiling about this because Nancy and I, in fact, have been trying to set this up for about six months. And it will happen and I think it will actually be a real positive step exactly on question 6, but we're still working it. So curiously, I actually already am volunteered, as is Nancy.

DR. HORLOCKER: We have about 10 minutes before we adjourn. What I'd like to do is just go around the table and have everybody make their final comments to the committee and to the agency, any parting remarks.

DR. RODEN: I think I probably said way too much today, but I'll just emphasize that it is not possible to develop a scenario where the risk is going to be reduced to zero. And that applies to the unusual risk of torsade, as well as many other unusual risks to many other drugs that your community uses and our community uses. The idea of Marek's spectrum of risk is actually very appealing, that when the risk estimate -- people like Tom Fleming talk

about point estimates -- when that falls below some number that is 1 in a million, it can't enter into your risk-benefit thinking. This one doesn't.

I think there are ways of managing the risk. The idea of the pre-drug cardiogram didn't get as much discussion as I would have liked, but I think that's one way of doing it. There are demographics. Old women with atrial fibrillation should not get droperidol. Young men with normal baseline ECGs and normal serum potassiums can get droperidol, and even if they have the long QT syndrome mutations, probably nothing will happen. So there are ways of identifying and managing risk, but that doesn't mean it's ever going to be zero.

DR. KOWEY: I think Nancy said earlier that we've gotten caught in a time warp because at the time when many of these drugs were initially considered, we didn't even know about the QT interval being a liability, and it's obviously now a very, very hot topic everywhere that we discuss cardiac active drugs. So it's unfortunate that this particular drug got caught kind of in the machinery. It's not really the drug's fault. It sounds like at the doses that are being used clinically it might be just exactly what anesthesiologists like to use and need. I personally think that it would be great to have drugs available for doctors to use when they think they're

valuable drugs.

What I said earlier is a disappointment that leading up this advisory committee, unfortunately, we just don't have any data to chew on, and I think that's what you need. We've heard a lot of suggestions about how to get those data with the minimum of muss and fuss. But unfortunately, it's going to require some resources. I don't know where those resources are going to come from. I secretly am very pessimistic that it's going to happen. But whatever we can do as committee members or ad hoc committee members to encourage the agency to try to find those resources and work with industry to partner to try to find a way to do this I think would be extremely helpful.

DR. SHAFER: From everything I've heard today and from the material I've read here and elsewhere, I think it's a doable hurdle. It's going to require a combination of in vitro studies -- the wedge model I think is an excellent model -- probably two human volunteer trials, the basic PK trial and then the volunteer targeted control delivery trial perhaps combined with a human clinical trial.

The question I would propose is it seems to me that there is going to be information in here that is both clinically relevant and will also provide mechanistic insight. Given that combination, it's not clear to me that

the NIH would not be an interesting source of funding for an appropriately motivated investigator.

DR. FLEMING: I think in view of the limited amount of information that we have in key areas and in view of the level of evidence that there is an association with torsade and with QTc, I think what the FDA has done I think has been reasoned.

My own sense is the major issue in going forward is addressing this issue of paucity of data in critical areas of understanding safety and understanding for the lower doses efficacy in a rigorous fashion. And without repeating all of the elements, I'm hopeful that there will be creative and effective solutions to being able to get much better data in both the efficacy and safety domains to enable the FDA to be in a position to reassess this.

DR. HOLMBOE: I'll just make two points. One addition to what's been stated earlier. I'd just encourage the FDA to try to take advantage of what it can from the clinical data that is available. I think it would be a shame if we didn't try to delve deeper into that if it's at all possible, recognizing there are serious resource constraints and the other studies that have been mentioned are clearly important.

The other point I made that didn't get a lot of

attention today is how risk communication should be conducted with patients. They've not been part of the equation today, and I think that given that we have a rare side effect that potentially is fatal, how you deal with that as patients I think is something else the FDA should take into consideration. It's a difficult issue, but again it's one that I think patients want to know about. They've made that abundantly clear, and I think it also needs to be part of the future discussions about risk communication.

DR. KAHANA: I too think the FDA did, with some reason, put a black box warning on this drug given our paucity of information about it and our inability to define a numerator or denominator, but a signal that I think is unmistakably clear. I think the most important message we can give as a committee to the FDA and to the industry is that we are in desperate need of a little additional information and it may well be that low doses of droperidol are very safe and should be used without an electrocardiogram, without prolonged monitoring. We simply just don't have the data to say that at this point. I think removing that warning prior to the acquisition of that data would be premature.

DR. HORLOCKER: I agree with the previous speakers, and also I'd just like to really try to encourage the manufacturer to put forth an extensive review because

that's really literature that's already been done. That's kind of the first step and we could get the FDA at least working on the information to document the efficacy at lower doses. At the same time, we need the ongoing clinical and laboratory studies.

DR. BRIL: I would agree. We need more information and we really need it clinically.

DR. ROSE: I have one feeling of discomfort about some of the information that was presented to us today, and that was some of the information that Dr. Chang presented to us on her slides later this afternoon. I know she admitted that those slides didn't have a lot of research behind them and that she was basically saying this really doesn't say that much, but she presented them anyway. I had a feeling of discomfort when she presented the slide that was entitled sedatives and yet included in that were lidocaine and vecuronium. Vecuronium is a muscle relaxing drug and not a sedative.

Then when you have numbers of vials or numbers of bottles or something like that that were sold, I mean, we sell pentothal in large bottles that may be administered to 25 people and droperidol, even in the small vials, I'm sure when it's used in 0.625 doses, an anesthesiologist can get many doses out of that vial. So that information was just really meaningless and yet was used to support the

following slide which wanted to show that there was more risk with droperidol than there was with these other drugs. So I would say that that was some really inappropriate red herrings.

Other than that, this has been a wonderful day for me, very educational. This is very important. I do hope that something will come out. Not being a researcher, you're not going to get a paper from me. I do look forward to droperidol having more appropriate guidelines for use of droperidol in the clinical setting that I'm in every day. Thank you.

DR. BITETTI: I'd agree with the previous statements. It seems to me the biggest problem that we have is basically resources to do the adequate studies for risk. One would hope that maybe some small in vitro studies and volunteer studies that would give us -- as the cardiologists and Dr. Shafer talked about, that they might be the least expensive way to give some degree of comfort to what's routine use these days of low-dose droperidol. One would hope that we could come up with a small enough study that would be acceptable to the FDA that perhaps the drug company or some other group like the NIH would fund it because I think a large enough study to make us all totally comfortable is completely impractical.

DR. WLODY: Well, I think I leave here with

sort of the same opinion that I had when I came in, which is that I'm really not at all convinced that the doses that we're talking about that are clinically used really pose a significant risk. I sort of despair of the possibility of accumulating enough data to change the black box warning. I don't know that that's going to happen.

But at the same time, I'd like to say that I don't think FDA could have done anything different based on the information that they have had. I just sort of regret some of the criticism that's been addressed to FDA in some letters to the editor because I have come to know how tough a job you have. Again, I think with the information that you had, you really didn't have a whole lot of choice.

DR. DWORKIN: I really have only one thing to add which is I very much look forward to reading the series of articles that Dr. Shafer and Dr. Chang are going to be co-authoring together.

(Laughter.)

DR. BOBEK: I just hope some day the label actually reflects what we do in clinical practice, and that's the bottom line. I'm a pharmacist and you guys are physicians. We're all out of the label practicing with this drug. I hope some day it changes and you guys do the research.

DR. EISENACH: The anesthesia field is not a

rich one. We have very little pharmaceutical development in this area, and this is a generic drug. So there are no resources to do what we suggested today. I would be amazed if a study section at the NIH would fund something without a novel mechanism associated with it.

I think the best bet was something one of you suggested which was to discuss this, and I would suggest either Nancy or Bob talk with Bruce Cullen, who is the Vice President and will become the president of the national organization. Clearly the clinical group of the anesthesiologists is very interested in seeing something done, and if there's something that could be funded by that organization, which isn't terribly wealthy either, but they have some resources, I think that would be the best bet to move forward. I hope that you could do that.

DR. GILLETT: I was worried that there would be no discussion of the ethical nature of the problem here. It seems to be well accepted by the group that there is a serious dilemma to the physician, to the patient, and to the agency.

Years ago, we ran into this with pesticides when integrated pest management started lowering the doses of pesticides to be applied below that recommended by the agency and approved on the label. This was an off-label use of a pesticide even though the agency wanted the

pesticides to be used in lower amounts. So we went through the same dialogue or sometimes lack of dialogue. Sometimes it was shouting. But you do have to work this through to find out that there is a degree of cooperation between the communities. They can solve this problem.

DR. McLESKEY: Well, just a couple of final comments. Thanks for allowing me to make them, Madam Chairperson.

DR. HORLOCKER: I didn't know you'd be last, Charlie.

(Laughter.)

DR. McLESKEY: I'm not. That guy to your left will be.

But I want to remind the committee members also that as Jim just said, it's a generic drug, and the incentive for -- the commercial driver here to move forward with this project is not great. I think we as clinicians would like to see the label reflect how the drug is used, but there's very little incentive for the maker of this product to do that. The maker of the product might be incented to do something to get the black box warning removed, of course, because that would improve the potential market. But I like the idea of maybe partnering in this case with one of the major trade organizations in order to potentially move the project forward.

And then my final comment was about question number 6. Are there other ways of risk communication? I was quite curious why that question was even there because it seems to me that in this case the agency has been extremely effective in communicating this risk, so much so that there's tremendous backlash among the community members for that, and for your just calling this session at all, I wanted to thank you for at least taking the time to reconsider the issue.

DR. HORLOCKER: Dr. Chang.

DR. CHANG: (Inaudible.)

DR. RODEN: Marek, you're being asked to talk.

DR. MALIK: I will not take your time. I will just thank you for listening to me.

DR. HORLOCKER: Thank you.

With that, I'd like to turn the meeting over to Dr. Katz who has been so gracious to sit patiently next to me all these hours.

DR. KATZ: Well, my only final comment is to thank everybody for coming and being so giving of their time and support and for Dr. Horlocker for being so gracious as to come down and chair this meeting for us.

Any final comments from the FDA side? Nancy, Bob, any final comments from you guys?

(No response.)

DR. KATZ: Well, then the meeting is adjourned. Thanks.

(Whereupon, at 4:39 p.m., the committee was recessed, to reconvene in closed session at 8:00 a.m., Wednesday, November 19, 2003.)