FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF

ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE

8:05 a.m.

Thursday, February 5, 1998

Versailles Ballrooms I & II
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

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C O N T E N T S

P R O C E E D I N G S

(8:05 a.m.)

DR. HORLOCKER: Good morning. I'd like to call this meeting to order.

I'm Terese Horlocker from the Mayo Clinic. I'm the Acting Chair of the Anesthetic and Life Support Advisory committee. I'd like to welcome you all here and congratulate on getting here despite the weather outside.

The focus of the meeting today will be the risk of spinal hematoma in patients that have undergone regional techniques while receiving the low molecular weight heparins and heparinoids perioperatively. Specifically, it's the job of this advisory committee to assist the FDA with the labeling aspects of these medications, as well as the decision to request additional information that would allow for the safe management of patients receiving these medications while they undergo regional anesthesia.

What I'd like to do now is just take a few moments to have the members of the advisory committee and the guests introduce themselves. I'd like you to state your name, your affiliation, and in addition, with each subsequent presentation, please identify yourself so the stenographer is able to know who is speaking. If we can just start over on the right here.

DR. STEINBERG: My name is Marvin Steinberg. I'm professor and Vice Chairman, Department of Orthopedic Surgery at the University of Pennsylvania School of Medicine.

DR. ALVING: I'm Barbara Alving, Director of Hematology/Medical Oncology at Washington Hospital Center in Washington, D.C., and I'm a hematologist.

DR. BAUER: I'm Ken Bauer. I'm Associate Professor of Medicine at Harvard Medical School, Chief of Hematology-Oncology at the VA Hospital in West Roxbury, and also a physician at Beth Israel Deaconess Medical Center in Boston.

DR. PALMER: Hi. I'm Susan Palmer and I'm a professor of anesthesiology at the University of Colorado Medical School.

DR. YOUNG: Marie Young, Associate Professor of Anesthesia, University of Pennsylvania Medical Center.

DR. CARLISLE: Sue Carlisle, Professor of Anesthesia and Medicine, University of California, San Francisco.

DR. REVES: Jerry Reves, Professor of Anesthesia, Duke University.

DR. TEMPLETON-SOMERS: Karen Templeton-Somers, Executive Secretary for the committee, FDA.

MS. CURLL: Mary Gomez Curll, Associate Professor of Nursing, San Antonio College, San Antonio, Texas.

DR. RHODE: I'm Charles Rhode, Professor of Biostatistics at Johns Hopkins University.

DR. WOOD: Margaret Wood, Professor and Chairman, Columbia University in New York.

DR. WYSOWSKI: Diane Wysowski, epidemiologist, Office of Epidemiology and Biostatistics, FDA.

DR. TALARICO: I'm Julia Talarico, the Director of the Division of Gastrointestinal and Blood Coagulation Drug Products of the FDA.

DR. BOTSTEIN: I'm Paula Botstein, Head of the Office of Drug Evaluation III in the Center for Drugs.

DR. HORLOCKER: Dr. Somers, would you like to read the conflict of interest statement please?

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard 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 for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in

firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting.

We would like to disclose for the record that Dr. Terese Horlocker's employer, the Mayo Clinic's Department of Anesthesiology, has an interest which does not constitute a financial interest within the meaning of 18 U.S.C. 208(a) but which could create the appearance of a conflict. The agency has determined, notwithstanding this interest, that the interest in the government in Dr. Horlocker's participation outweighs the concern that the integrity of the agency's programs may be questioned. Therefore, Dr. Horlocker may participate fully in today's meeting.

With respect to FDA's invited guest experts, Drs. Barbara Alving and Kenneth Bauer have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Alving would like to disclose for the record that she may be receiving a research grant from Pharmacia & Upjohn. In addition, Dr. Alving has reported that she is a speaker for Rhone-Polenc Rorer.

Dr. Bauer would like to disclose that he is a member of one of Organon's steering committees.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has 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 products they may wish to comment upon.

Thank you.

DR. HORLOCKER: Dr. Talarico, would you like to make your comments please?

DR. TALARICO: I'd like to thank the Anesthetic and Life Support Advisory Committee for taking the opportunity so that we can address the risk of epidural/spinal hematomas in patients receiving neuraxial anesthesia with concomitant thromboprophylaxis with low molecular weight heparins and heparinoids.

At the present time in the United States, there are three low molecular weight heparins which have been approved and one heparinoid which has also been approved for thromboprophylaxis.

The first low molecular weight heparin to be

approved was Lovenox, which was approved in March of 1993, for prevention of DVT which may lead to pulmonary embolism following hip replacement surgery. The dosing regimen was 30 milligrams subQ which was the initial dose given following surgery and then b.i.d. for a duration of 7 to 10 days postoperatively.

There were supplements to the Lovenox NDA for additional indications. The first supplement was in March of 1995 and addressed the prevention of DVT which may lead to pulmonary embolism following knee replacement surgery. The dosing regimen was similar to that used for hip replacement surgery.

Supplement 008 was approved in May 1997 and was for prevention of DVT which may lead again to pulmonary embolism in patients undergoing abdominal surgery who are at risk of thromboembolic complications. Here the dosing regimen is different. It was 40 milligrams subQ with the initial dose given preoperatively and then once daily for a duration of 7 to 10 days.

The last supplement, 010, which has recently been approved, is for prevention of DVT which may lead to pulmonary embolism during and following hospitalization in patients undergoing hip replacement surgery. Here the dosing regimen consists of two phases. There is a

perioperative phase where patients receive 40 milligrams subQ beginning 12 hours before surgery and then once daily for 7 to 10 days, or 30 milligrams subQ beginning 24 hours after surgery and then twice daily for 7 to 10 days.

After this perioperative treatment, patients who were found to be free of DVT can be then put on an extended prophylaxis regimen which consists of 40 milligrams of Lovenox subQ once daily and for a duration of 3 weeks.

Now, the second low molecular weight heparin available in the United States was approved in 1994 and is Fragmin. This low molecular weight heparin was approved for prophylaxis of DVT which may lead to pulmonary embolism in patients undergoing abdominal surgery who are at risk for thromboembolic complications. For patients just at risk of thromboembolic complications, the regimen of 2,500 anti-X units of Fragmin to be started 1 to 2 hours before surgery and then given once daily postoperatively for a duration of 5 to 10 days.

A supplement was then submitted for the indication in patients who are at high risk of thromboembolic complications, such as for example patients operated on for malignancies. Here the indication is again abdominal surgery and the dosing regimen is 5,000 anti-Xa

international units subQ, to be given once daily starting again before surgery. On the first day of surgery, the 5,000 anti-X units can be given in two divided doses, like 2,500 preoperatively and 2,500 postoperatively, and then once daily at the dose of 5,000, for again 5 to 10 days, or until the risk of thromboembolic complication is considered to be reduced.

The next preparation to be approved in the United States is Orgaran. Orgaran is not actually a low molecular weight heparin. It's a heparinoid substance. This compound was approved in 1996 for prevention of DVT which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery. The dosing regimen was 750 anti-Xa units starting 1 to 4 hours preoperatively and then twice daily for 7 to 10 days or until the risk of thromboembolic complications is diminished.

The most recent compound approved is again a low molecular weight heparin, Normiflo, which was approved in 1997 for prevention of DVT following knee replacement surgery. Here the dosing regimen is 50 anti-X units subQ on the evening of the day of surgery or the following morning, and then twice daily postoperatively again for 10-14 days or until the patient is ambulatory.

Many thousands of patients were recruited in

the studies which led to the approval of all these drugs, including many thousands of patients who had undergone surgery with spinal or epidural anesthesia. We are talking about something like 10,000-15,000 patients, and during the clinical development of the low molecular weight heparins or heparinoids, there were no cases reported of epidural hematomas.

The first cases that we became aware of was in October 28, 1994 when two cases of spinal/epidural hematomas were reported to the FDA, and this occurred with Lovenox. The labeling for Lovenox was revised to address specifically a warning of this adverse event.

Subsequently in July 1995, a review of all the incidents of spinal bleeding with Lovenox and indwelling catheters was again undertaken, and in September 1995, a total of 8 cases had been found and reported to the FDA.

I'll now review the cases and again in January 1996, the labeling was gain revised to specifically address the following issues. I might say that when the low molecular weight heparins were approved, the labeling initially included in the warnings section that caution should be used with the use of low molecular weight heparin in patients who are at risk of hemorrhagic complications, and patients who have undergone special surgical procedures

like brain, spinal, or ophthalmological surgery.

The labeling of Lovenox was revised the first time to include specifically the statement that special precaution should be used in patients with indwelling catheters and epidural catheters and in patients treated concomitantly with antiplatelet drugs.

The second revision of the Lovenox labeling, which took place in 1995, again addressed the warning for this specific adverse event. In the warnings section of the labeling and the hemorrhage subsection of the labeling, a new subsection was included addressing specifically neuraxial anesthesia and postoperative indwelling catheter use.

The labeling also included the experience from post-marketing surveillance, that cases had been reported and that the cases reported of epidural or spinal hematoma had resulted in many patients in long-term or permanent paralysis.

As time went by, more cases were reported, and in June 1996 there were 16 cases. Again, the revision of the labeling that I mentioned occurred again in 1997 addressing specifically the risk of epidural and spinal anesthesia.

In November 1997, Rhone-Polenc Rorer, the

sponsor of Lovenox, provided a cumulative summary of the spinal/epidural hematomas associated with the use of Lovenox, and as of November 1997, there were a little over 30 cases of spinal/epidural hematomas which had been reported to the FDA.

From November 1997, the FDA, in conjunction with Rhone-Polenc Rorer, has issued several changes. First of all, in December 1997, there were letters issued by the FDA to all manufacturers of low molecular weight heparins and heparinoids to request specifically, one, the addition of a boxed warning that addressed the warning and the precaution for the risk of spinal hematomas in patients receiving thromboprophylaxis with low molecular weight heparin and spinal anesthesia.

This warning was extended to all the other low molecular weight heparins and heparinoids based on the assumption that these drugs, although they differ one from the other, they can be considered in the same class. Therefore, it would be likely that the same complications would be seen with all the other drugs.

In addition to the inclusion of a boxed warning, the sponsors were to notify the health care providers with a Dear Doctor letter addressing the labeling changes.

A health advisory was issued on December 15, as well as a Talk Paper, concerning again the post-marketing reporting of these patients and the risk of epidural and spinal hematoma with the concurrent use of low molecular weight heparin and spinal/epidural anesthesia.

In addition to this revision of the labeling, health advisory, and Talk Paper, arrangements were made for putting together an advisory committee meeting to address specifically the risk of epidural hematoma in patients receiving concomitant spinal anesthesia and low molecular weight heparin.

So, the purpose of this meeting today is again to address this issue and to see if we can change the labeling, introduce new revisions into the labeling, or have we addressed sufficiently the risk?

If the labeling can be changed in any way, what else should be included?

Do we have any information which might allow us to advise the health provider on how to use the low molecular weight heparin in relation to the placement or removal of catheters or in spinal anesthesia?

Should the low molecular weight heparin, in concomitance with spinal anesthesia, be restricted to special circumstances in patients who have fulfilled

special requirements for the combination of both?

The other issues. Should the use of intrathecal catheters be contraindicated in patients who receive spinal anesthesia and low molecular weight heparin?

During this review of all the adverse events, and particularly the spinal hematoma, it became obvious that the risk factors were playing a very important role. Among the risk factors, the introduction of epidural catheters for analgesia was considered a significant risk factor. The other risk factor was the concomitant administration to patients of compounds that affect platelet function.

Now, if further revisions can be introduced in the labeling, what are they? How can we select them?

The other issue to be discussed for today is whether this warning should be extended to other anticoagulants, namely heparin and Coumadin.

Dr. Diane Wysowski will present the cases that we have analyzed, the 30-plus cases, with all the characteristics.

Before addressing the specific cases and what characterized each event and all the risk factors that could be recognized in the analysis of these cases, we would hear from industry with their presentations.

DR. HORLOCKER: Thank you, Dr. Talarico.

Before the industry membership gets up to make their presentations, I would like to make one request of them in addition to paying very close attention to the 25-minute time allotment. Dr. Talarico alluded to the fact that there were 30 cases of spinal hematoma reported in the United States, and obviously not all those have been published as case reports. Low molecular weight heparins have been used in Europe for approximately 10 or 11 years, and I suspect that there are probably reported but unpublished case reports of spinal hematoma that are in Europe also, and if you have information from your European branches or your Canadian branches, could you please present that information during your presentation also? Thank you.

The first company we'll hear from will be Organon.

MR. DELVERS: Good morning. My name is Tom Delvers. I am the Senior Drug Information Specialist at Organon, Inc. in West Orange, New Jersey.

I'd like to talk about Orgaran, which is danaparoid sodium injection this morning. I'd first like to describe the product, talk a little bit about the pharmacology, and how this product relates to the issue at

hand which is spinal/epidural anesthesia.

Orgaran was FDA approved on December 24, 1996 for DVT prophylaxis in patients undergoing elective hip replacement. Orgaran is given subcutaneously at 750 anti-Xa units twice daily.

Orgaran is a compound comprised of three components. The major component is heparan sulfate, which is about 84 percent. There's dermatan sulfate, approximately 12 percent, and chondroitin sulfate, about 4 percent.

The heparan sulfate actually has two fractions: one fraction that has a high affinity for Factor Xa, and a fraction that has low affinity.

The average molecular weight of Orgaran is 5,500 daltons.

The heparan sulfate component is different from heparin in that there is less sulfination and less of a negative charge on the repeating units as compared with heparin. I can point that out. There is less sulfination and less of a negative charge than on the heparin molecule.

The heparan sulfate component selectively inhibits Factor Xa by binding to and therefore enhancing the effect of antithrombin III. Because of the uniformity of the heparan sulfate molecule, Orgaran has very high

specificity for Factor Xa. The anti-IIa activity is attributed to the dermatan sulfate component.

The anti-Xa to anti-IIa ratio is greater than 22 to 1.

Orgaran has only a minor effect on platelet function and platelet aggregability as compared with heparin which has a higher affinity for platelets, as demonstrated by this table. In this table we see an in vitro platelet aggregability test where Orgaran was compared with heparin, which explains why in animal models, Orgaran has demonstrated less of a capacity to induce bleeding. Please note the peak blood loss is less with Orgaran as is the area under the curve. Here the peak blood loss is less and also the area under the curve. This is the heparin; that's the Orgaran.

This slide shows how Orgaran compares with the low molecular weight heparins with regards to anti-Xa activity as well as the prototype antithrombotic heparin. As we can see, Orgaran has an anti-Xa to anti-IIa ratio of greater than 22 to 1. The low molecular weights have various ratios, and unfractionated heparin is 1 to 1.

Unfractionated heparin is made up of fragments of a broad range of molecular weights from 3,000 to 30,000 daltons. When these fragments bind to antithrombin III,

they affect several steps in the clotting cascade that results in an exponential dose-response curve necessitating careful monitoring. Orgaran, having high specificity for Factor Xa, has a predictable linear dose-response curve. Therefore, no monitoring is normally necessary of prophylactic doses.

This table describes some clinical trial data. There are 11 studies in which spinal or epidural anesthesia was reported. In these studies, 1,106 patients received some form of anesthesia. The majority of these patients received Orgaran preoperatively. 378 of these patients were known to have received spinal or epidural anesthesia. There were no reports of spinal hematomas.

Therefore, in approximately 4,500 subjects exposed to Orgaran during clinical trials, 378 received spinal/epidural anesthesia alone or in combination with general anesthesia. There were no reports of spinal hematomas.

Orgaran was first approved in 1991 in the Netherlands. Since then, Orgaran has been approved in 18 countries for DVT prophylaxis. In eight of these countries, Orgaran has been approved for the use in hip patients. That's heparin-induced thrombocytopenia.

In addition to clinical trials, there have been

no reports of spinal/epidural hematoma in worldwide post-marketing surveillance.

In conclusion, Organon concurs with the inclusion of the black boxed warning in the labeling for Orgaran. However, we feel this warning should further emphasize the risk of the procedure. We also believe health care providers need guidance with regards to safe use of antithrombotics curing spinal and epidural procedures. As a manufacturer of heparin as well, Organon believes this black boxed warning should be extended to include all parenteral and oral antithrombotic agents.

Thank you. Are there any questions?

(No response.)

MR. DELVERS: Thank you.

DR. HORLOCKER: All right. Our next presenters will be Pharmacia & Upjohn.

MR. CHAMBERS: Good morning. James Chambers representing Pharmacia & Upjohn. We'd like to thank the committee and the agency for the opportunity to present some information that we hope will be helpful in the deliberations today.

Our presentation will be in two parts. First, Dr. Graham Pineo from the University of Calgary, Director of the Thrombosis Research Unit, will present some general

risk/benefit considerations in the prevention of thromboembolic events with the use of low molecular weight heparins. Second, Dr. Marten Rosenqvist, Medical Director, Cardiovascular Disease and Thrombosis, at Pharmacia & Upjohn will present our experience with Fragmin.

Dr. Pineo.

DR. PINEO: Good morning, ladies and gentlemen.

As mentioned, I've been asked by Pharmacia & Upjohn to make some general comments about this area of thromboembolism, low molecular weight heparin, and spinal hematoma, and in particular to describe a clinical trial that Russell Hull and I recently completed in North America called the North American Fragmin Trial, or NAFT. Because we had a preoperative dose of low molecular weight heparin involved, we designed into the study mechanisms to try to avoid or minimize the risk of spinal hematoma. This may be of use to you in your deliberations.

I would also point out that I'm not employed by Pharmacia & Upjohn. We do clinical trials with other low molecular weight heparins.

This may be elementary but to put the problem in perspective, I show you some slides. This comes from the familiar October 1995 Chest, data that you'll be familiar with, reviewed by Anderson, showing that fatal

pulmonary embolism is a common cause of death or contributes to death in a large number of patients, still felt to be one of the most common preventable causes of death in hospitals.

The incidence of total PE in general surgery without prophylaxis and fatal PE, and you'll recall that in the international multi-center study that figure was brought to .8 percent with the use of low dose heparin. Orthopedic surgery patients are at particular risk for thromboembolism.

Next is also from Clagett's article in the same issue showing the incidence of DVT and fatal and total PE in patients from clinical trials that were placebo-controlled using venography as the endpoint. In hip surgery and knee replacement surgery, these are the incidences that were seen in those days, and the high incidence of fatal pulmonary embolism.

Now, fatal PE is an unusual event today where active agents are being used, usually two active agents. But they still rarely do occur, and fatal PEs do occur off study, for example, as evidenced by information from the mortality and morbidity reviews in the UK and elsewhere. So, we are dealing with a serious problem.

The issue of whether regional anesthesia

decreases the incidence of venous thrombosis. Early studies demonstrated that they in fact did. If prophylaxis weren't used, DVTs were more common in patients having general anesthetic than a regional anesthetic. And these were venographically proven.

Now where we're using active agents, that doesn't appear to be the case anymore. I show you some data from a study that we published in the New England Journal in 1993, 1,207 patients, this many receiving spinal/epidural or a combination with general, comparing low molecular weight heparin and warfarin. And we saw no difference in the DVT rates in those receiving general or epidural anesthesia. Others have shown the same. Unless there are new data that I'm not aware of, I don't think we can attribute an advantage to regional anesthesia in terms of preventing deep vein thrombosis.

Again, you're familiar with this. When compared with unfractionated heparin, low molecular weight heparin is at least as good or better than low-dose heparin in the prevention of DVT in general surgery, and in the recent meta-analysis from the British Journal of Surgery, this was true for orthopedic surgery as well.

In North America, prophylaxis with low molecular weight heparin started postoperatively -- and I'm

showing you the trials that compared warfarin and low molecular weight heparin. These show that for total hip replacement, warfarin and low molecular weight heparin are equally beneficial. When we come to total knee replacement, low molecular weight heparin is superior to warfarin, warfarin started either on the night of surgery or the night before surgery.

This was one trial that was recently published by Francis and his group in the U.S. using preoperative low molecular weight heparin, and they showed that the low molecular weight heparin significantly decreased the incidence of total DVT in these total hip replacement patients.

So, coming to spinal hematoma and low molecular weight heparin and regional anesthesia, you're familiar with these reviews. In randomized clinical trials, we are not seeing any spinal hematomas. These patients are more carefully selected.

But in case reports initially that were coming from Europe, a review by Vandermeulen, there were some risk factors that were starting to stand out, and these are mentioned here. At the time that we designed the study that I mentioned, these were already well recognized. So, we tried very hard to avoid the complications.

I'll tell you a little bit more about this study, a multi-center double-blind study. It was carried out in 32 different centers: 9 in Canada and the rest were in the U.S. It was completed in November. The last patient came in exactly 3 months ago. So, we have just finished follow-up, and I'm not able to report the results as yet.

It was a three-arm study, and we compared preoperative low molecular weight heparin -- and this was started within 2 hours of surgery, and if patients had a spinal or epidural, it was given only after the needle was inserted and was atraumatic. The dose was split, 2,500 units pre-op and 2,500 that night, and then 5,000 daily with a post-op arm which is 5,000 the night of surgery and warfarin started on the night of surgery. The main objective here was to see if preoperative low molecular weight heparin was superior to warfarin in the prevention of venous thrombosis and that it was safe.

So, we were looking at major bleeding, and in our clinical report forms, we demanded that people explain what kind of anesthetic the patient received and if there were any bleeding complications that could be related to the regional anesthesia.

So, that study is completed. We can tell you

from the safety data that there were no spinal hematomas. Major bleeding was rare and our safety monitor had no concerns about bleeding in any of the three arms.

This is what we had done in the protocol, that we did not permit epidural or spinal puncture in patients who had previously been on anticoagulants or on NSAIDs up till the time of admission or on steroids. We strongly discouraged the use of epidural anesthesia and did not permit the use of epidural catheters for more than 12 hours.

So, the low molecular weight heparin was given only after the regional anesthetic was commenced, and if there were bleeding, a complicated puncture or any kind of bleeding disorder, the patient was not included in the study, did not receive either the placebo or the active agent.

I've described the dosage here.

If they did have a catheter, the catheter had to be removed well before the second dose the evening of surgery.

So, we offer these as possible guidelines to help minimize the risk of spinal hematoma in patients receiving low molecular weight heparin.

Thank you.

DR. ROSENQVIST: Good morning.

My task here is to give you the background information on the experience with Fragmin in patients receiving spinal or epidural anesthesia.

Fragmin was introduced in 1985 and is presently marketed for prophylactic use and for treatment in 48 countries. Based on our sales figures, worldwide 27 million patients have received Fragmin for thromboprophylaxis.

The dosing regimen has been divided into patients who had a moderate or a high risk for thromboembolic complications.

For patients with a moderate risk, 2,500 units are administered 1 to 2 hours preoperatively and 2,500 units daily starting on the first postoperative day.

For patients at a high risk, we have recommended 2,500 units 1 to 2 hours preoperatively and another 2,500 units the evening of surgery followed by 5,000 units daily starting on the first postoperative day.

An alternate dosing regimen is to provide 5,000 units 10 to 12 hours pre-op and repeated once daily until the risk for thromboembolic complications has diminished.

These recommendations have also the pharmacokinetic capacities shown in this slide where you

can see that measured as anti-Xa activity for a dose of Fragmin of either 5,000 or 2,500 units, the anti-Xa activity is going down, approaching 0 after 12 hours. This is despite the fact that we do have a proven clinical efficacy in thromboembolic prophylaxis.

When it comes to the question of epidural or spinal hematomas, we have compiled our experience from clinical trials of patients receiving the combination of Fragmin together with epidural or spinal anesthesia. We had 1,653 patients receiving this combination without any cases of spinal hematomas.

We also did a conservative estimate from our sales figures suggesting that at least 2,700,000 patients have received Fragmin in the setting of epidural/spinal anesthesia.

And we have two spontaneous reports of spinal hematoma that have been recently published in the Norwegian weekly medical journal, and I would like to review these two cases with you.

The first case is a 65-year-old male who was admitted with right costal pain and jaundice. He underwent a complicated surgical procedure with a cholecystectomy and a partial pancreatectomy due to a necrotic pancreatitis. Preoperatively he received 2,500 units and then 2,500 units

postoperatively daily.

After the sixth postoperative day, when the patient had received Fragmin for 6 days, the physicians decided to place an epidural catheter for pain control. The alternative, due to the severe pain, was to put him on a ventilator. He received his last dose of Fragmin at 8:00 a.m., and the epidural catheter was placed 3 and a half hours later. It was a complicated puncture and 10 minutes after the puncture, the patient had a rapid drop in blood pressure and a sensory and motor blockade. A decompressive laminectomy was performed 18 hours later and the patient at follow-up has paraplegia.

As you can see from this case, there are several risk factors involved. This patient had been on 6 days of anticoagulation treatment when the epidural catheter was placed. It was also a complicated puncture and several attempts had to be made.

Next case. This was a 51-year-old female who came to the hospital because of a left femoral neck fracture. Her previous medical history included multiple sclerosis with partial lower extremity paralysis. Her concomitant medication included Toradol, a potent NSAID drug, which was also given the day of surgery.

Preoperatively she received 2,500 units of

Fragmin, and after that, a spinal puncture was performed which was slightly blood-tinged but thereafter cleared.

10 hours postoperatively she received 5,000 units of Fragmin, and the postoperative course then was that she developed signs of increasing back pain and decompressive laminectomy was delayed and wasn't performed until 40 hours after the spinal anesthesia.

On follow-up, the patient has an almost complete extremity paralysis.

Again, there are several risk factors in this patient. She was on a potent NSAID drug, Toradol, and she received already 10 hours postoperatively a dose of 5,000 units of Fragmin.

Based on our clinical experience and on the NAFT protocol, we would like to advocate the following risk reduction strategy for Fragmin.

Epidural/spinal puncture should not be allowed for patients receiving anticoagulation therapy, including NSAIDs or steroids.

Low molecular heparin should be administered after a safe epidural or spinal puncture has been performed, in order to make sure that the puncture has been uncomplicated without any signs of bleeding.

There should be no low molecular heparin

provided if there has been a complicated puncture or the patient has a clotting disorder.

And the doses that we advocate are preoperatively 2,500 units times 1; postoperatively the evening after surgery, 2,500 units; and then 5,000 units daily until the risks for thromboembolic complication has diminished.

And finally, the epidural catheter, if such is left in place, should be removed 8 to 12 hours after the last dose of Fragmin has been given.

In summary, DVT and PE remain a significant clinical problem in postoperative patients.

Low molecular heparin significantly reduces the risk of thromboembolic events.

The use of regional anesthesia is increasing.

Risk factors for epidural/spinal hematomas can be identified prior to surgery and must be weighed against potential benefits.

Clinical practice guidelines for the concurrent use of regional anesthesia and anticoagulant prophylactic therapy should be developed.

Thank you.

DR. PALMER: Question.

DR. HORLOCKER: Would you identify yourself

please?

DR. PALMER: Dr. Palmer.

Your case one, isn't that the one we read about that was a direct thoracic puncture of the dura and direct needle trauma to the cord?

DR. ROSENQVIST: Yes.

DR. PALMER: So, really with the symptoms developing within 10 minutes of direct needle puncture to the cord, I don't think any of these guidelines apply to this case, do you?

DR. ROSENQVIST: No.

Yes?

DR. STEINBERG: Yes. I'd like to bring up a few points. This is based on practical orthopedic usage.

First of all, you stated that the Clagett study showed 3.4 to 6 percent fatal PEs after total hip replacement. This is one order of magnitude greater than most studies.

Next, you talked about the use of preoperative low molecular weight heparins. In practical use, most of us do not use these preoperatively. We start at 12 hours, and even that's dangerous. So, usually 18 or 24 hours.

Third, you spoke about the contraindications to spinal or epidural in the face of NSAIDs or steroids.

Again, many of our patients who are on steroids receive booster doses before spinals and we do use these in the face of nonsteroidals and we do not have problems.

Would you respond to these please?

DR. ROSENQVIST: I would like to respond to the fact that these are the guidelines that we have provided in our clinical studies, that patients should not be included if they are on a steroid or anti-inflammatory drugs. The regimen we have, the preoperative administration of Fragmin, is the one that we have documentation on and that we have done in our clinical trials.

I don't know if Dr. Pineo might have a comment on the incidence of pulmonary embolism.

DR. PINEO: I also agree these are very high rates. These data did come from randomized clinical trials that were placebo-based, and I was just quoting what has been in a familiar table that appears in Chest and in Colman's book and other places. I agree those are high rates, but that's what we've seen in early clinical trials.

DR. HORLOCKER: Dr. Wood.

DR. WOOD: Yes, but that was going to be my question. If you look at the protocols that you've shown, those quite complicated protocols as regards when the low molecular weight heparin or heparinoid started vis-a-vis

the neuraxial anesthesia, but it was my impression that there's no evidence whatsoever thus far that preoperative commencement versus postoperative commencement is any significant difference in the incidence of deep venous thrombosis. Is that correct? Or do you have other data to show that there is a difference?

DR. PINEO: No. The only data comparing low molecular weight heparin given either pre-op or post-op within the same trial is the study I mentioned, the NAFT trial. We'll have those results later in the spring. Otherwise you're just comparing across trials, the European trials where they start pre-op and North American where they start post-op.

DR. WOOD: Which is not the same thing.

DR. PINEO: Which is not the same thing. So, we will have evidence whether or not there's any benefit in starting preoperatively.

DR. HORLOCKER: I would just like to address the issue that there is not a synergistic or healthful effect of regional anesthesia in patients that also receive low molecular weight heparin. There was a recent publication in the New England Journal of Medicine, November 1997, comparing recombinant hirudin with low molecular weight heparin after total hip arthroplasty. The

authors did a multivariable analysis and found that type of anesthesia, general versus regional, did significantly affect the risk of deep venous thrombosis. That was a p value of .001. So, there is actually some data out there to support the use of regional anesthesia in these patients and justifies at least some benefit.

Other questions, comments? Yes, Dr. Reves.

DR. REVES: I'm curious as to why you're recommending -- back to the question earlier -- that patients who are on nonsteroidals, steroids should not receive any spinal or epidural anesthesia.

DR. PINEO: In the clinical trial, we were trying to avoid any possible danger --

DR. REVES: I'm not talking about protocols. This was a sweeping kind of statement that seemed to sweep across this room and I think caused some curious questions.

DR. ROSENQVIST: In most of the reports in spinal hematomas, it's clear that clotting disorders is a precaution when you do a spinal puncture.

DR. REVES: I'm asking for data. Do you have data like an incidence that makes you say such a statement?

DR. ROSENQVIST: No, we don't have.

DR. HORLOCKER: We can proceed with our next presentation then, Rhone-Polenc Rorer.

DR. RUSH: I'm Janet Rush from the Clinical Research Group at Rhone-Polenc Rorer.

Dr. Horlocker, Dr. Botstein, Dr. Talarico, and members of the committee and members and guests, on behalf of RPR, I would like to thank the FDA and the advisory committee for providing the opportunity to participate in today's session addressing a very important patient safety issue.

As detailed in the documentation provided to the committee, RPR has been working with FDA since 1995 to provide appropriate warnings to the prescribing physician in the package circular and in promotional materials concerning the risk of neuraxial hematoma. The recent FDA advisory, the Dear Doctor mailing, and the revision of package circulars all are important steps to bringing this issue to the attention of health care professionals.

Low molecular weight heparins, such as Lovenox, are very effective anticoagulants for the prevention of deep vein thrombosis and pulmonary embolism associated with orthopedic surgery and major abdominal surgery, as you've already heard today.

When neuraxial anesthesia and analgesia have been used, neuraxial hematomas have occurred.

Even with previous labeling changes and efforts

to inform the medical community, cases continue to be reported and the message needs to be repeatedly disseminated and reemphasized using a variety of methods.

As you will hear in this presentation and as you've already heard some of today, we believe there are certain factors that tend to increase the likelihood that neuraxial hematomas might occur. With additional guidance on the management of anticoagulated patients and patients scheduled to be anticoagulated, the chances of neuraxial hematoma formation and their serious sequelae can be greatly reduced.

One of the important additional steps which could be taken to improve the uptake of the message would be the inclusion of clinical guidelines at least in a brief format in the physician prescribing information for each of the package circulars, with more detailed recommendations being issued by a professional society, such as the American Society of Regional Anaesthesia.

Inclusion of brief clinical guidance in the package circular would facilitate the dissemination of this important patient management information to health care professionals. Additionally, inclusion of the information in the package circular will allow the pharmaceutical industry to take a more direct, proactive role in this

process through direct interactions of professional representatives with health care professionals and make the information known to a broader audience of caregivers outside the discipline of anesthesiology.

Most of the cases which bring us together today occurred in patients receiving Lovenox and the majority of these cases occurred in the United States. However, it is important to put this information in context with the use of other anticoagulants in the setting of neuraxial anesthesia.

There are a number of literature reports of neuraxial hematoma associated with heparin, including subcutaneous heparin, warfarin, and dextran, as well as antiplatelet agents such as aspirin. Many of these case reports are referred to in the publication by Dr. Vandermeulen and included as the first reference in the briefing document provided to the committee. Rates cannot be determined because of the large uncertainty associated with the population exposed.

However, this does emphasize that neuraxial hematoma is not related only to low molecular weight heparins and heparinoids. Since the risk of neuraxial hematoma in the setting of neuraxial anesthesia exists with all anticoagulants, including heparin and warfarin, the

product circulars of all anticoagulants should emphasize this risk.

There are many low molecular weight heparins marketed outside the U.S. The most widely used are Lovenox, Fragmin, Fraxiparin from Sanofi, and Sandoparin from Novartis. This slide shows these four widely used low molecular weight heparins and the number of prefilled syringes or unit doses sold outside the U.S. since market introduction. These unit-dose data are from IMS audit reports and thus all data are from the same independent source rather than from individual manufacturers.

Based upon literature reports outside the U.S., the number of reports in relation to sales appears relatively similar, as indicated by these overlapping confidence intervals.

RPR is aware of four published cases and two additional non-U.S. cases that were reported to RPR but not published. If we include all these cases, the six cases, for the sake of completeness, this would make a total of six Lovenox cases outside the U.S. and again the confidence intervals all overlap.

RPR does not have access to the data on the other manufacturers for reports that may have been reported just to the manufacturer and not published, but we did hear

from Pharmacia & Upjohn that these are the only two cases that have occurred outside the U.S. with Fragmin.

The number of cases reported from outside the U.S. is lower than the number reported to FDA relative to the volume of low molecular weight heparins in use. There are many possible reasons which could contribute to the occurrence in reporting of more cases in the U.S., including anesthetic and surgical practices, reporting differences, and the dose regimen which differs in orthopedic surgery.

With respect to anesthetic practices, there may be differences in the percentage of patients receiving spinal or epidural anesthesia, the frequency of indwelling catheter use for pain control, the length and stiffness of the catheters, the anesthetic agents of choice, and the demographics of the patients who receive hip and knee replacements.

There may also be differences between the U.S. and other countries in traditions of adverse event reporting. In some countries it is less common to report an adverse event that is related to the pharmacology of the drug and epidural hematomas occurring in anticoagulant patients may be considered expected based on the known potential effects of anticoagulants. This is particularly

important in the case we're discussing today because physicians may have considered the neuraxial hematomas to be related to the procedure not to the drug and then may not have reported them to the manufacturer of the drug.

Another important factor is the length of time that the drug has been in use. It's well documented that adverse events reports are higher during the initial introduction of the product and decline with time. Cases associated with heparin and warfarin which have been marketed for many years may be less likely to be reported. Public awareness also influences adverse event reporting, and this can differ worldwide.

Some of you might be familiar with the example of Suprofen, a nonsteroidal anti-inflammatory agent with many parallels to the situation with low molecular weight heparins. The clinical trials of Suprofen, which served as the basis of approval of this product, included up to 3,000 patients in Europe and 2,100 patients in the U.S.

It was marketed in Europe in 1982 and flank pain syndrome was not identified. Suprofen was first marketed in the U.S. in 1986. 6 cases of flank pain syndrome prompted a Dear Doctor letter and with the ensuing months, 163 cases in the U.S. were reported and only 17 cases in the other 24 countries in which this product was

marketed, giving relative to use a case rate of 23.3 per estimated 100,000 patients exposed in the U.S. and .7 for 100,000 exposed outside the U.S.

Another possible factor which could influence the distribution of reported cases is that the dose of Lovenox approved outside North America for orthopedic surgery is 40 milligrams once daily initiated preoperatively, whereas 30 milligrams every 12 hours initiated postoperatively is approved for orthopedic surgery in the U.S. and Canada.

While both regimens are effective, it was the conclusion of RPR and FDA that the 30 milligram, every 12 hour regimen was more efficacious in the high risk setting of orthopedic surgery. This was based on the results of two studies in patients undergoing hip replacement surgery. In both studies the regimen of 30 milligrams every 12 hours tended to be more efficacious than the 40 milligram, once daily regimen which was initiated postoperatively in this trial. In one study, the 525 study, this difference was significant.

For the prevention of DVT in major abdominal surgery, 40 milligrams once daily initiated preoperatively is the approved prophylactic regimen worldwide.

As Dr. Talarico mentioned, Lovenox was the

first low molecular weight heparin to be approved in the U.S. and was introduced in 1993. On this slide, we see the syringes sold in the U.S. through September 1997 for two of the four products being discussed today, Lovenox and Fragmin. Since 1993, 97 percent of the units sold in the U.S. have been Lovenox 3-milligram prefilled syringes and an additional .5 percent for Lovenox 40-milligram syringes. Only 2 percent were Fragmin and less than .5 percent were Normiflo and Orgaran.

Because epidural hematoma is an infrequent event, Lovenox is the only low molecular weight heparin with sufficient use to have had cases reported and observed, cases of neuraxial hematoma. This slide shows the U.S. reports of neuraxial hematomas over time and indicates the sales -- and here are the cases -- over time in the U.S.

Even with the revisions to the Lovenox package insert and efforts to inform the medical community, cases have continued to occur. The initial revision to the Lovenox package insert, as mentioned by Dr. Talarico, was made in response to the reporting of the first two cases of epidural hematoma, and there have been a total of three labeling changes, as shown here.

As part of a program to increase awareness of

the problem, there have been three Dear Health Care Professional and Dear Doctor mailings to bring this information to the attention of a wide audience. RPR has also provided the details of the case histories to several individuals, Drs. Hynson, Horlocker, and Tryba, who have analyzed them and published the case series in professional journals.

However, as I mentioned, interactions of professional representatives and physicians are limited to the information contained in the package circular and the inclusion of more specific information would enable the pharmaceutical industry to take a more direct role in communication of the recommendations that would come from a meeting such as this.

In RPR's examination of the cases of neuraxial hematoma, certain common elements appear repeatedly and may be factors which should be taken into account in the development of product labeling and professional society guidelines. These numbers have been updated since the list provided in the briefing document.

It's clear that the majority of patients were females. Two-thirds had epidural anesthesia. One-third had an indwelling catheter for more than 24 hours for postoperative analgesia. Other characteristics include

concomitant use of medications with antiplatelet properties, such as NSAIDs, nonconformance with the recommended dosing interval for the anticoagulant, multiple attempts to position the needle or catheter, the occurrence of a bloody tap, or catheter withdrawal at the peak of anticoagulant activity. This list is consistent with the characteristics of the literature cases reported with other anticoagulants.

From the 16 patients in our series in whom the weight is known, it does not appear as though low weight is a risk factor since all Lovenox patients who developed neuraxial hematoma weighed 62 kilos or more.

19 of the reported cases occurred in patients who received Lovenox and neuraxial anesthesia in the setting of hip or knee arthroplasty during the years 1995 through 1997. So, on this slide, you're looking just at the subset of cases who had hip or knee replacement surgery and neuraxial anesthesia.

Through marketing survey data, we have attempted to quantify the number of patients who received Lovenox during these years and who had various forms of regional anesthesia or analgesia. We must all acknowledge the considerable uncertainty regarding the accuracy of the population estimates which come from a market survey which

is fraught with a lot of uncertainty.

However, a rather striking difference does become evident when the data are examined in this way. In patients exposed to Lovenox in whom an indwelling catheter remains in place for more than 24 hours, the risk of neuraxial hematoma appears to be considerably higher than in patients who received spinal anesthesia or epidural anesthesia for less than 24 hours.

In some of the reported cases, the symptoms of neuraxial hematoma can be linked to two critical time points, the time of insertion and time of removal of the needle or catheter. It's logical to postulate that the level of anticoagulation at these two critical time points should be given careful consideration.

For the low molecular weight heparins and heparinoids, the level of anticoagulant activity is lowest at the end of the dosing interval, and some practitioners have assumed that this is the safest time to remove an indwelling catheter. However, in the case of a low molecular weight heparin administered on a twice daily schedule, there is substantial anticoagulant activity present even at trough.

In order to increase the safety margin, some experts have recommended skipping a dose of low molecular

weight heparin allowing 24 hours to elapse since the last previous dose before discontinuing an indwelling catheter. This recommendation is mentioned in the reference by Dr. Horlocker reproduced in your briefing document.

For Lovenox, a 24-hour interval before discontinuing an indwelling catheter will enable the anti-Xa level to drop to near the limit of detection which would provide an added safety margin. This recommended interval would need to be adjusted based upon the specific pharmacokinetic characteristics of each of the low molecular weight heparins or heparinoids.

In order to take this into account, RPR has previously proposed brief prescribing guidelines which could provide the practitioner with specific information. The elements which we believe should be addressed in the package circular are, first, omission of any preoperative dose if neuraxial anesthesia is planned; second, removal of the epidural catheter at least 2 to 8 hours prior to the initiation of anticoagulant, if possible; and in the case of an indwelling catheter for postoperative analgesia, 24 hours should elapse between the previous dose of anticoagulant and the removal of the catheter, the next dose to be given no sooner than 2 to 8 hours after catheter removal.

The interval recommended between the removal of the catheter and the initiation of anticoagulant differs markedly in the published guidelines and references commenting on this topic, and we believe the recommended interval needs to be defined based upon the collective wisdom of people who write the guidelines which will issue following this and other meetings.

In 1995 the American College of Chest Physicians published consensus guidelines on antithrombotic therapy for the prevention of thromboembolic disease.

In the setting of total hip arthroplasty, the most effective thromboprophylactic modalities were low molecular weight heparin in a fixed dose twice daily, oral anticoagulation titrated to an INR of 2 to 3, and adjusted dose heparin. Considered less effective were low-dose heparin, aspirin, dextran, or intermittent pneumatic compression.

In the setting of knee arthroplasty, the recommendations are somewhat different. The only pharmacologic modality recommended was low molecular weight heparin in a fixed dose twice daily and intermittent pneumatic compression.

Low-dose heparin, aspirin, dextran, and intermittent compression, therefore, are not recommended in

the setting of hip replacement surgery.

Regional anesthesia does confer some protection from DVT relative to general anesthesia, but the effect is relatively modest. This study demonstrates the additional benefit of Lovenox in this setting. In this series of 153 patients, all of whom received spinal anesthesia, a DVT rate of 37 percent in the placebo group -- this is DVT diagnosed by a venographic exam which was performed on all the patients enrolled in the trial, and this rate was reduced to 14 percent in the group which received Lovenox 40 milligrams once daily. In this study the 40 milligrams once daily was initiated postoperatively.

Of special note is the reduction of proximal DVT from 16 to 2.6 percent, both of these reductions being highly significant.

Other than Lovenox, warfarin is the most widely used agent for DVT prophylaxis in the U.S.

Whereas warfarin and low molecular weight heparin are both effective prophylactic agents in the setting of total hip arthroplasty, the situation is very different in total knee arthroplasty, as was observed in this study of Normiflo versus warfarin. In total hip arthroplasty, there was a trend favoring twice daily Normiflo over warfarin with a p value of .07.

In patients undergoing knee replacement, the advantage of low molecular weight heparin was striking, with a reduction of deep vein thrombosis or pulmonary embolism from 43 percent, 26 percent with twice daily Normiflo.

This advantage of low molecular weight heparin over warfarin following total knee arthroplasty has been observed in a number of studies now, including this study in which the DVT rate of 45 percent with warfarin was reduced to 25 percent with Lovenox. And even more striking was the reduction of proximal DVT from 11 percent to 1.7 percent in the Lovenox group.

So, in conclusion, low molecular weight heparins are efficacious pharmacologic agents for the prevention of thromboembolic complications of hip and knee replacement surgery. When anticoagulants are used in the setting of neuraxial anesthesia, cases of neuraxial hematoma have been reported.

Even with the changes that have been made and efforts to inform the medical community, cases continue to occur. Educational efforts must be increased, including development of guidelines. Recommendations for the use of thromboprophylaxis in the setting of neuraxial anesthesia should be included in the respective package circulars. We

are confident that guidance will emerge from this committee today that will enable the safer use of anticoagulants in the surgical setting.

Thank you.

DR. HORLOCKER: Questions?

DR. PALMER: Question.

DR. HORLOCKER: Dr. Palmer.

DR. PALMER: Could you go back to your steady state plasma anti-X activity slide?

DR. RUSH: Okay.

DR. PALMER: It's seventh from the last, if that helps.

I was just wondering if you could help me understand what this would look like in percent of normal Xa activity because this international units doesn't compute for me. In other words, when you get at the peak of action at 2 hours, how much of the normal activity does a person have as opposed to when you get out to 20 hours there, how much of normal activity is returned?

DR. RUSH: Well, this is all pharmacologic activity, anti-Xa activity.

DR. PALMER: Right. What I'm having trouble with is how that compares to normal activity rather than international units.

DR. RUSH: Normal activity.

DR. PALMER: Yes. I guess maybe I'm not making it clear but maybe there is someone in the room who could help me with this. I want to know when we're above 50 percent normal activity.

DR. MAGNANI: Harry Magnani from Organon.

The problem with the anti-Xa units is for all these compounds that they're not equivalent. Each one has to be measured against its own control. So, Lovenox is measured against a Lovenox control; Orgaran against an Orgaran control; heparin against a heparin control. So, that means that you can't just say that so many units of anti-Xa activity of Lovenox are equivalent to so many units -- well, you can say they're equivalent, but you can't say they're the same as so many units of heparin. So, it doesn't make any, in a sense, sense to say how many units of heparin is this because they have other activities on the coagulation cascade, and therefore it's not really an equivalent situation.

DR. PALMER: I guess I'm not asking my question clearly enough. What I'm trying to get at is at what point in the hours does a person's Xa activity return to 50 percent of normal. I don't really care about heparin equivalence.

DR. ALVING: Well, basically it's a way to monitor the heparin activity since we can't do an APTT. We just say how do we measure its anticoagulant activity. So, we say let's measure that activity against an activated factor like Xa. So, when you do the assay, you're adding the Xa into the plasma, and you measure the potency of the heparin by its activity against anti-Xa.

So, one way to look at it would be if you want to have someone therapeutically anticoagulated against deep venous thrombosis, you would like to have an anti Factor Xa activity of .3 to .7 units per ml. So, when you see that peak there, you'd say, gee, that little peak represents full anticoagulant activity as full protection against DVT.

DR. PALMER: So, what you're saying is once you get below .3, which looks like it occurs at about 7 or 8 hours out -- 7 hours out, that you would not have a therapeutic level of anticoagulation. Is that what you're saying?

DR. ALVING: That's correct. It's getting lower and lower. Right. So, in other words, when you're between .3 and .7, that would be equivalent to full-dose heparinization with unfractionated heparin.

DR. PALMER: Thank you. That's helpful.

DR. HORLOCKER: Yes. Please identify yourself,

sir.

DR. STEINBERG: Marvin Steinberg.

Dr. Rush, you and the previous speakers keep referring to the changes in the incidence of DVT with these various agents. Now, DVT, especially below the knee, may be of almost no clinical consequence. Would you relate this to PEs and more specifically fatal PEs, which is really the only thing that is significant here? And is there any data and can there be any data, because of the numbers involved, that lead to statistically significant differences?

DR. RUSH: Yes. I think that's a very good point. I think we all recognize that the rate of fatal PE in these patients is fairly low, but we have to keep in mind we're not only trying to prevent fatal PE, we're also trying to prevent the morbidity and additional hospitalization and morbidity of patients who have nonfatal PEs and proximal vein thrombosis. So, the magnitude of the clinical problem is greater than just the fatal PE rate.

DR. STEINBERG: Well, do you have any data showing fatal PEs? That is really what counts.

DR. RUSH: Yes. There have been several studies of fatal PEs in the setting of orthopedic surgery. I think the data that Dr. Pineo showed you is well-known.

It's widely quoted. There are several other series which find fatal PE rates more in the range of 1 percent or less. But in this day where thromboprophylaxis is so widely used, it probably is not very easy to sort out the differences between the way surgical practices have evolved and the thromboprophylaxis. We're all using the best efforts we can to reduce fatal PE and that's why the rate is low.

DR. STEINBERG: To be the devil's advocate, some very good statisticians have stated that it requires over 30,000 patients with prospective double-blind controls to prove that there's any significant difference in the instance of fatal PEs and therefore have come to the conclusion that the definitive study cannot be done. Do you agree with that?

DR. RUSH: It certainly would be difficult to show a difference in fatal PEs if you were to compare various effective modalities, modalities known to be effective. It would probably be unethical to do a trial where you did not use any DVT prophylaxis, and so such a trial would be very difficult to perform.

DR. HORLOCKER: Questions? Dr. Bauer.

DR. BAUER: I have a question related to the issue of the pharmacology and the dosing. Maybe you could put that last overhead up again.

It would seem to me that the potential exists with Q12 hourly dosing with repetitive doses for accumulation of anti-Xa activity over time with repetitive dosing at the 12-hour --

DR. RUSH: Well, this --

DR. BAUER: I know it's a single dose.

DR. RUSH: No. This is a steady state. So, here we are at .1, and this is the steady state trough level. So, this is all the accumulation that we see.

DR. BAUER: Okay. So, that's into repetitive dosing. Okay.

DR. RUSH: This is the last dose administered on day 8.

DR. BAUER: Okay, I see that. Thanks for that clarification.

DR. HORLOCKER: Dr. Wood.

DR. WOOD: I agree with Dr. Steinberg, and it's really a philosophical comment as to the way the data has been analyzed. When we all started medicine, the thing that we were taught as part of the Hippocratic Oath was first do no harm. That has changed now. If you look at the antithrombolytic therapy that's used for myocardial ischemia, cerebral hemorrhage and stroke is an inevitable consequence of quite proper antithrombolytic therapy. But

when the data was analyzed it was done very well comparing risk-benefit ratio of cerebral bleed/stroke versus incidence of myocardial ischemia.

If you actually look at the way the data is being analyzed here, we haven't really seen the risk of epidural hematoma versus what really is a surrogate endpoint, deep venous thrombosis, versus pulmonary embolism. And I think it could be done. It would be very difficult to do, but I think it could be done in the way it was done for myocardial ischemia and antithrombolytic therapy.

DR. HORLOCKER: Any other questions?

(No response.)

DR. HORLOCKER: We'll proceed with Wyeth.

DR. CHAIKIN: Phil Chaikin with RPR Clinical Research.

I think there should be some additional discussion about the effect of anti-Xa levels, though, this .3 to .7 and differentiating between what's effective anticoagulation for therapy of a DVT as opposed to prevention. Even in Dr. Horlocker's review article, she had mentioned that peak anti-Xa levels at .1 to .2 units per ml were effective as far as prevention of DVT. So, I think there's a differentiation that has to be made between

what you need with respect to anti-Xa levels inhibition with respect to treatment of a DVT as opposed to prophylaxis for a DVT.

DR. HORLOCKER: Thank you.

Sir, could you please identify yourself to the stenographer.

DR. DeVANE: Good morning. Dr. Horlocker, Dr. Talarico, members of the advisory committee and guests, ladies and gentlemen, I'm Philip DeVane, Vice President of Clinical Affairs and the North American Medical Director, representing Wyeth-Ayerst ESI.

I'd like to thank you for the opportunity to take part in the discussion this morning and I'm going to make some very brief remarks. This morning I'll present information regarding the reports of spinal hematomata associated with Wyeth-Ayerst low molecular weight heparin, Normiflo, and a description of such reports associated with our heparin products. We're a major manufacturer of heparin sodium in the United States.

Regarding Normiflo, which is dosed by patient weight to allow plasma anti-Xa levels to be relatively constant over a range of patient weights, in the clinical trials 4,185 patients received Normiflo in the trials, of which about a quarter, 1,119 patients, received epidural or

spinal anesthesia. As you've already heard, no cases of spinal or epidural hematomata were reported.

Similarly in post-marketing experience, no cases of spinal or epidural hematoma have been reported in the U.S. to us from the time of product launch, which was in July of last year, 1997, through the period, the end of January 1998.

However, under the circumstances, we believe that the safety issue of patients is paramount, and we've accepted the recent revisions to the package insert of the low molecular weight heparins and heparinoid products in order to convey the risks associated with the use of these products when neuraxial anesthesia is employed or diagnostic lumbar puncture is undertaken.

With regard to spinal hematomata associated with heparin products and neuraxial anesthesia, since 1990 our post-marketing database of spontaneous reports includes two cases of epidural hematomas, both literature reports. During this time frame, over 340 million units of our therapeutic heparin sodium and over 380 million units of our nontherapeutic heparin sodium -- that is, Hep-Lock and heparin flush -- units have been sold.

We acknowledge that this is a controversial issue where the true incidence is unknown, in part because

of the lack of controlled clinical trials and in part due to an unknown degree of under-reporting. However, we've ont seen any increased reporting spinal hematomata associated with the use of our heparin products, and thus based on this information, we do not believe that the current heparin labeling needs to be changed.

I'm sure the committee appreciates the differences between therapeutic heparinization versus the use of heparin flush units. These products have very different risk-to-benefit ratios and in fact have very different package inserts.

Thank you very much.

DR. HORLOCKER: Questions.

One question for you. So, you're saying there are no unpublished case reports of spinal hematoma from your product.

DR. DeVANE: That's correct.

DR. HORLOCKER: Both in the United States and in Europe.

DR. DeVANE: We only market the drug in the United States and it's not commercially available outside the United States. So, no, there are no unpublished cases.

Thank you.

DR. HORLOCKER: We can adjourn for a quick

break. Shall we reconvene at 10 o'clock? Thank you.

(Recess.)

DR. HORLOCKER: I'd like to get started with our FDA presentations please. Our first presenter will be Dr. Diane Wysowski who will talk about the spinal/epidural hematomas and bleeds in the U.S. Lovenox users.

DR. WYSOWSKI: From marketing of enoxaparin, or Lovenox, in May 1993 through January 7th of this year, the FDA received reports of 33 patients in the United States administered Lovenox who developed spinal and epidural hematomas or bleeds. Two additional reports were received after January 7th and are not included in this analysis.

I'm here to summarize the 33 case reports for you today. The number 33 may represent the tip of the iceberg since for most adverse events there is significant under-reporting to the FDA.

Also, the reports that we received are sometimes sketchy and do not contain all the information that we would like, and obtaining follow-up information is usually difficult. Despite these problems, we can still summarize information from the cases reported.

As you can see from this slide, most of the cases occurred in 1997. 75 percent of the patients were women. They were elderly. The median age of the patients

was about 77 years. They were administered Lovenox for thromboprophylaxis primarily in association with knee and hip replacement surgery.

Lovenox was also administered for thromboprophylaxis in association with spine and back surgery in 3 patients, hip surgery in 3 patients, and prolonged bed rest in 1 patient who received a steroid injection in her spine. In addition, one woman had repeated administration of Lovenox with knee replacement and two GI surgeries that occurred within a few weeks of each other. A 60-year-old woman had a lateral meniscectomy and a 59-year-old man was administered Lovenox in an IND study for vascular rejection after cardiac transplant. For 2 patients, the indication was not specified.

Except for the patient with the cardiac transplant who received 80 milligrams of Lovenox per day and a patient who received 120 milligrams within the day of surgery, most of the patients for whom dose information was provided received the recommended dose of 30 milligrams b.i.d.

The average and median time from use of Lovenox to onset of neurological symptoms was about 3 days.

21 patients had emergency decompressive surgery to evacuate the epidural hematoma. 1 patient refused the

procedure.

Reports in 10 patients made no mention of surgery to evacuate the clot, and for 1 patient who had a bleed, but no hematoma by MRI, leg symptoms resolved with removal of the epidural catheter.

Not all of the 33 patients had outcome information, but of the 26 who did, 13 were reported to have permanent paralysis. 7 had partial resolution of paralysis or neurologic symptoms and 6 had apparently full resolution of paralysis or neurologic symptoms.

12, or 36 percent, of the 33 patients were administered concomitant medications that likely increased the risk of bleeding. These included warfarin, ketorolac or Toradol, naproxen, aspirin, Persantine, and Timentin administered singly or in combination.

As mentioned previously, the reports sometimes lacked full information, but I counted 23, or 70 percent, of the 33 patients with mention of epidural catheter attempts or placements, including 4 with multiple attempts or traumatic placements. There were 12 patients with specific mention of the catheter left indwelling postoperatively.

Because we do not have controls, we can only speculate on potential risk factors for development of

spinal and epidural hematoma in Lovenox exposed patients. All of the patients for whom there was information had an invasive procedure performed in the epidural or spinal area whether by placement of anesthesia, analgesia, tap, surgery, or injection. All of the 32 patients with data reported had an invasive procedure to the spine if the heart transplant patient who had a thoracentesis and developed a hematoma at the thoracic level is included.

Other potential risk factors include exceeding the recommended dose of Lovenox. The dose was exceeded in 2 patients.

Use of epidural catheters. 23, or 70 percent, of the patients had epidural catheters.

Leaving the epidural catheters in postoperatively. 12, or 36 percent, of the patients had catheters left indwelling.

Concomitant medications that may have increased the risk of bleeding. 12, or 36 percent, were taking these medications.

Older age. 23, or 70 percent, of patients were 70 years of age and older.

And female gender. 24, or 73 percent, were women.

Other potential risk factors include ankylosing

spondylitis, a history of previous laminectomy, repeated surgeries with repeated administration of Lovenox within a short time period, renal and hepatic dysfunction, coagulopathies such as prolonged clotting time and low Factor X, and abnormal blood values pre- and postoperatively.

In an attempt to put the 33 cases into a context of risk, this slide shows the number of syringes of Lovenox purchased by hospitals and long-term care facilities by year since marketing. According to IMS America data, in the four and a half years from marketing through December 1997, about 28.6 million prefilled syringes of Lovenox were purchased by hospitals in the United States. During this period, the number of dispensed outpatient prescriptions for Lovenox increased from about 6,000 in 1994 to about 87,000 in 1997.

If we assume 80 percent of the 28.6 million syringes purchased were used, then 22.9 million syringes were used. If we assume 10 Lovenox syringes were administered to each patient, then 22.9 million divided by 10 equals 2.29 million patients treated with Lovenox since marketing. 33 cases divided by 2.29 million patients treated equals 1.4 cases of epidural hematoma or bleed per 100,000 patients treated with Lovenox.

This reporting rate is equal to 2 to 2.8 times the rate quoted in the literature of 0.5 to 0.7 per 100,000 of neurologic dysfunction due to bleeding after neuraxial blockade. Unfortunately, this reporting rate is limited by possible under-reporting of cases in the numerator and by a possibly inaccurate estimate of Lovenox-exposed persons in the denominator. However, if there is significant under-reporting of cases to the FDA, then the reporting rate would be considerably higher.

In summary, over the four and a half years for marketing of Lovenox through January 7th, 1998, the FDA received 33 reports of spinal or epidural hematomas or bleeds in United States patients administered Lovenox. I've described the characteristics of these patients and mentioned what may be possible risk factors for development of this rare but potentially devastating event. I've also presented information on the use of Lovenox and calculated a reporting rate that shows that the risk of spinal and epidural hematoma in Lovenox users may be higher than the rate quoted in the literature for neurologic dysfunction due to bleeding after neuraxial blockade.

Thank you.

DR. HORLOCKER: Any questions?

I have one. I'm wondering if there are reports

of spinal hematomas in patients that received unfractionated heparin or warfarin that have been reported to the FDA that we haven't published because those two anticoagulant have been around for a number of years.

DR. WYSOWSKI: Actually I could just read this. This is the information that we have currently. 33 reports. These are United States anticoagulant users. 33 in the SRS, spontaneous reporting system; 2 in the medical literature for Lovenox; Fragmin, 0 in the spontaneous reporting system. As you can see, the marketing dates here. Note that Fragmin was marketed in November of 1995, and then the two Norwegian reports that we heard about earlier this morning from the literature. Normiflo, 0 and 0.

And wasn't there a report in the literature that you mentioned for Normiflo this morning? I'm not sure, but in any case Orgaran, 0 and 0; warfarin, 8. Now, warfarin has been available in the United States from about the 1950's, 1950 or so. The spontaneous reporting system came into existence in the United States I guess it was in 1969, late 1960's. So, we have 8 in the SRS dating from 1979 and approximately 17 United States patients not in the SRS that are in the medical literature.

For regular heparin, about 8 dating from 1974,

and 21 reported worldwide in the literature from the review by Vandermeulen plus 11 more from a recent Medline search.

Those are the numbers that we have currently.

DR. HORLOCKER: Yes. Dr. Alving.

DR. ALVING: I would just like to make a comment and that is that from the time of their inception, one of the most attractive features about low molecular weight heparins is that they do not require monitoring, and if they did require monitoring, it would be very difficult because again it would require that anti-Factor Xa assay, which is largely unavailable because of its expense.

It's my opinion that anesthesiologists love to be able to have a handle on the pro time and PTT. So, they're very careful when they know someone is on warfarin or on heparin. But the fact that these low molecular weight heparins do not require monitoring and are not monitored and do not influence the PTT or the PT and yet can have full therapeutic activity, if you were to look at the anti-Xa activity, means essentially out of sight/out of mind for many physicians.

So, I don't consider them any more dangerous than Coumadin or heparin by any means. It's just that we have a handle on Coumadin and we can check the pro time, the PTT, and then decide about invasive procedures, but

this tends not to be the case, at least up till now, perhaps as stringently for the low molecular weight heparins.

DR. HORLOCKER: In addition to Dr. Alving's comments, we can't really reverse the effect of low molecular weight heparin which makes it a little more difficult for us, too. So, exactly.

Yes.

DR. BOTSTEIN: I think that's an important point. There has been a perception perhaps that Lovenox and the other low molecular weight heparins are safer than heparin and Coumadin because you don't have to monitor. In fact, you can't monitor. There's no good, easily available test. We have just changed Lovenox's package insert to say that explicitly. You can't monitor.

DR. ALVING: Hopefully we can discuss this later because, as you brought up, what happens if there is a bleed? The data out there on what to do is essentially nonexistent, and you can only partially reverse it with protamine, but if you have no clue if the low molecular weight heparin is responsible or still exerting its anticoagulant activity, it's hard to know how to treat that bleed and that can perhaps be addressed later.

DR. HORLOCKER: Other questions?

(No response.)

DR. HORLOCKER: All right. We'll proceed then with Dr. Bauer.

DR. BAUER: Thank you for inviting me. I was asked to provide discussion of the biology in clinical use of low molecular weight heparin. Much of what I'm going to say is really an overview and hopefully will focus on some of the issues that have just been brought up in the discussion. It is fairly rudimentary, but I realize we may have a somewhat diverse audience here to review the issue of low molecular weight heparin biology in clinical applications.

Well, heparin and antithrombin III actually were discovered in the 20th century and found to work together, and the way that heparin works as an anticoagulant is by neutralizing many of the serine proteases generated by the coagulation cascade, particularly thrombin Factor Xa but also some of the higher up factors cascade and cascade Factor IXa and XIa and XIIa, albeit to a more limited extent. There are other protease inhibitors that are important for those factors as well.

The mechanism of how heparin actually works as an anticoagulant was clearly worked out around 1970. Antithrombin III at that point was clearly purified.

Heparin was shown to bind to lysine binding sites on antithrombin III and induce an allosteric change in the confirmation of antithrombin III so that it would turn from a relatively slow serine protease inhibitor in terms of neutralizing thrombin and Factor Xa to be able to do it much more rapidly as a classic catalyst. So, thrombin and antithrombin would then form a complex which would then be cleared. The activity of thrombin would be neutralized and heparin could go on to catalyze other antithrombin III, thrombin, or antithrombin III, Xa, IXa interactions.

What was also learned, though, is that it wasn't solely heparin's binding to antithrombin III but also heparin did have some interaction with thrombin in terms of what was called an approximation effect as opposed to this allosteric effect. I'll come back to that because it's related to one of the biological differences between unfractionated heparin and the low molecular weight heparins.

Heparin is a mucopolysaccharide. It contains a heterogeneous population of saccharide chains with roughly a mean molecular weight of 15,000. Low molecular weight is derived from unfractionated heparin by chemical or enzymatic depolymerization methods and has a mean molecular weight roughly around 5,000. But each low molecular weight

heparin preparation is slightly different in terms of its mean molecular weight, as well as I'll get to anti-Xa vis-a-vis antithrombin activity.

A couple of important things about low molecular weight heparin vis-a-vis unfractionated heparin and one of the rationales for why low molecular weight heparin is actually a better drug than unfractionated heparin is in fact it was learned that some of the higher molecular weight species of unfractionated heparin have antiplatelet effects in terms of qualitatively interfering with platelet function. So, if you rid heparin of these higher molecular weight fractions, you get less of this antiplatelet effect. This is distinct from the effect of heparin-induced thrombocytopenia, which I'll touch on as well.

Another important biological property of lower molecular weight heparin as opposed to unfractionated heparin is related to its interaction with thrombin as opposed to Factor Xa. Standard unfractionated heparin, if you look at the larger molecule, as I mentioned for thrombin neutralization by antithrombin, as depicted in this cartoon with this larger guy with this long arm representing the more extended sugar chain, there are domains on antithrombin III through which smaller fragments

of heparin interact, but then when you have more extended domains, you bring in this approximation effect. When you have low molecular weight heparins, like this guy without this very long arm, you don't get this approximation effect and you don't have it with Factor Xa.

So, in fact, low molecular weight heparins have relatively more anti-Factor Xa than antithrombin activity, and that's an important biological difference between these properties. And we'll come then in a minute to the pharmacological differences.

So, to summarize just merely the biological characteristics. Lower mean molecular weight, longer size in terms of saccharide units. There is a critical pentasaccharide unit, a five sugar group that binds to the antithrombin III site. But you can see the mean molecular sizes or in terms of saccharide units between low molecular weight heparin and unfractionated heparin.

As I mentioned, because of the extended domains and the approximation effect, for unfractionated heparin the anti-Xa to anti-IIa activity of the heparin, as measured by its effect on antithrombin in terms of neutralizing thrombin, which is Factor IIa and anti-Xa, there's a 1 to 1 relationship; whereas for the low molecular weight heparins, they vary from 2 to 1 to 4 to 1

based on the property and, as I mentioned, this impairment of platelet function.

So, we have these biological differences, but it's really the pharmacological differences in my view that really make low molecular weight turn out to have a very favorable profile for clinical application, and I really want to spend then the next portion talking about those pharmacological properties.

One of the things that was recognized about unfractionated heparin in terms of dosing is that there is a fair amount of binding to other constituents in the blood in the vascular wall besides antithrombin III. So, in fact, unfractionated heparin will bind to other plasma proteins, other cells, macrophages, monocytes in the blood, also can bind to endothelial cells. So, you do have this nonspecific protein binding of heparin which you do not have with lower molecular weight heparin species.

The other issue and partly as a consequence of the nonspecific binding, when you use heparin at clinical doses, you can see that there are a dose-dependent differences in plasma half-life in clearance so that at relatively low doses that are used for prophylactic regimens you have relatively shorter half-lives. As the dose increases, the half-life becomes more prolonged and

ultimately asymptoting at very, very high doses.

A consequence of this when you use unfractionated heparin in clinical practice for therapy for therapeutic cases, you need to monitor patients in terms of monitoring their APTTs. As has already been pointed out, low molecular weight heparins, because they have more anti-Xa to antithrombin activity, have relatively little effect on the APTT so that the APTT doesn't reflect their anticoagulant activity.

However, despite that, one of the huge advantages of low molecular weight heparin is that because they have less of a nonspecific binding, their T1 half is relatively constant along dose ranging. So, in fact, you can dose people accordingly and reproducibly and get reproducible plasma levels without worrying about monitoring.

So, the advantages then are the predictable anticoagulant response which really makes laboratory monitoring seemingly unnecessary and frankly we don't really know how to actually monitor it reliably in terms of using it in clinical practice. As mentioned the one method of using anti-Xa levels is not that widely available quite yet, and this is because of the dose-independent clearance mechanism of low molecular weight heparin and less

nonspecific binding.

Another attribute of the drug is in fact it has a longer half-life -- low molecular weight heparin does -- as opposed to unfractionated heparin, and for some of the regimens we've heard about, it's allowed not only twice daily dosing but once daily dosing regimens both for prophylaxis and for therapy.

Now, this issue of do they cause less bleeding then -- unfractionated heparin. You have to realize this is a double-edge sword because we're trying to prevent thrombosis, but the tradeoff is bleeding. So, all of this becomes in the eye of the beholder in terms of weighing off the relative antithrombotic efficacy versus the bleeding risk, and I think you have to keep those two things in mind when you say it causes less bleeding.

But there are some advocates who claim that it does cause less bleeding when given in therapeutic doses. But as I say, I think some of this is in the eye of the beholder and it is a double-edge sword because you have to look at the counterpart side in terms of looking at antithrombotic efficacy. Clearly, if you go to much, much higher doses, you can improve your antithrombotic efficacy, but at a cost.

There's also seemingly an attribute of low

molecular weight heparin, that it has a lower incidence of this problem of heparin-induced thrombocytopenia. I won't discuss it in great detail, but this is something that clinicians using heparin need to be aware of because about 5 percent of people getting unfractionated heparin can develop thrombocytopenia and about 10 percent of that 5 percent, if you will, can develop paradoxically thrombosis which, in the presence of heparin-induced thrombocytopenia, can be very morbid and even result in mortality.

This just summarizes something from the Medical Letter, and I know it's a moving target in terms of the FDA-approved indications. It just shows you the various preparations: enoxaparin, dalteparin, ardeparin. And important to realize for clinicians, as we've heard about, each of the drugs has a different dosing schedule when used for prophylaxis, and of course they have somewhat different indications with enoxaparin for hip and knee replacement, abdominal surgery, and dalteparin for abdominal surgery, and ardeparin for knee replacement, and danaparoid, the heparinoid, which as we've heard about is a different compound for hip replacement.

I think a lot of the use in this country, as we've heard about, is in orthopedic surgical replacement. I think this population obviously is the group of patients

who is at highest thrombotic risk. And as we've heard about, the thing we're really worried about is fatal PE with reporting rates without prophylaxis now somewhere between 1 and 10 percent and calf vein DVT between 40 and 80 percent and proximal DVT 10 to 30 percent if there is no prophylaxis.

There are other situations between hip and knee arthroplasty that carry high thrombotic risks, major surgery for the pelvis, also major surgery in extensive cancer, but I think we'll focus on the orthopedic hip and knee arthroplasty.

We've already seen some of this data. This was really some of the initial randomized trials at this point in hip replacement comparing the low molecular weight heparin or lomoparan or the heparinoid danaparoid versus placebo in terms of its efficacy in reducing DVT. This is total DVT, showing that these compounds were highly efficacious in reducing DVT with bleeding risks at least for enoxaparin and placebo that were quite comparable.

So, it's safe and effective. How about for hip replacement overall? Actually there still is a school of thought that likes to use warfarin postoperatively in the United States, and this is data actually from Hull and Pineo from a couple of studies they did I think with a

different low molecular weight heparin that's not licensed in the United States.

But if you look across hip surgery in terms of venous thrombosis and prophylaxis, warfarin and low molecular weight heparin were roughly comparable in this analysis. You will find different results from some different studies when you compare these two, but you already heard from the consensus conference that they considered low molecular weight heparin or warfarin started postoperatively as alternatives for hip replacement.

Knees are more problematic and still remain so. They still have a relatively high thrombosis rate even with low molecular weight heparin, quite high in this series, still 45 percent, but showing that in knees that low molecular weight heparin was more efficacious than warfarin.

I want to really now just briefly turn to therapy. I know it's not the purview of the deliberations here to address this issue, but I think it's obviously coming down the track in terms of use certainly in the U.S. And I want to review the topic very briefly just to round things out.

This was one of the initial studies, the initial treatment studies, for patients with venous

thrombosis, done again by Hull's group, comparing low molecular weight heparin now with dosing that was weight-adjusted, unmonitoried therapy, in hospital compared to unfractionated heparin using usual dosing regimens with monitoring.

They showed in this study that both at 10 days and 3 months that the results with low molecular weight heparin unmonitored in therapeutic doses was as good, if not better, both in terms of preventing recurrences, in terms of bleeding complications, at least for major bleeding complications, and finally suggesting for mortality as well that it was at least as good as unfractionated heparin.

Obviously, if you then have a compound that can be administered -- and low molecular weight heparin has been in all these studies administered subcutaneously whereas heparin has usually been used intravenously is another advantage that you can give the drug without the need to have a constant IV and the attention that goes with the IV.

Finally, all the treatment issues that have gone beyond that -- and I think this is of great interest to the clinicians out there who are in practice, and of course, with all the pressures going on to shorten length

of stay, we've seen now a number of trials comparing home treatment for venous thrombosis using low molecular weight heparin unmonitored as compared to inpatient treatment, indicating that home treatment of deep venous thrombosis in selected patients who don't have significant other comorbidities is as effective as inpatient hospitalization with unfractionated heparin.

This has been extended, at least in the inpatient setting, to the treatment of pulmonary embolism with only exclusions in one of the trials for massive pulmonary embolism requiring lysis or embolectomy using different low molecular weight heparin preparations -- two studies in the New England Journal this year or just last year -- and finally, extending it across to unstable angina patients with several different low molecular weight heparins, both dalteparin and enoxaparin, comparing low molecular weight heparin with unfractionated heparin, suggesting -- indicating actually -- significant improvement in outcomes with low molecular weight heparin over unfractionated heparin. This again is unmonitored.

I think clearly the advantages in being able to give a drug for therapy, as well as potentially prophylaxis, in terms of getting better clinical outcomes in terms of antithrombotic efficacy, relate to the fact

that you get patients into a therapeutic range immediately when you give a low molecular weight heparin. I think when you use it in orthopedic prophylaxis too, as opposed to using, let's say, a warfarin program postoperatively, you're immediately getting your antithrombotic effect from your low molecular weight heparin. Whereas when warfarin has been used postoperatively, it takes several days for the antithrombotic effect to build up. So, I think you do get the advantage in that respect, but of course it is a double-edge sword.

I'll stop there.

DR. HORLOCKER: Questions for Dr. Bauer. Dr. Palmer.

DR. PALMER: A clarification. Is there an agreed upon definition of proximal DVT?

DR. BAUER: There is. Occlusion of the popliteal vein or above.

DR. PALMER: So, we're still talking about leg clots, not intrapelvic or intra-abdominal clots.

DR. BAUER: Well, in almost all of these studies, the ways in which the clots are visualized in these orthopedic surgical things are usually venograms actually. So, their definition of it is that.

But I might add that those studies also do look

at calf vein thrombosis, so you have to look at calf vein and proximal. With the data I was presenting, I was lumping everything together and not subdividing as you heard from previous speakers, proximal and calf vein. They don't obviously visualize pelvic clots in these studies.

DR. HORLOCKER: Other questions? Dr. Alving.

DR. ALVING: For the purposes of my thinking about low molecular weight heparins -- and I want to see if you agree with me, Ken -- is I consider them all equal except for heparinoid. That's in a class by itself because, as you've said, the anti-Xa activity to thrombin is 22 to 1. The rest of them are like 2 to 1, 4 to 1.

So, although we have different indications and slightly different dosings, they really aren't that different when you look at all of them. So, I consider low molecular weight heparin A equal to low molecular weight heparin B. Only one is expressed in terms of milligrams, but it has a specific activity of about 100 units per milligram. So, as you've done, you can convert it to anti-Xa units. I think maybe I just have to think real simply like that, but when I do, it's much easier to understand the whole gamut of what we're trying to talk about here.

Do you agree with that, or do you have any other ideas?

DR. BAUER: Yes, I think as a class they're quite similar, and I do tend to think about them quite globally. I think as we look across clinical studies at outcomes, I think the results with one preparation at a given dosing regimen compare pretty well across another.

But I think one has to still be a little bit careful because each one is dosed slightly differently, even for prophylaxis and therapy. Some people talk about milligrams and units, and while there are clear-cut easy conversions, I think what's clearly come out in prophylaxis is that dosing is different from one compound to the other.

I think that's only important in terms of clinicians and pharmacies as they start to use more of these one compounds to realize and for clinicians to realize that keep your dosing straight based on what are the approved dosing schedules for each one. I would be fairly religious in sticking by what the manufacturer and clinical studies have shown what the recommended dosing regimens are across the board, particularly for prophylaxis. Once we get to therapy, I think there may be more nuances.

I think one of the issues I didn't mention and worth mentioning are issues of the -- since it is primarily renally excreted, the cautions that are going to have to be

made for patients who have significant renal dysfunction -- and I think as these come into much, much wider uses, in sicker patients, particularly medical patients for therapy, I think we're going to need to be cognizant of that. It may push this issue of monitoring for us because I think in those patients we're probably going to need start monitoring, and we're going to have to fall back on anti-Xa units, however imperfect they are in terms of monitoring.

DR. TALARICO: I would like to add that as far as we're concerned, they're all different drugs. They are new molecular entities which differ one from the other. The only thing they share is probably the indication. If one works for thromboprophylaxis of hip replacement, another one would work, but you cannot possibly interchange based on anti-X activity. In other words, if a patient needs 5,000 units of anti-X, you cannot use any one because the ratio of anti-X to anti-II is quite different from one to the other. There might be other subtle differences which we don't know yet about it. So, we want to be clear that they are not interchangeable.

DR. BAUER: It's obvious I'm not a regulator.

(Laughter.)

DR. HORLOCKER: Any other questions?

(No response.)

DR. HORLOCKER: I'll introduce myself as the next speaker then.

What I'd like to do for about the next 10 or 15 minutes is just give an anesthesiologist's perspective on the risk of spinal hematoma in patients that are undergoing regional anesthetic techniques and try to put the relative risk of the other anticoagulant drugs in perspective with the low molecular weight heparins just to give you a brief overview on this. If you'd like to go into any detail, I'd be happy to do that, but I wanted to just keep this discussion fairly brief.

First of all, we all agree that this is a very rare event, and the most recent calculation of this was done by Michael Tryba in 1993 where he assumed that the incidence of spinal hematoma in patients undergoing epidural anesthesia was 1 in 150,000, which is higher than that of patients undergoing spinal anesthesia, which he reported as 1 in 200,000.

The etiology can be anything. It doesn't have to just be from the trauma of needle placement. You could have a patient with a preexisting vascular malformation. There could be a preexisting undiagnosed neoplasm, and you could just be in the wrong place at the wrong time.

There also are spontaneous spinal hematomas

that have occurred, and as of about 1980, there have been 100 spontaneous spinal hematomas reported. About 25 percent of those occurred in patients that were on oral anticoagulant drugs.

So, again, as anesthesiologists, we can just happen to be in the wrong place at the wrong time. Sometimes I wonder a little bit about this because if you look at the level of needle placement in the case reports and the level of where the spinal hematoma occurred, it's not always that close in proximity. Again, it's the smoking gun. We had a needle back there and we're blamed for it, but we have to be aware that these do occur spontaneously.

The site of bleeding tends to be the epidural space just because of the prominent venous plexus, although you'll notice after some of the spinal anesthetics, there were subarachnoid bleeds and then actual compression of the spinal cord from intrathecal blood collection.

Vandermeulen reviewed all of the English and non-English literature in 1994 and published the most comprehensive compilation of spinal hematomas associated with regional anesthesia. There has not been a more recent one since then.

He was able to find 61 cases of spinal hematoma

associated with spinal or epidural anesthesia. It's really important to note here that 68 percent of the patients had evidence of some sort of hemostatic abnormality and by far the most representative hemostatic abnormality was caused by some form of heparin, whether it was unfractionated subcutaneous or intravenous heparin, or low molecular weight heparin. In fact, 4 of those 25 were low molecular weight heparin preparations.

There was 1 patient on an oral anticoagulant drug and 3 patients on antiplatelet agents, including one that was on Ticlid.

Now, I just would like to stop for a moment and talk about the antiplatelet problem. When you consider how prevalent antiplatelet therapy is, especially the one aspirin a day that nearly all of us in this room are probably on, the fact that there are only 3 reported spinal hematomas among these patients is truly remarkable. Most anesthesiologists do not consider antiplatelet therapy by itself, a contraindication to regional anesthesia and most people do not even advise checking a bleeding time prior to spinal or epidural needle placement. So, I think we have to keep that in mind when we go about trying to establish guidelines, that antiplatelet agents by themselves are not a clinically significant risk factor for spinal hematoma.

There were also 2 patients that were on thrombolytic therapy and 11 patients that had a preexisting coagulopathy from thrombocytopenia or hemophilia.

Needle placement was described as difficult in 25 percent or bloody in 25 percent of the cases, and these have been previously identified as risk factors by Eddie Owens who did a review of the literature back in the 1980's.

When you break down what the anesthetic technique was, you can see that 15 of these 61 were spinal anesthetics and 46 were epidural anesthetics, including 6 single dose and 32 continuous catheter. As usual, there are always some that we just cannot really classify, and there were 8 unspecified epidural anesthetic techniques.

12 of the 32 indwelling epidural catheters that we know of were removed in the presence of systemic heparinization. In about half of those, they were actually therapeutically anticoagulated. So, this is what most of us would consider a true breach of practice, to remove a catheter while a patient is anticoagulated to a therapeutic level.

An important bit of data that Vandermeulen noted that had never been previously reported was that the spinal bleeding occurred at the time of catheter removal in

nearly half of the cases.

Now, before this report came out, we used to have discussions about how traumatic is catheter removal. We used to think that it was needle and catheter placement that caused the significant trauma and that we didn't have to be careful about what happened while the catheter was in and most importantly what the patient's hemostatic status was at the time of catheter removal.

However, Vandermeulen raised this issue for the first time and it has come up in subsequent reports also. We do have to be aware of what the catheter removal is.

As far as the neurologic outcome, interestingly enough 3 of the patients who were neurologically intact died of unrelated causes and were found to have a spinal hematoma at autopsy. However, the really disappointing bit of information here is that only 40 percent had a partial or good neurologic recovery, and I think this is pretty similar to what we've seen in our 33 cases that have occurred here within the United States.

We have to note what time the laminectomies were performed relative to the initiation of neurologic symptoms. For example, in these patients there were 15 laminectomies performed, but 10 were performed within 8 hours of the development of paraplegia. In other words,

they had an early intervention.

There were also several patients that had complete or partial spontaneous recovery, and 6 in which we don't know the intervention.

Unfortunately, about 50 percent of the patients had poor neurologic recovery despite the fact that 17 of the 29 actually had laminectomies performed. However, look at the timing of these laminectomies. 10 were performed more than 24 hours after the development of paraplegia, and I think that's another lesson that we can take home today when you review these 33 cases. Many times the patients were neurologically symptomatic for a long time, at least 12 or 24 hours before an intervention was taken, and we have to be aware of not only the risk of spinal hematoma but what to do when one develops.

In addition, there were some patients that didn't undergo surgery, 4 in which the intervention was not reported, and 6 of the 61 in which the neurologic outcome was unknown.

Jumping now to the low molecular weight safety factors. The first report was in the French literature back in 1991 by Schwander and Bachman. They reviewed the practice in France and noted that spinal or epidural anesthesia was given in combination in a large number of

patients. Particularly, 5,000 patients received standard subcutaneous heparin, various doses, various dosage schedules. However, there were also 14,000 patients noted by them that had received some formulation of low molecular weight heparin, but they were different formulations, different doses, and different dosage schedules. So, we can't make any real major results from this study. However, among those 14,000 patients, there were no neurologic sequelae reported.

Bergqvist performed the next review back in 1992, and at that time by looking at the literature of the combined cases and studies that had been done, he could document 9,013 patients that had received spinal or epidural in conjunction with low molecular weight heparin thromboprophylaxis. There were no cases of spinal hematoma among those patients, and at that time the pharmaceutical companies in Europe estimated that approximately a million patients had safely received the combination of low molecular weight heparin and regional anesthesia.

Now, at that time Michael Tryba in Germany had reported a single case report, and that was published in 1989. Subsequently there were several more, for a total of 10 cases that had been reported and published in Europe, and that includes the 3 Norwegian cases that we heard about

today. So, there are a total of 10 cases in Europe that have been reported over about a 10-year period.

John Heit and I looked at the United States experience with low molecular weight heparin recently. First of all, we went to all of the English literature because I can't read French or German very well, and we were able to document that among all the studies that have been performed worldwide but published in English, 15,000 patients that have received spinal or epidural anesthesia in combination with low molecular weight heparin.

You can see that about half of those were spinal anesthetics, several of which, 20 specifically, were continuous spinals, and there were about 3,000 epidural anesthetics. Only 457 were specifically identified as continuous epidurals. In most of those cases, we don't know if an epidural catheter was left in or not, and we can't make an assumption one way or the other because many times in Europe, they do a single-dose epidural technique which is different than typically the way we practice here.

There were also nearly 5,000 patients that underwent some sort of regional anesthesia. They would say spinal or epidural anesthesia, but we don't know, and there is a significant difference because of the needle gauge and the possible placement of a catheter.

Over those 15,000 patients, preoperative dosing was initiated in nearly 90 percent of the cases, and the low molecular weight heparin was administered once daily in over about 95 percent of the cases. So, again, you can see this really represents a lot of the European experience relative to the United States formulations which are given twice daily.

At that time, there were 8 published case reports in the literature in Europe and the United States and also 16 that had been reported to the FDA. This was complete up through December of 1996. So, the additional cases have all occurred in 1997, as Dr. Wysowski has gone over.

So, when you put those together, John Heit's report included 24 spinal hematomas associated with regional anesthesia. You can see the tally is very similar to what we have even now, a lot of continuous epidurals, 1 single-dose epidural, 3 spinals, including one that was a spinal after a failed epidural, and several unspecified.

As in Vandermeulen's study, we noted that 7 of the 18 patients with indwelling catheters became paraplegic or had worsening of their neurologic deficits upon catheter removal. So, we again documented that we have to be aware of what goes on in the patient's hemostasis at the time of

catheter removal.

When you look at additional risk factors, there were several of the patients that had received intra-operative dextran and intravenous heparin, 5 that were on antiplatelet medications, and most of these were Toradol. 6 patients received preoperative low molecular weight heparin therapy, and there were 12 in which the low molecular weight heparin was initiated within 24 hours. So, you can see 18 in that short time, right around the performance of the regional anesthetic technique.

So, what is different between the United States and Europe? Why have we had more case reports than have been reported in Europe?

There could be a difference in the reporting system. There's no doubt on that. However, when I go to international meetings, anesthesiologists in Europe are not concerned about the risk of spinal hematoma among these patients. They feel that they have established practice guidelines and that they can safely perform regional anesthesia in a patient receiving low molecular weight heparin.

Michael Tryba has performed a recent survey and documents approximately 50,000 epidural catheters are left in over 24 hours in Germany every year. So, you can see

they really do practice what they believe, and they are leaving epidural catheters in these patients. However, we have to look at what their recommendations are for the safe practice of anesthesia among the populations.

You can see here that they actually delay the first dose of low molecular weight heparin until 8 to 12 hours postoperatively. If the patient is on preoperative medication, they wait at least that amount of time before they place a needle or catheter. So, you can see they have a patient with normal hemostasis at the time of needle or catheter placement.

In addition, when they remove the catheter, they wait another either 2 or 8 hours, depending on whether it's the Scandinavian guidelines or the German guidelines of when that subsequent dose can be administered.

They also have very stringent guidelines for monitoring the patient's neurologic status. They formally go in and make sure that the patient is able to -- you know, document a normal neurologic exam.

We have to remember, though, they have the advantage in that they give a smaller daily dose, and they give the dose only once daily. That is very simple to find a trough during which you can place and remove a needle and catheter. It's a little bit more difficult here.

There's also some data that suggests perhaps they are a little bit innovative in their thinking and they decided to put more spinals than epidural anesthetics among these patients. So, there could be just a switch to the less traumatic regional anesthetic techniques also that have assisted with the lack of a problem with spinal hematoma among the Europeans.

So, in summary then, we know that bleeding can occur after any regional anesthetic technique. However, when it occurs in a fixed and concealed space, such as a spinal canal, the results can be catastrophic. I think that most of us here would believe that spinal hematoma is probably the most catastrophic of all of the regional anesthetic complications.

Fortunately, it's a rare event. Unfortunately, for us because of that, it's difficult to truly identify risk factors as a randomized study, and we have to base our practice guidelines on the pharmacology of the drugs. We've talked about the anti-Xa level and the lack of being able to accurately monitor that and having to rely heavily on the pharmacology.

We have to look at the clinical studies in patients that have safely received these medications, as well as the case reports of the patients that have

developed spinal hematomas while receiving the medications and undergoing regional anesthetic techniques. Based on that, we can come up with an anesthetic management on an individual patient basis that should be safe and effective and allows DVT prophylaxis, as well as adequate analgesia perioperatively.

Thank you.

Any questions? Yes. Please identify yourself for the stenographer.

DR. MAGNANI: Dr. Magnani, Organon.

Dr. Horlocker, the figure of 1 in 200,000 to 1 in 150,000 for patients who don't have an anticoagulant, do you think that's the tip of an iceberg, or do you think it's a realistic figure to compare the anticoagulants with?

DR. HORLOCKER: I think we have to know what a perfect world is before we can assess a relative risk. So, I think we do need to know if there's a risk at all, what the risk would be if they aren't on anticoagulant medications, and then say what is the risk with the anticoagulant medication, and is it an undue risk relative to the benefit for the individual patient. So, I think that is a fair comparison.

DR. SHAKIR: Shakir, RPR.

The point which you made about antiplatelet

agents and their effects on anticoagulation, do you extend that to agents like ketorolac or the higher doses of oral NSAIDs and you put them in the same category as low-dose aspirin?

DR. HORLOCKER: Actually low-dose aspirin would be the most effective antiplatelet regimen, and we all know that because they say take a baby aspirin a day or one aspirin a day. If you think about that, higher doses of aspirin start inhibiting the endothelial cells which have a fibrinolytic effect. So, actually higher doses of aspirin are safer relative to low doses.

I would group them all together. There is a study in the neurologic literature by Ruff and Dougherty published I believe in 1981, 342 patients that underwent lumbar puncture for evaluation of cerebral ischemia. The patients developed 2 percent incidence of spinal hematoma and a multivariable analysis identified pre-lumbar puncture aspirin therapy as one of the risk factors in association with concomitant heparinization within 1 hour. So, there is data to support even with unfractionated standard heparin that the combination of heparin and aspirin together is a more potent anticoagulant effect and could increase our risk of spinal hematoma.

Yes.

DR. CARLISLE: Sue Carlisle, panel member.

Do we have any information in the pharmacology of these drugs with renal insufficiency, and is that a separate category that we should be thinking about?

DR. HORLOCKER: I'd like to refer that to the hematologists and Dr. Talarico.

DR. TALARICO: The relationship?

DR. CARLISLE: In patients with renal insufficiency, how are these drugs --

DR. TALARICO: Oh. They're eliminated much more slowly, so there is an increased effect. In fact, the only monitoring which seems to be now more and more accepted is in patients with renal insufficiency. This should be monitored by Factor Xa.

DR. CARLISLE: And do we know at what level of renal insufficiency one should become worried about the use of these drugs?

DR. TALARICO: I don't know that that is clearly established, but probably you don't need very, very severe renal insufficiency. Elderly patients, for example, might be more susceptible to the effect of the drug. An elderly subject may have borderline or mild renal insufficiency.

DR. ALVING: I'm not aware of data from --

well, the data that I am aware of or guidelines that I am aware of are from studies done in Europe with the Orgaran product, and I don't know if there are other products, but they have I think put into recommendations some guidelines.

Then you'd say, well, why do you want that when it's used prophylactically? Because actually the Orgaran product, the heparinoid, is the only thing that we have available that we can treat when patients develop heparin-induced thrombocytopenia with or without thrombosis because it really is a lifesaving drug. So, there we really do care about using it. But they do have some guidelines.

But I think that's an excellent point, especially as we get into the use of drugs for the active treatment of DVT and PE which is not FDA-approved but which is often approved at a local pharmacy and therapeutics committee level by some hospitals because clinicians are running away with this use of low molecular weight heparin.

DR. HORLOCKER: Do you have a question? Could you identify yourself and your affiliation?

DR. RHODES: Yes. My name is Gerry Rhodes. I'm with drug metabolism and pharmacokinetics at Rhone-Polenc Rorer.

I'd just like to make a comment on the issue with renal insufficiency. I think for enoxaparin, for

instance, in mild and moderate cases of renal insufficiency, we have not seen significant changes in the pharmacokinetic characteristics of enoxaparin. The biggest changes that we have seen are in patients with renal insufficiency that would be characterized as creatinine clearance below 30 mls per minute. That's where we have seen the biggest differences.

So, I think my comment would be that dosage adjustment may not be necessary in mild and moderate renal impairment, but perhaps only in severe.

DR. TALARICO: Pharmacologically. If you do pharmacology studies, you do pick up a difference in excretion of the drug with mild renal insufficiency. Clinical studies have shown that you really need severe renal impairment to make a difference. As you mentioned, there was no difference with mild renal impairment in terms of safety.

DR. HORLOCKER: Yes, sir.

DR. MUNTZ: I'm Jim Muntz. I'm an associate professor of medicine and assistant professor of orthopedic surgery at Baylor in Houston. I'm a consultant to RPR.

Excellent talk.

When guidelines or pathways are set up, I think one of the weak points of some of these things are that

doctors will have to be meticulous on finding out what medications people are on. Aspirin, motrin, all the anti-inflammatories. Are they truly stopping these drugs a week before they come to the hospital? Some of these people take these drugs up until one day before surgery. Then we come in, we're using an epidural catheters, we're using enoxaparin. I think we have to be meticulous as physicians to get these people off drugs at the appropriate time before we ever see them in the hospital.

DR. HORLOCKER: Yes, sir.

DR. PINEO: I'd just like to make a comment about Xa and IIa levels because I think there's a sense here that they will help detect patients who may be at risk of bleeding or having thrombosis. And I don't think that's true.

We do see good outcomes in terms of efficacy in patients on treatment with either once or twice a day low molecular weight heparin. For many hours of the day, they have barely detectable Xa levels or antithrombin levels.

In the study that Ken Bauer mentioned, a treatment study comparing heparin and low molecular weight heparin, we drew these levels, Xa and IIa levels, if the patient had major or minor bleeding or a thrombotic event. As many other people have shown, there was no correlation.

So, I think with the exception of renal failure where they may be a good argument made for measuring Xa levels, I haven't seen any convincing evidence that it's useful in other settings. So, I would hope that we don't go back to doing Xa levels which may have very little clinical relevance.

DR. HORLOCKER: Any other questions?

We can proceed with the open public -- I'm sorry. Dr. Bauer.

DR. BAUER: One area we didn't discuss is dosing implications, particularly for very obese. I think we heard some data about some people who are light or under 60 kilograms about not being an effect in some of these studies in terms of spinal hematomas, but I wonder whether we actually have data about people who are way above their ideal body weight in terms of pharmacology. Maybe one of the industry representatives has direct information. I think it's one of the precautions too that's written in there.

DR. TALARICO: Some preparations have the limit of the dosage over a certain number of kilograms. So, that is taken into consideration.

Going back to some dosages like, for example, Lovenox 30 milligrams b.i.d., we should consider also the

opposite, very small individuals. A fixed dose may be a relative overdose for somebody who has a very small body size.

I would like also to address again the monitoring of these drugs. Monitoring for low molecular weight heparin would not be that valuable to detect a risk factor. What we are concerned of is that it might give a false sense of security to the practicing physician. If a physician gets an APTT which is normal, they might think that nothing can happen to this patient, that there is no abnormality of hemostasis that may result in increased bleeding. I don't think that has been emphasized enough with low molecular weight heparins. The normality of PT, PTT, clotting, tap, whatever test that one wants to use, does not mean that the patient is not at risk of bleeding.

DR. ALVING: My interest in monitoring would be in the patient who's receiving this and is bleeding, and I would like to know is there still a sufficient amount of low molecular weight heparin on board as evidenced by an anti-Xa level that I should now try to do something with protamine or something creative with some factor, or is this indeed nothing that requires attention directed at the low molecular weight heparin. I agree to monitor for monitoring's sake should be done with clinical trials, but

I would like to have it when I'm faced with a bleeding patient who has been taking low molecular weight heparin because then I don't have a clue as to really where to start.

DR. TALARICO: True. Yes, if that leads to introducing a therapeutic measure, absolutely. But again, the normal PTT does not indicate that the patient's hemostasis is not affected.

DR. HORLOCKER: Yes.

DR. PINEO: I'd like to make another comment following up on the comment about weight. Weight in people on continuous intravenous heparin is clearly a risk factor for bleeding. So, the lower the body weight, the higher the risk of bleeding and the higher the heparin levels per dose.

But we and other people have shown that there are two other factors and they're coming out in these studies too I think. One is age over 65. Others have shown that as independent variables, taking weight into account, and the other is female gender. Females over the age of 65 are at increased risk. So, age and gender are additional independent risk factors for bleeding upon regular heparin, and it's likely that that's having some impact here. The data do show that most of these people

happen to be women over 75. This may be useful when you're looking at your practice guidelines.

DR. HORLOCKER: Other questions. I'm sorry. Go ahead.

DR. MAGNANI: I may be saying something heretic here because there's a lot of orthopedic surgeons about, so I better be careful.

I really don't think that the anti-Xa levels -- and I want to confirm what other people have said -- have anything much to do at the level that we're dosing for DVT prophylaxis with either bleeding or with antithrombotic activity. One should be guided by the amount of drug that the manufacturer has recommended for these indications.

My feeling for Orgaran is that most of the severe bleeds that we've seen have been surgical bleeds which have been exacerbated by the drug. That's why I say I may be treading on some sensitive toes, but in fact in such circumstances, you may find very low anti-Xa levels but severe bleeding. So, you wouldn't learn anything by doing an anti-Xa level.

DR. HORLOCKER: We can proceed with the open public hearing then if DuPont is ready to do that. Is Dr. Grandison here?

DR. GRANDISON: Madam Chair, Dr. Talarico,

members of the committee, and ladies and gentlemen, I'm David Grandison from DuPont Merck Pharmaceutical Company.

DuPont Merck appreciates the opportunity to address the committee. DuPont Merck shares the agency's concern about the safe use of anticoagulant drugs in patients who undergo epidural and spinal anesthesia or spinal puncture.

DuPont Merck's oral anticoagulant, Coumadin, has been marketed since 1954 to address the concerns about the use of warfarin in patients who undergo epidural/spinal anesthesia or puncture. During this presentation, I will attempt to summarize our review of pertinent Coumadin labeling, our adverse event database, and the clinical literature.

The next slide shows that within the Coumadin labeling in the contraindication section, Coumadin is contraindicated in spinal punctures and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding, as well as major regional, lumbar block anesthesia.

In the warnings section of the labeling, it states, the most serious risks associated with anticoagulant therapy with sodium warfarin is hemorrhage in any organ or tissue. The risk of hemorrhage is related to

the level of intensity and duration of anticoagulation therapy.

It indicates further for cautions, caution should be observed when Coumadin is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage is present. The decision to administer anticoagulants in the following conditions must be based upon clinical judgment in which the risks of anticoagulation therapy are weighed against the benefits. One of these conditions is in fact the indwelling catheters that you see at the bottom.

Under the adverse reactions section of the package insert, it states potential adverse reactions to Coumadin may include fatal or nonfatal hemorrhages from any tissue or organ. This is a consequence of the anticoagulant effect. The signs and symptoms and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdominal, joint, muscle or other pain; dizziness; shortness of breath, difficulty breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock.

We have reviewed adverse reports to DuPont over the past 30 years as well as pertinent literature over this

same period of time. During the period of time, we have identified only four cases of epidural or spinal hematomas following epidural anesthesia or spinal puncture in association with the use of warfarin. This slide summarizes these four cases, and let me just briefly review those for you.

The first case involved a 19-year-old female with a complex medical history of renal disease requiring hemodialysis and a history of grand mal seizures with neurological deficits. The patient was diagnosed with a lumbar, sacral, subarachnoid hematoma about 6 hours after an atraumatic lumbar puncture. Warfarin therapy was discontinued 1 hour prior to the lumbar puncture. However, the patient remained therapeutically anticoagulated for at least 3 days. This patient subsequently died following a fall.

The second case briefly involved a patient, a 51-year-old female, who had a diagnostic lumbar puncture while receiving heparin. Approximately 3 days later, she began taking warfarin concomitantly with heparin. Although neurological signs and symptoms developed on the day warfarin was initiated, the diagnosis of a hematoma was not made until 10 days after the initiation of warfarin. The patient's neurological symptoms improved with treatment.

The third case involved a patient with an indwelling epidural catheter that was inserted during orthopedic surgery and used postoperatively for 3 days for analgesia. An epidural hematoma is thought to have occurred when the catheter was removed and while the patient was therapeutically anticoagulated with warfarin. The patient recovered with only a residual right foot drop.

The fourth cases involves a patient, a 47-year-old male, whose warfarin was stopped approximately 4 days prior to epidural anesthesia for varicose vein surgery. The patient developed an extradural hematoma resulting in paraplegia that did not resolve.

A review of the pertinent literature indicates that there are four published studies in which a total of 746 patients on warfarin had epidural or spinal anesthesia associated with orthopedic surgery. No epidural or spinal hematomas were reported among the 746 patients.

In summary, we have identified in our review only 4 patients who have developed epidural or spinal hematomas associated with the use of warfarin following epidural or spinal anesthesia or spinal puncture. The results of our review indicate that epidural or spinal hematomas associated with the concurrent use of warfarin and spinal/epidural anesthesia or spinal punctures appears

to be a rare occurrence.

An explanation for this low number of events may be that clinicians understand and don't minimize the risk of Coumadin therapy in patients undergoing these procedures. In addition, physicians understand and follow the information in the current Coumadin labeling under contraindications, warnings, and adverse events.

In conclusion, based on our extensive review of our company's adverse event database and pertinent literature during the past 30 years, epidural or spinal hematoma appears to be a rare occurrence in association with warfarin therapy in patients requiring epidural and spinal procedures. Hence, we believe that the current labeling has been adequate to protect this patient population.

Although DuPont Merck has not had the opportunity to review all of the data related to the risk of epidural or spinal hematomas with the use of low molecular weight heparin products in patients having these procedures, our data indicates that the event seems to be much lower with the use of warfarin. Therefore, we believe that the proposed class labeling and boxed warning for low molecular weight heparins should not be extended to include warfarin products.

Thank you very much.

Any questions?

(No response.)

DR. HORLOCKER: We can proceed then with Pharmacia's open public hearing statement.

DR. ROSENQVIST: I'm Marten Rosenqvist representing Pharmacia & Upjohn.

As a manufacturer of heparin, Pharmacia & Upjohn feels that the risks of spinal hematoma in patients having regional anesthesia are increased with any method of anticoagulation, including IV and low-dose subcutaneous heparin.

To exclude other products affecting coagulation parameters implies a greater degree of safety which is not supported by our data.

We recommend the inclusion of a black boxed warning in our insert for heparin.

Thank you.

DR. HORLOCKER: Questions?

What's the committee's decision? Would you like to have a longer lunch or start some of our discussion now? Start discussion?

DR. WYSOWSKI: That's my preference.

DR. HORLOCKER: What I'd just like to do for

about five minutes here is just try to summarize very briefly some of the important things. I want you really to help each other with the discussion on this. The considerations that I'm making are not only as the acting Chair of this advisory committee but also as someone who's very interested in regional anesthesia because I think we have to keep everything in perspective and keep our discussion balanced. It's not just what the risk of this but also in terms of benefits to our patients.

We know that low molecular weight heparin is a very efficacious thromboprophylactic agent. It's probably the most commonly used agent in Europe, and it's among the top two in the United States.

In addition, the previous studies back in the 1970's by Modig show that there were decreased thromboembolic complications in patients that underwent regional anesthesia. None of those patients, importantly, were anticoagulated even with aspirin. So, it's only been recently with the article that I previously cited by Eriksson in the New England Journal where we show that even in the presence of low molecular weight heparin or hirudin anticoagulation, there is an additional benefit of having a regional anesthetic.

What we really need to do is to perform a study

to show what degree this addition or synergy is so that we could perhaps reduce the amount of anticoagulant that's delivered pharmacologically while patients have an indwelling epidural providing a sympathectomy and still come up with the same rate of DVT frequency. That's really what one of our challenges is for the future.

We have to keep in mind that in Europe the risk of spinal hematoma does not appear to be clinically significant. They do have sporadic cases. There's no doubt about that. They've established practice guidelines and it seems to have decreased the frequency of this, although not completely eradicated it as a problem.

So, the objectives of the committees here today -- we have Dr. Talarico from the Anticoagulant and Gastrointestinal Drug Committee, we have some very esteemed guests, and then we have the members of our Anesthetic and Life Support Drugs Committee -- is to find out -- I'd like to get more details from Dr. Talarico about the alternate dosing of low molecular weight heparin available for the hip patients and if this will be extended to the total knee arthroplasty patients because basically this is establishing the European dosage schedule within the United States which at least as an anesthesiologist I feel much more comfortable with, delivering a regional anesthetic

among those patients.

In addition, we have to advise the FDA on product labeling, whether the proposed changes are enough or whether we need additional changes. And if they aren't, what changes do we need? Are there additional investigations, is there additional information that's needed before we can make prudent guidelines for the management of patients that undergo regional anesthesia while receiving low molecular weight heparin thromboprophylaxis?

Then in addition, I would like to bring to your attention that the American Society of Regional Anaesthesia will convene a consensus conference the first weekend in May during which we will discuss North American practice guidelines, not only for the low molecular weight heparins, but also the other anticoagulant drugs, so we can talk about them all in a single event and try to, again, weigh the relative risks of each and come up with practice guidelines that are based on the optimal management of our patients.

With that, I'd like to open the discussion. Dr. Wood.

DR. WOOD: I've got two points to make. One is that there's evidence that twice daily low molecular weight

heparin is more effective than one dose daily, but one dose daily is better than unfractionated heparin. So, I think what's important to look at is that if we change the dosing regimen, that the benefit remains.

The other point is that low molecular weight heparins are expensive. The efficacy of low molecular weight heparin versus heparin is minimal I think for general surgery. So, are we discussing this just as far as orthopedic total knee replacement or hip replacement surgery is concerned, or do we extend the guidelines for general surgery?

DR. HORLOCKER: Dr. Talarico?

DR. TALARICO: We have recently approved Lovenox at the dose of 40 milligrams per day in the perioperative period with the possibility of extending thromboprophylaxis for 3 more weeks. So, we do have now an alternative dosage to the 30 milligrams b.i.d. for hip replacement.

For knee replacement surgery, there are two difficulties. First, we don't have studies. Only 30 milligrams b.i.d. has been assessed. And second, there is theoretical possibility that it may not be as effective as 30 milligrams b.i.d. because of much higher risk of thrombosis with knee replacement versus hip replacement.

That's where we are now.

DR. HORLOCKER: Will you ask for additional investigations evaluating those, or has it been definitively decided then that for total knee arthroplasty, the b.i.d. dosage will be required, that there's no chance of that being altered?

DR. TALARICO: For knee replacement, we cannot make any change because we don't have the data to support the change.

DR. HORLOCKER: Will there be data forthcoming?

DR. TALARICO: I don't know about that.

DR. BOTSTEIN: Let's ask the manufacturers what they have in mind.

DR. RUSH: Janet Rush from Rhone-Polenc Rorer.

We do not have any studies assessing the efficacy of the 40 milligram once daily dose in the knee that would be able to be used. We have studies ongoing.

DR. HORLOCKER: One thing I'd like to ask the manufacturers is when John Heit and I reviewed the studies of the patients that had received low molecular weight heparin checked the efficacy whether it was after total hip or total knee, we noticed that there was no stratification for regional anesthetic technique. They always recorded it and then evaluated that.

But why haven't you somehow initiated a study where they actually were randomized and you had that as a variable? Because we have all this tremendous data from before patients were anticoagulated postoperatively to show that it does decrease it.

Now, we know that spinal anesthesia or epidural anesthesia by themselves does not decrease it as much as low molecular weight heparin. But in combination there has to be some additive or maybe even synergistic effect, and that would have a significant impact on our practice. I'm just wondering why nobody has thought of this. It seems kind of intuitive.

DR. RUSH: One of the slides I showed was in fact a study in which everyone received regional anesthesia, and then Lovenox on top of that conferred an additive benefit. Do you want me to put that up again? It was a significant additive benefit over regional anesthesia alone.

DR. HORLOCKER: So, the two legs were regional anesthesia and regional anesthesia with?

DR. RUSH: Right, and then everyone got stockings as thromboembolic prophylaxis in the study.

DR. HORLOCKER: Was that spinal anesthesia?

DR. RUSH: It was spinal anesthesia, yes.

DR. HORLOCKER: Because what we need to know are the indwelling epidural catheters. It seems to be most people are fearful of leaving a catheter in these patients and it's really with the prolonged sympathectomy that the thromboembolic complications appear to be most attenuated. So, that would be the ultimate study from our anesthesia standpoint.

Dr. Palmer had a comment.

DR. PALMER: Yes, I have a couple of comments. One is along the lines of what you said. Let's be careful of what we do here because there are benefits to epidural anesthesia, especially in these orthopedic patients, which haven't even been mentioned here today, and we should be careful about making guidelines that might make problems for those people more frequent.

So, to be concrete, what I'm talking about is the fragile elderly patient who benefits from the regional anesthetic not only during the surgery but in the perioperative period when they would be at much more cardiovascular risk, for instance, if their pain were uncontrolled. We haven't even mentioned today that there is no argument, I don't think, that an epidural in a continuous setting is really the most efficient form of pain relief postoperatively and that postoperative stress

is a real risk for these people not only for embolic phenomena but for many others.

So, the thing that I seem to focus in on is that there are a number of things we can do based on these cases which may help us reduce the number of these incidences, but we can never get to 0. We all agree that there are spontaneous epidural hematomas.

So, if we can never get to 0, my question is why shouldn't we concentrate our efforts on the recognition of the problem in the highest risk group. Unfortunately or fortunately, most of us will only see one of these in a career. We'll either have it ourselves or our colleague in a larger hospital will have one of these. That's not enough to keep us educated about early detection and it's not enough also to alert our neurosurgical colleagues about how they need to respond to us when we do have the case that we think may be the epidural compressive hematoma.

So, I would see efforts not only on trying to decide whether a shorter epidural catheter or whether pre-op versus post-op with the -- you know, and all this stuff. I would really like to see us also put into the labels on these something about what to do when you suspect this rare complication. It doesn't have to be extensive. We can refer them to the literature, but I really think, at least

for half of these people that are going to be saved, the real reason they get saved is because they have an unusual complication, somebody recognizes it who has never seen one before, realizes the importance, gets consultation in a timely fashion, and surgery when necessary is performed. I really would like to see us add that. It wasn't even in the questions to the committee, but something needs to be in the labels here about what to do if, or at least what the cardinal symptoms are and then here's what you do.

DR. TALARICO: This has been addressed in the labeling now. The boxed warning does include awareness of what can happen and to be alert to the possible consequences.

DR. PALMER: My reading of that so far is that it's too vague. In other words, saying watch for neurological symptoms is too vague because the average nurse knows that a patient having a postoperative epidural is going to have some tingling, some numbness, but they should be alerted to the fact that the recurrence or sudden occurrence of low back pain, flank pain, hip pain and perineal dysfunction is a cardinal event that shouldn't happen when someone is on low-dose, postoperative analgesia type doses. And that has got to be in a different category than tingling or a little bit of numbness in a foot.

DR. TALARICO: Yes. It's difficult to tell exactly how extensive one has to be in the description of symptoms because in the case of hip replacement surgery, there are other confounding factors. Patients may have pain in the leg and patients might have some weakness. They may be on very powerful analgesic products. So, even the neurological pain may be masked up to a certain extent.

DR. PALMER: No. I really don't think that's true. In the case reports, the kind of pain that usually occurs with a compressive process in the canal really is very specific. It really has to do with the perineal dysfunction as well. Operations don't cause dysfunction of the bladder and relaxation of the anal sphincter. They don't cause a sudden change in the perineum the way that these processes do. I really think the pain and then the following dysfunction and -- you know, the flaccid paralysis no one misses. But the pain is so prominent in 40 or 50 percent of the subjects that it shouldn't be mixed up with surgical site pain.

DR. TALARICO: Interestingly enough, this was not the predominant symptoms in the cases we have looked at. It seems that these symptoms have to be looked for. Being alert of the possibility of a spinal hematoma is probably the only thing that may save the patient from

irreversible damage.

DR. PALMER: Well, in a conscious patient there is a time when the compression causes pain. If we miss it because the patient is too sedated or asleep, that can happen, but it's really not thought that you can have this process occur without significant and very typical kinds of pain.

DR. HORLOCKER: Actually, though, Dr. Palmer, when we reviewed these histories, I was surprised too. There were very few of them that had the severe radicular pain that's typically described in the neurological literature that that's what you're supposed to look for. I suspect that's one of the reasons they went so long. But it really wasn't. It was more of an extension of their preexisting block so to speak. I think that's why people missed it because it progressed. But that's what we have to alert people to, is a densening of their sensory or motor deficits. But I was amazed to see it.

DR. PALMER: Well, I should think that the pain, even the reported pain, is right around 40 percent.

DR. HORLOCKER: But still, that means 60 percent didn't have what we always thought was the number one symptom, radicular pain.

DR. PALMER: Right, but also the other part of

it is patients, especially elderly patients, complain of pain, a bedside attendant comes and says, oh, you're having pain, and they don't really define it. The elderly patients are not as aggressive as some of our younger patients as a group. So, I really think that that is under-reporting of some of the pain symptoms, and if we could alert the nursing personnel, the patients themselves and enlist them to look for this, we really might be able to uncover a few more cases earlier.

DR. TALARICO: That probably would be the most effective way of minimizing the risk.

Going back to procedure, we cannot really control or we don't intend to say which patient should have an epidural or a catheter, et cetera.

What we would like to see, if we can strike a balance so that the patients get the best surgical orthopedic anesthetic care and at the same time is exposed to the minimal risk from again a therapeutic intervention, namely the prevention of a thromboembolic event. What can we do to make this balance take place? That's what we would like to discuss.

DR. PALMER: I guess this is kind of a political statement, but what I don't want to see come out of this committee or out of the FDA is such a discouraging

statement that epidural analgesia is denied an entire universe of patients who would benefit from it because we're in a unique situation in the United States with the legal watchdogs who are willing to help patients sue for any bad outcome, whether it was one that could be predicted, prevented, or not. A lot of doctors, unfortunately, who are discouraged today may read this this way. In other words, oh, one more problem? Don't even offer the patient a regional block for these types of surgeries. That would be criminal in itself.

So, somehow we have to make sure that physicians understand that this is a problem which is rare but which really could be watched for, which really could be predicted, and maybe we can think of some guidelines so it's even less frequent. But I hope that the result of this discussion and guidelines is not to discourage the use of this very helpful form of anesthesia in this group of patients.

DR. TALARICO: Oh, absolutely.

DR. HORLOCKER: I think Dr. Talarico's proposed label is very ambiguous in a positive way, saying that indwelling catheters may increase the risk but you have to use your clinical judgment. I agree. We don't want to tie anybody's hands.

The one thing I did not like about the Vandermeulen review article is that they actually published pro times and platelet counts above which or below which you shouldn't do a regional anesthetic technique. That's silly. There probably are ultimate numbers that you would or wouldn't, but we need to be thinking clinicians. That's why we went to medical school, but we need to know what the data are too so that we can make an informed decision at the same time.

DR. HYNSON: Can I make a comment?

DR. HORLOCKER: Yes, go ahead.

DR. HYNSON: I'm James Hynson from the University of California, San Francisco. I'm a guest of Rhone-Polenc Rorer.

Just getting back to the back pain issue, I wanted to make the comment that I think one of the reasons that back pain may not be a clear-cut symptom in these patients is that the bleeding may be much slower and that the rate of bleeding may correlate with the onset of back pain. Those who are anesthesiologists will recall that when we do an epidural blood patch, if you inject very rapidly, you develop back pain. If you inject slowly, you don't get back pain. So, I think that may be an indication that the type of bleeding we're seeing in these cases is

very slow, that it may be going on for hours, possibly days before it develops into symptoms.

MS. CURLL: Mary Curll.

I'd like to agree with Dr. Palmer's comment about educating the staff nurses. We're seeing less and less patients staying in the hospital very long, and the discharge teaching is put on the nurses. Unless they know what to look for, it won't be done, and then the patient won't know when they get home what to report.

The other thing I noted, while looking at the package inserts, was that one of the companies, Organon, did break out some of their clinical trials by gender, and I thought that was interesting. They've got the male/female problems and how they developed. That was a positive sign. Maybe some others could do that too.

DR. HORLOCKER: Other discussion?

(No response.)

DR. HORLOCKER: I think we're all ready for lunch. So, we'll reconvene at 1 o'clock.

(Whereupon, at 11:53 a.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:02 p.m.)

DR. HORLOCKER: We actually performed our open public hearing in the morning. However, the previously set time was for 1 o'clock. Are there any additional people that would like to speak as part of the open public hearing at this time?

(No response.)

DR. HORLOCKER: All right. What we'll do then is continue with our discussion. What I thought I'd do -- I know that there are a lot things that still need to be said, but I thought I'd bring us back to what we're really here for, and that at least is initially to discuss the labeling of the low molecular weight heparins. So, what I'm going to do is read question number 1 under Questions for the Committee.

Are the revisions sufficient to convey the risks associated with these products when spinal/epidural anesthesia or spinal puncture is used?

Now I'm going to read the proposed revision or the actual revision of the low molecular weight heparins as of January 1998. When neuraxial anesthesia (epidural/spinal anesthesia) or spinal anesthesia is employed, patients anticoagulated or scheduled to be

anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of non-indwelling catheters for administration of anesthesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs, platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

And then it refers the reader to the warnings and precautions.

Under the warnings section the following has been added in bold print: Cases of epidural or spinal hematomas have been reported with the associated use of enoxaparin and spinal or epidural anesthesia or spinal

puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of postoperative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as nonsteroidal anti-inflammatories.

And then in addition, there is something added to the ongoing surveillance. In bold print, ongoing safety surveillance. Since 1993, there have been more than 30 reports of spinal or epidural hematoma formation with concurrent use of enoxaparin and spinal/epidural anesthesia or spinal puncture. The majority of patients had a postoperative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Obviously, I read from the enoxaparin labeling and a similar report is for all the various preparations of low molecular weight heparin.

So, we go back to question number 1 then: Is this a sufficient revision that conveys the risks?

What I'd like to do is just go around the table

and have everybody speak their mind on this issue. Go ahead, Dr. Steinberg.

DR. STEINBERG: Well, since we seem to be focusing largely on orthopedic problems, I'm going to ask for a little bit of indulgence to take a somewhat broader view than we have been discussing. I'll be discussing this strictly from the point of view of an orthopedic surgeon and his patients.

First of all, I think it's important to realize that the status of prophylaxis for thromboembolic disease is quite unclear. In the United States today, most people would advocate some type of pharmacologic approach. Coumadin is perhaps the most commonly used, regular or low molecular weight heparin probably second, but there are people who still use aspirin and other methods.

For example, at the University of Pennsylvania, we have been working on this for 10 years, and we found, in what I think was a good study, no differences between the results with aspirin and warfarin.

In England, as you may know, there have been some editorials stating that many English surgeons do not use any chemical agents and questioning whether any chemical prophylaxis is really better than physical means.

Also, when we try to evaluate the results, we

don't have good endpoints, and we tend to equate the presence of DVTs to fatal pulmonary emboli because they're easier to monitor. You can't necessarily do this. They do not equate. The problem is, as I mentioned earlier, that the incidence of fatal PE is so low that it may not be possible to do a definitive study telling us that one agent is better than another to prevent them, and thus is a major dilemma we have here.

Now, we recognize the fact that all anticoagulants have some risks, and our goal is to weigh the benefits versus the risks. We've been focusing only on the risks of spinal bleeding. What about bleeding into the wound which can be as high as 4 or 5 percent and can be catastrophic? Intracranial bleeds, GI bleeds? So that you can't lose focus of some of these agents, and the stronger and the more effective this agent is as an anticoagulant, the more dangerous it is.

There are definite advantages to the use of various types of spinal anesthesia of epidural, especially with indwelling catheters, and I would have concern about any agent which might limit our use of this type of anesthesia.

This presents us with a real dilemma because once a catheter is put in, we do not know whether it will

remain in 24, 48, or 72 hours. On the other hand, if we begin prophylaxis with a low molecular weight heparin, we've acknowledged that it should start by 24 hours and sometimes by 12. Thus, a dilemma: The proper use of one may contradict the proper use of the other.

We also have a problem because we've been trying to compare the use of low molecular weight heparins to warfarin. We can't do that in the setting that we've been doing this.

First of all, it has been pointed out that you can monitor warfarin, whereas you can't the low molecular weight heparins.

Also, keep in mind the delay in onset of action of warfarin is usually 2 or 3 days, and thus the anticoagulant effect of warfarin as used is much later than the low molecular weight heparins. We may, therefore, not be comparing equals.

Now, we can write very elaborate guidelines. I've seen some and they're very, very good. However, in the real world in clinical practice, what assurances do we have that once those guidelines are written, people will follow them? They don't. There are many, many places for error. As a result at my own institution, some people simplified the matter and said simply if any type of spinal

or epidural is used, do not use low molecular weight heparin. Period. This perhaps will obviate some of these errors from taking place.

And finally, I think we have to be very, very careful not to set down rigid guidelines which will be carved into stone, I can assure you, in an area where there is so much difference of opinion and where there are so many questions and so few answers.

Thank you.

DR. HORLOCKER: Could you also address the issue of whether you think that we've adequately revised the labeling on the Lovenox and other low molecular weight preparations to what we know about the risks?

DR. STEINBERG: Well, I'm certainly not familiar with the regulatory processes. From what you've said, it seems quite satisfactory to me.

DR. HORLOCKER: Dr. Alving.

DR. ALVING: I think that most people will not read the circulars. Almost no one will read the circulars except the FDA.

(Laughter.)

DR. ALVING: I read them when I was at the FDA religiously.

So, I think what has been very helpful is the

letter that was sent out to physicians. I think these are very, very general but they do wake up people to the fact that low molecular weight heparins are not entirely benign, so they do serve that purpose.

It might be a good idea, if you're sending out this boxed warning, to maybe send it out again as a letter to physicians and give a little background about the low molecular weight heparins. For example, what is their half-life? All the time I'm asked by surgeons, I'm going to do so and so, what about the low molecular weight heparin? Do I have to skip a dose or what? And then you might make the point that more specific recommendations are coming.

I really like that idea in Europe where there are specific guidelines. That's really what people need. This is very general but it does alert people to the fact that this is not benign.

I think what you could also say in a letter and not in a boxed warning is that when you do use low molecular weight heparin prophylactically, there are times when the level really reaches a therapeutic level, according to anti-Factor Xa levels. I don't know if you want to put it in a letter, but in other words, it's not always at this very low, undetectable level. There are

times when these patients are really fully anticoagulated as if they were on unfractionated heparin. We just can't measure the PTT, but as determined by the anti-Factor Xa level.

DR. HORLOCKER: Dr. Bauer.

DR. BAUER: Yes, I would echo those concerns. I think the warning as written is good.

I think, though, that given the issues about preserving epidural analgesia as a modality and not to exclude the use of low molecular weight heparin, I think maybe some definitive guidance, particularly about the issue of time for pulling out the catheter in relationship to the last dose might somehow be given consideration for being included. So, there is more discrete guidance and also support the practice of not, obviously, excluding patients from epidural analgesia and concurrent use of low molecular weight heparin.

DR. HORLOCKER: Dr. Talarico, we typically don't put that sort of thing in the label, do we?

DR. TALARICO: Well, the labeling actually should include only facts that are known from studies. But in this case, that's one of the questions for the committee. The next question, if you think that the labeling needs more, if you look at the question here,

there is an allowance for adding more information based on several things, clinical experience, case reports, pharmacology of each low molecular weight heparin. So, that is one consideration. That's what we would like some input on.

DR. HORLOCKER: Dr. Reves.

DR. REVES: I think the issue of timing is appealing because we'd like to know when to do things. It would help us all in our practices. But I actually don't think we have the data that says when you should or shouldn't commingle these things. I think it's all coincidental, and I don't know that we know when you should do what from the information that at least I've seen here. These case reports and everything else are very vague about all of that. We know what the Europeans are doing and we know what we are doing in our hospital, et cetera, but I don't think we have good data that address that particular issue. I think it would probably be a mistake to pretend that we do.

DR. TALARICO: Well, perhaps the knowledge of the pharmacology of the drug might be helpful --

DR. REVES: Might be.

DR. TALARICO: -- if we know what's the Cmax, what's the Tmax, how many hours does it take to go back to

baseline, and so forth.

DR. REVES: But the thing that struck me about the cases that we have is they tend to be what we call the high risk people anyway. They're older. What you might be telling is that what applies in the young people doesn't apply to these people because of pharmacodynamic variations that were seen in these patients, irrespective of the whole population and what one would think one might see.

DR. TALARICO: Yes. We can say this happened in X percent of the cases. This was found in so many other cases. The cases are really over the place, and they don't really give a pattern that one can use.

DR. REVES: You can make an argument and a rationale, but the facts probably wouldn't support that.

DR. TALARICO: Well, the aim here is to minimize as much as possible the risk. Granted, we will never eliminate it completely, but is there any information that we can use that the physician can then use.

DR. HORLOCKER: Yes, Dr. Bauer.

DR. BAUER: Well, there is the issue that I guess almost half the cases or more occurred when the epidural catheters were removed. If the warning doesn't state that, perhaps something could be stated to that effect.

DR. BOTSTEIN: Let me ask Diane. Was it when the catheter was removed or was it with an indwelling catheter left after surgery?

DR. REVES: Having had an experience with one case, it's hard to diagnose it and know when it occurred to begin with.

DR. HORLOCKER: There are some, though, that became acutely paraplegic within several hours of catheter removal. Those are for sure more than a smoking gun.

DR. WOOD: Catheter removal takes a minute. Two to three hours is very different from a minute. I don't think that gives you any idea of when the hematoma occurred.

DR. REVES: Yes. If we were doing imaging all along and looking for hematoma formation and everything and knew exactly when, but we don't have that kind of data.

DR. HORLOCKER: I would argue, though, that if a patient had an indwelling catheter for 24 or 48 or 72 hours and became paraplegic within 3 to 8 hours of when the catheter is removed that that's a little more than circumstantial evidence to support that something critical happened that may have made a preexisting collection of blood a significant amount. So, there probably is something to do with catheter removal.

DR. REVES: Or placing the catheter.

DR. HORLOCKER: Right.

DR. BAUER: I'm just trying to get some way to phrase this in some way that maybe these complications may be related to removal of the catheter and clinicians should be cognizant of the dosing of low molecular weight heparin relevant to the time of catheter removal, some vague statement to know that there may be some causal relationship just to get at this issue of knowing that the drug, which you can say somewhere else in the product insert, has a prolonged half-life, some way to alert in the warnings that you got to know that the drug may be around when you're doing this, not that we know that they're truly causally related, but some way that that may be a red flag if it's seemingly from the cases that it may be.

DR. REVES: Is there any animal data or anything that shows that pulling a catheter is more likely to cause a hematoma than having the catheter in there? Is this true ignorance we have or is it --

DR. HORLOCKER: There's no animal data. There is one continuous spinal study that shows that the presence of an indwelling catheter, whether it's in a patient that is receiving an anticoagulant drug or not, will be more likely to have red cells present at the time of catheter

removal 24 hours later. So, it shows that the presence of an indwelling catheter, at least intrathecally, does cause ongoing trauma in some patients. But we all know surgically that there are patients that bleed when we take out stitches or drains, and so we have to be aware that this could also happen within the epidural or intrathecal spaces also. But there are no lab data or animal data to support what we're saying. You're correct.

DR. REVES: I think the data do indicate that there's probably a higher risk for a patient who has an indwelling catheter than one who does not. You've looked at the data. Is that right or wrong?

DR. HORLOCKER: It's always the patients with an indwelling catheter and concomitant low molecular weight heparin use. If you had a catheter in and took it out before they started the therapy, we don't know if that would bring the risk down to 0.

DR. REVES: Do we know if you just did a single shot epidural, no catheter, whether those people will have the same -- and get the low molecular weight dextrans in about the same time period, do we know if they have a lower incidence of this problem?

DR. HORLOCKER: We don't know because everybody that's had an epidural that we have been able to identify

with an indwelling catheter got the drug while the catheter was indwelling. What you're talking about is giving a single shot epidural and then the drug would be given later, so the two would never coexist at the same time. We don't have data that shows that that decreases the risk. Intuitively we want to think it does.

Yes, Dr. Carlisle.

DR. CARLISLE: Do we actually know whether stopping the low molecular weight heparin prior to the removal of the catheter makes any difference? Do we really know that?

DR. HORLOCKER: No, we do not. It would only approximate what they've been experiencing in Europe which doesn't appear to be a clinically significant risk. So, I actually talked to Dr. Steinberg during the break and said what if we did -- or maybe it was Dr. Bauer -- what if we did hold a dose and so they go 24 hours? Is that going to significantly increase their chance of DVT? Probably not because it would be past their main thrombogenic time period.

So, that might appear to be the best way to do that. We could dose at twice daily while it's in, hold one dose before you take it out. But again, that implies that you know exactly when that catheter is going to come out,

and sometimes they fall out while the patient is rolling around in bed or at PT. So, there's still a little difficulty there.

DR. CARLISLE: It also still bothers me that we are not addressing the variability amongst patients. I mentioned earlier renal failure. One of the reasons that that particular issue struck me is that we do know that the highest incidence of this is in elderly females who would be the person who would have no muscle mass, so would not have a significant bump in creatinine, who might also be the person who would develop just a little bit of liver failure or maybe just a little bit of platelet dysfunction from an infection or from a more dilutional coagulopathy than someone else, and that we're not addressing any of those issues as well in terms of trying to set up guidelines.

DR. HORLOCKER: Dr. Talarico, within this is there a warning regarding patients with renal failure?

DR. TALARICO: If there was somebody with renal failure, it might have been the exception.

We were wondering about the dosage, whether 30 milligrams twice a day would represent a big dose for a tiny, little patient.

DR. CARLISLE: But the issue that I'm trying to

address is not the tiny, little patient. It is the elderly woman who is the patient population that we're dealing with who might have a creatinine of 1.1 which no one would ever pay any attention to, but she's someone whose creatinine clearance with a plasma creatinine of 1.1 is less than 30, which would then put her in the severe renal failure category without it being recognized. I'm just using that as one example of the kinds of concomitant situations that we might have that we're not recognizing that may be additive and lead us into these problems that we have with hematoma.

DR. TALARICO: Yes, that in addition to the fact that they might have, as you say, reduced muscle mass. So, therefore, if it was going by weight, they would have received a lower dose. But it turns out that the mean weight was 61 kilos, whatever.

Also, in the clinical trials, elderly patients were not necessarily at greater risk. The pharmacology studies did show that the clearance was different in elderly, but the bleeding risks were not greater in older patients. Maybe when you combine several things together, it might add up but I don't know that.

DR. CARLISLE: Am I incorrect in remembering that the largest group of epidural hematomas occurred in

the elderly women?

DR. TALARICO: Yes.

DR. HORLOCKER: Dr. Palmer, your thoughts on the labeling.

DR. PALMER: I have a problem because I cannot locate in my materials a copy of what you read.

(Pause.)

DR. PALMER: It's becoming clearer now.

One of my problems is with the wording which has remained the same in this old copy I had as well as the one I've just been handed. If you look at the wording, it says, when neuraxial anesthesia is employed, patients are at risk. I really think that's not the case. I think that, yes, maybe 70 percent of them are associated with neuraxial anesthesia, but 20, 30 percent probably are not. So, I really think the wording, although it can emphasize neuraxial anesthesia, has to indicate that patients anticoagulated with these drugs are at risk of CNS hematomas, which the risk may be increased with the presence --

DR. HORLOCKER: I think there has only been one spontaneous one, in that patient with the allograft, and then a couple lumbar laminectomy ones. So, they had surgical procedures.

DR. PALMER: No, no. Of the 33 cases that are summarized for us, I count between 4 and 6 of those 33 that either had no epidural anesthesia or if you have the information in the other articles, the actual hematoma is remote from the site of insertion and probably not within the reach of the catheter either. I have serious questions about whether those are spontaneous hematomas or not.

I just think that we know that there is an irreducible risk of spontaneous hematoma and what we may be seeing is some increase with these drugs. So, I really think that somehow we need to indicate you need to look for these signs regardless of whether they used neuraxial anesthesia or not.

So, if you could change the wording to say anticoagulated patients are at risk for neuraxial hematomas which may be increased with the use of spinal or epidural and may be further increased with the presence, the prolonged presence, of an indwelling catheter, then it would make sense to me because the risk does seem to be graduated.

The other issue I had with this change in the boxed warning is who's getting it. From what I've read in here, the Dear Doctor letter and the other attempts so far have been directed at anesthesiologists, orthopedic

surgeons, pain experts, but have not included neurosurgeons, as I said, who need to be our backup here and need to be very informed on this issue. And it hasn't included like orthopedic nursing as a specialty, since this is the greatest group of people who will be caring for these patients and educating them before they go home.

DR. HORLOCKER: Go ahead.

DR. BOTSTEIN: Dr. Palmer, you're absolutely right. It needs to go to a wide audience.

Can we ask the companies just who our health advisory was sent to? We didn't have enough money to send it to all the doctors. The companies did that. Could somebody please --

MR. DONNELLY: Yes, we have a list.

DR. TALARICO: While you are getting the list, 94 percent of the patients had some spinal manipulation, whether it was anesthesia, spinal tap, analgesia, or injection or whatever.

DR. PALMER: That 94 percent includes, though, cases where a lumbar catheter was placed and the clot was actually found in the thoracic region.

DR. TALARICO: No. These are just invasion of the epidural space.

DR. PALMER: That's what I'm saying, but it's

hard for me to understand a spinal anesthetic or even an epidural given at L3-4 and a clot that occurs at T10, above the area, because most patients who are in bed are not head down. If anything, they're usually head up. So, finding a clot above the level of the invasion of the spinal canal is a bit hard to reconcile.

I don't mean to say that I don't think that these are related issues, but I'm just concerned that we're missing the boat by just concentrating only on the epidural catheter.

MR. DONNELLY: My name is Tom Donnelly from Rhone-Polenc Rorer.

As you can see, the list, the recipients of the mailing, that is, the health care advisory letter, that went out by the companies at the end of January. It went to a very broad list, including nurse anesthetists, all hospital pharmacists, all hospital nurses, and so forth and a broad category of physicians. So, in that way the companies were trying to bring this to the attention to as broad a group as possible.

DR. PALMER: Thank you. That really helps clarify who got it so far.

Then my other problem with the boxed warning is as I mentioned earlier. The sentence that says patients

should be frequently monitored for signs and symptoms of neurological impairment I think is too vague and would recommend adding wording that has to do with unexplained flank or a perineal pain or radiating pain, and then followed with unexplained increase in weakness or paresthesias in the lower extremities, something that is specific about this.

DR. HORLOCKER: Dr. Young.

DR. YOUNG: Aside from what Dr. Palmer has already said, I don't have any additional modifications or suggestions for the boxed warning.

Through this whole discussion, I have difficulty understanding how there could be so many thousands of cases done without any reported problem and then suddenly there's this rash of incidences over the past three or four years. My concern is that, as has been pointed out, the reporting mechanism for these problems, whether there's some way that the companies can increase their vigilance of that so that there are more data to reevaluate this over time and come to some better conclusion in terms of what the contributing factors are.

DR. HORLOCKER: Is the section that was added under the surveillance appropriate then? I don't have it in front of me anymore. There will be ongoing surveillance

and reporting of the events.

DR. PALMER: If I can break in just for a minute, I would really like to see them collecting data that we didn't have, for instance, things like the technique of insertion, the amount of catheter inserted, the type of catheter. These are things I think most any anesthesiologist would want to know. That just isn't in most of these. So, if we could add a few things to their surveillance.

DR. HORLOCKER: I believe that some of the drug companies are even doing that to go back and try to collect additional data for the FDA to fill in some of the follow-ups. Is that correct?

DR. YOUNG: Are you still waiting for me? Come back to me.

DR. HORLOCKER: All right. Dr. Carlisle.

DR. CARLISLE: I think I've voiced some of my concerns. I also agree with Dr. Palmer in that I think the wording could be changed so that there is an increased awareness without it being a strict cause and effect assumption.

DR. HORLOCKER: Dr. Reves.

DR. REVES: I think we're talking about a catastrophic complication that's extraordinarily rare. I

believe that what we can do is education to try to prevent it. I think that this proposal continues that educational venture, and with the modifications that have been discussed, I would approve it. But I think a long-term educational plan by the pharmaceutical industry who actually, along with all of the physicians like us that put them in, have vested interest in making certain that we all are aware of this potentially devastating but extraordinarily rare complication.

So, to answer the question, I would approve with slight modifications what this warning has, but I would also suggest that there be an ongoing effort to keep this issue out there.

DR. HORLOCKER: For the record, I also agree that the labeling revision is adequate, and I would add that we need to work on the earlier detection by education of our nursing staff and patients in addition to perhaps a more safe placement and removal of needles and catheters by looking at the pharmacology within patients so that a higher awareness with what the pharmacology is, what the assumed hemostasis is at the time of catheter removal and placement.

Ms. Curll.

MS. CURLL: Yes, I too agree. But I was

wondering if anywhere in the labeling you could put a warning or a precaution that elderly women have been shown to be at an increased risk for these hematomas when used with this drug because unless you spell it out, they won't see it or someone may see it in the package insert and tell someone else, did you see such and such. As we found out today, the numbers are women and they're older women, and we're all getting older.

(Laughter.)

DR. REVES: I have one question related to that because I was thinking of that also. But many of the orthopedic procedures are done in elderly women and I'm not certain that again the data would support that this group is in fact the ones that have a -- maybe they're just exposed the most. I don't know if we have that data. If we have it, then it should be included.

DR. HORLOCKER: Dr. Wysowski, do you think we do? Is there actually a numerator and denominator and we can identify that as a risk factor?

DR. WYSOWSKI: Probably not. As I pointed out during my presentation, these are potential risk factors and not definite risk factors. As you stated, there's a high proportion of orthopedic surgery being done in elderly women, and so they are the people that are most exposed.

On the other hand, I guess it's my own personal feeling that it might be useful to put something like that in the label nonetheless.

DR. REVES: Yes, I would have no problem. You can state one fact which is most of these adverse events have occurred in them for sure because that is the data.

DR. WYSOWSKI: Right.

DR. HORLOCKER: What's very interesting about that finding is at Mayo when we did our prospective study evaluating antiplatelet medications as a potential risk factor for spinal hematoma, we looked at every patient and anesthetic variable we could, and miraculously antiplatelet drugs were not associated with more blood through the needle or catheter than patients that weren't on those. But female gender, increased age, hip fracture patients all were associated. That's actually what you're sort of seeing which is really fascinating for me.

DR. WYSOWSKI: Well, the other thing that I question is whether elderly women who have higher incidences of osteoporosis and greater spinal deformity might be at increased risk for that reason.

DR. HORLOCKER: Dr. Rhode.

DR. RHODE: I've been sitting here listening to people try to tease out causes and evidence from what is an

extremely pauce amount of data. There's just not much here.

I agree with the suggestions that the increased surveillance is perhaps the best thing that we can do at this point. It strikes me to say that older women would be at higher risk is probably premature. We simply don't have the data to support that. However, there would be nothing wrong in saying that to date most of the cases have occurred in these groups, and that's sort of a buyer beware or a user beware kind of thing and that's probably the best thing we can do at this point and certainly the wisest thing both from the scientific point of view of this committee and from the FDA's integrity, and it would also alert, properly so, the users. So, I would agree with the comments that were made so far.

DR. HORLOCKER: Dr. Wood.

DR. WOOD: I would agree. I think the label should remain pretty general because we don't have a lot of data. I agree that it probably would be better to say 30 of 38, or whatever the number were, of the case reports occurred in female patients rather than surmising on inadequate data.

DR. HORLOCKER: Dr. Wysowski.

DR. WYSOWSKI: I'm not part of the committee.

DR. HORLOCKER: Oh, you don't get to even comment, though?

DR. WYSOWSKI: No.

DR. HORLOCKER: We're always interested in what you say.

DR. WYSOWSKI: It's also my personal opinion that it wouldn't hurt to put some specific symptoms in, neurological symptoms. I think that might be useful.

DR. HORLOCKER: Dr. Talarico, any other comments?

DR. TALARICO: No. We appreciate any suggestions. I think the idea of including the facts as they are is okay, just specifying how many women, what was the age range, even possibly when it happened in relation to surgery if we have that information. But that is probably as far as we can go in the boxed warning.

DR. HORLOCKER: Any further comments?

DR. BOTSTEIN: I don't have anything else.

When we went through these cases and batted this around, we couldn't come up with good recommendations about timing of stopping, starting, et cetera. I'm sorry that you all couldn't either, but then you had the same database.

DR. HORLOCKER: Dr. Talarico, do you feel that

you have enough comments to make minor revisions on that? Do you want an actual vote from this committee or are you happy with the comments that have been made here?

DR. TALARICO: No. I think we get the feeling that we do have to include all the facts as we know them, and we agree.

DR. ALVING: I'd just like to make one comment. I really think this risk reduction strategy for low molecular weight heparin that Dr. Pineo presented earlier could be very useful, just a couple of these points where they administered low molecular weight heparin after the epidural/spinal puncture and then they removed the catheter in their protocol 8 to 12 hours after the last dose. One might want to change that, and perhaps one could say some strategies that have been developed to avoid this, not to make it sound like a guideline, but this is what others have done could be very helpful, just maybe two points.

DR. HORLOCKER: Let's move to question number 2.

DR. MUNTZ: Dr. Horlocker, could I say one thing?

DR. HORLOCKER: Yes, go ahead.

DR. MUNTZ: I'm Jim Muntz from Houston, Texas from Baylor College of Medicine.

We have a series of 12,000 epidural catheters and about 5,500 of them are on Lovenox. I'm going to go home in two hours, and I need to tell 150 anesthesia people what to do. We're already doing a lot of it. Dr. Steinberg, I will go out of here and use aspirin and Coumadin. We'll continue to do what we do.

I think Dr. Pineo has a very good start, and I think we could somehow come up with -- they don't have to be guidelines, but things to minimize problems.

When I go back, I will probably recommend that we use spinal anesthesia, remove the catheter. Most of our catheters, or 5,000 of them, have been in 48 hours. What we'll probably do starting tomorrow is put in the catheters, do a spinal anesthesia or do an epidural catheter, remove it the morning after surgery. The patient has never gotten Lovenox or enoxaparin. We'll wait 2 hours before they get their first dose.

We have already prohibited Ticlid, aspirin. Nobody can mix drugs. Toradol. We've weight-based our low molecular weight heparin off label. We use a 30-milligram Q24 dose if somebody is under 90 pounds. If somebody is over 300 pounds, we change the dose. If we have an elderly female, 80-pound female, it's all in our pathways for both our hospitals, 1,200-bed hospital, and we alter the dose of

the drug because we had bleeding three or four years ago.

We never start enoxaparin before 24 hours post-op. Many times we'll start at 36 hours post-op with pumpers to avoid bleeding. We have had only one epidural hematoma out of 12,000 cases and it was when somebody used wrong drugs, multiple drugs.

I think there's a list of things. They don't have to be guidelines, but they can be issues to decrease the chances of epidural hematoma.

Age was another one. If the creatinine is over 2, we cut the drug, cut it down to 30 Q24 hours. This is used around Houston, and again we've had good results. It doesn't necessarily have to be scientifically based. All we want is I want to walk out of this room and make sure nobody ever gets an epidural hematoma that we could prevent.

Thanks.

DR. HORLOCKER: I don't think we could promise you that, unfortunately.

(Laughter.)

DR. PALMER: I'm concerned that that's probably going to be the take-away message because now you've got, in order to prevent one epidural hematoma that might have been treatable, how many MIs are you going to have and

total knee operations where the patient really needed profound pain relief because of their tenuous cardiovascular status and then they couldn't get it because they also had lung disease. The nurses won't give them the IM injections, but their epidural catheter was removed and that now becomes an unknown risk. So, I hope that if you do implement the guidelines that you've just talked about in summary, that you'll leave room for people to make individual decisions about patients like the one I'm describing.

DR. HORLOCKER: Dr. Wood.

DR. WOOD: I think it goes right back to my original point about myocardial infarction, thrombolytic therapy, and cerebral hemorrhage and stroke. It's a catastrophic event. So is a subarachnoid hemorrhage. But again, you're weighing the risk/benefit ratio. The aim may not be to completely abolish the adverse event. That nowadays might not be the ultimate goal.

DR. HORLOCKER: I agree with you. I don't think we ever can promise patients that they won't have an adverse event because they're at significant risk for a thromboembolic event too, and what we have to do is weigh the risks and benefits of our therapy, of the thromboprophylaxis, and our analgesic method and try to

come up with the best one for each individual patient based on their coexisting medical conditions.

So, I hope that nobody is coming out with concrete, written-in-stone guidelines based on these things because really what we're trying to do is make people thinking clinicians and do the best thing for their patients.

DR. MUNTZ: To answer your question, we still use a lot of epidurals in the knees and revision knees. We've almost totally quit using them in hips. Our patients go home on day 3 or 4. The nurses are happier without the epidural catheters. There's a good place for them. They're good. I think the epidural catheters help with pain, but I think the antithrombotic agents are paramount to saving lives and I think the anticoagulation issue is going to supersede epidural catheters for patient safety.

DR. HORLOCKER: Under question number 2 then, this was really if we did not find the new revisions sufficient. Are there any special circumstances or any phrases in questions 2(a), (b), or (c) that you would like to discuss at this time? For example, are there restricted circumstances only that you would prefer to have low molecular weight heparins given in combination with?

I think the general consensus here is that we

want to be able to do regional anesthetic techniques and tailor that technique to the individual patient. I think nobody is ready to have a restricted or total contraindication. Am I correct in that assumption?

All right. I guess the last thing that we need to really discuss then is should the class labeling be extended to all approved anticoagulants, including the intravenous -- oh, I'm sorry.

DR. BOTSTEIN: Before we get to that, could we just see if there's any advice you all think would be reasonable to put in about relative timing of the anticoagulation and catheter use? Anything at all?

DR. HORLOCKER: We don't actually have the data. You could put a generic statement saying to try to do it at a time when the anti-Xa activity is low, which is sort of ambiguous and intuitive, but that's what many of the other regional anesthesia techs say about intravenous heparin. That would require somebody to at least read the pharmacodynamic and pharmacokinetic information, which they probably have skipped over to get to the boxed warning. Maybe that would send people back to the real literature.

DR. PALMER: Why isn't one of the pharmacokinetic graphs that we looked at that at least shows you the peak activity within 2 hours and at least

shows you that after 8 hours you're significantly down included in this? I know that I'm pretty simple-minded, but a picture is worth a lot more than some of these tables. If we were going to include something, just sticking to the facts, we could say that half of the cases were associated with catheter manipulation or removal. Then if you could show the picture of the time course of action, the fact that it isn't cumulative. That's all different from heparin. I don't see it easily available here for the average clinician.

DR. BOTSTEIN: Yes. One problem I have with a graph like that is that it gives the idea that the anti-X activity is correlated with the anticoagulation in the patients tightly and directly. That we don't know.

DR. PALMER: It obviously isn't because the ordinate is the international units of anti-Xa activity, and no clinician, who's not a hematologist, probably knows what that means, but it does give you an indication of time course that at least there would be some information. There isn't anything here. That, plus the only other thing we have, which is that half of them were associated with catheter manipulation and removal, and just let them make their own conclusions.

DR. WYSOWSKI: Actually from the 33 cases that

I looked at for Lovenox, they were not associated with catheter removal. I think it was Dr. Horlocker who mentioned and in the Vandermeulen study the review of the --

DR. HORLOCKER: Also in the study that John Heit and I did, we also thought it was, but we only had 16 of your 33 reported cases.

DR. WYSOWSKI: Right. There wasn't very good information on timing and chronology of events in the reports that I looked at. Some of them were very meticulous and others had very sparse data. So, there's really not very much information on timing of catheter removal and the onset of neurological symptoms and bleeding.

DR. REVES: I have no argument with more information. That's fine, but to make any -- any -- inference that the peak level of that is related to an adverse event I think is a big stretch. I'll give you the easiest analogy I know. When you look at blood levels of drugs and one patient can be absolutely, totally wide awake and someone else will be totally asleep. So, these things often don't really have anything to do with consequences that are important to you as a clinician.

DR. TALARICO: Well, it would be reasonable

enough to assume that if enough time has gone by to the effect of the drug to be near baseline, probably that would be a less risky time for especially elective manipulation. Obviously, an emergency change of catheter or whatever is unpredictable, but if something is to be done on schedule, one can select the best time for doing that.

DR. ALVING: I would just like to say anti-Xa activity does correlate with anticoagulant activity. In other words, I'm not going to stick a needle in somebody if they have an anti-Xa activity of .7. I'd rather do it when it was .05. You really could highlight the clinical pharmacology because the half-life can be anywhere from 4 and a half to 12 -- well, 4 and a half hours half-life, but significant activity remains for 12 hours. If you bolded that so that you just say that, then somebody could say, maybe I'll wait 12 hours after this last dose.

Now, again with danaparoid, the half-life is, what, 22 hours? Right?

DR. MAGNANI: That's only the anti-Xa activity.

DR. ALVING: Well, let's go with anti-Xa activity. I mean, you may not want to.

So, danaparoid has a half-life of 22 hours by anti-Xa activity. So, if I've got someone on that and I'll be using it for heparin-induced thrombocytopenia off label,

I'm going to wait much longer to pull a catheter.

DR. HORLOCKER: I agree. There's actually that phrase in there that I was going to read. Following a 40-milligram dose, significant anti-Factor Xa activity persists in plasma for about 12 hours. So, just seeing that is going to scare people enough to at least think about what they're doing within that 12-hour time period. If we could just highlight those sorts of things because we don't have the information, as people have brought out, but at least if we can look a little bit at the pharmacology, take it into account when we place and remove the catheters, that might help. It should theoretically.

Any other things that you wanted? Okay.

Then on to question number 4. Should the class labeling be extended to all approved anticoagulants, such as intravenous heparin, subcutaneous heparin, and warfarin products?

Again, I think we should just go around the table here. Dr. Steinberg, would you like to start?

DR. STEINBERG: Yes. I think that these also. This is almost the same risk we've been talking about, although we've been focusing on low molecular weights. But we've seen clinically problems with these drugs as well. As I said, that's one of the reasons that some groups have

gone to aspirin though folks have said aspirin is not as effective. It certainly is safer.

DR. HORLOCKER: Dr. Alving?

DR. ALVING: I wouldn't do it for warfarin. It seems to be covered. Furthermore, you can monitor it, so you'll get an INR. If you know someone is on warfarin, you'll want to check the INR.

For heparin, again you've got people in 5,000 subQ still b.i.d. or t.i.d., and I guess it would not be a bad idea.

DR. HORLOCKER: Dr. Bauer?

DR. BAUER: I'd be inclined not to. I don't think we've heard any evidence today of any real problem with those agents as they're currently used in terms of this problem. I think to open that box and issue a wide warning about the problems that I don't think currently exist and probably aren't likely to exist because I don't see the way that warfarin being used or unfractionated heparin as prophylaxis being used changed will do it. I think it may actually be a dis-educational thing to do because I think we need better education about the properties of low molecular weight heparin rather than further education about heparin and warfarin.

I think people have always held heparin and

warfarin in relatively high regard to their hemorrhagic potential, and I think there may have been, to get back to the question somebody had, why do we suddenly see this in low molecular weight heparin, a sort of overzealous appreciation that maybe this is a free lunch, which obviously it's not.

DR. HORLOCKER: Dr. Palmer.

DR. PALMER: I'm sitting on the fence because of the subQ heparin that I see used and without PTT monitoring. I see it way too often where I will ask for that pre-op hip surgery and I'll be told by the young surgeon, well, that's not needed. It's not a therapeutic dose of heparin. And I'll say, well, how do you know what it is in this patient? At least we can settle it with a lab test about what it is to this patient.

So, as I said, I feel both ways about it. Really, if you're going to use heparin, you have to understand there are variable results with it and PTT should be checked before neuraxial invasions are made. So, I don't know if it's the same warning or if it's a different warning, but heparin should be respected for its variability.

DR. HORLOCKER: So, do you think then that heparin should have the label and not warfarin?

DR. PALMER: Well, I guess because I'm hospital based, I just see that as the bigger problem, whereas the warfarin is much more often used in the long term and it is usually carefully deleted before planned surgery. So, I don't see that we're having a problem with warfarin.

DR. HORLOCKER: It's still perhaps the number one thromboprophylactic agent, though. So, if patients have indwelling epidural catheters and warfarin therapy is initiated, they will have those concomitantly.

DR. PALMER: Yes, you're right. Without information, I just have a hard time making a firm opinion.

DR. HORLOCKER: Dr. Young?

DR. YOUNG: No.

DR. HORLOCKER: Dr. Carlisle.

DR. CARLISLE: Yes. I guess I'm not sure it should be same label, but I think that the labels should definitely include some statement to at least acknowledge the fact that we do have ways to monitor the effects of these drugs and that to do neuraxial procedures in the face of the effects of these drugs is foolish.

DR. HORLOCKER: Do you believe then that we should add a boxed warning similar to that for low molecular weight heparin or is the existing warning such as you saw for warfarin enough?

DR. CARLISLE: I think it's almost enough. I think that it's not quite specific enough, but it's almost enough.

DR. HORLOCKER: Dr. Reves?

DR. REVES: Well, I'm not impressed with the data actually, and I think the warfarin label we've already been shown is pretty direct and addresses this issue. I guess if I have to say, which I do --

(Laughter.)

DR. REVES: -- I think warfarin is handled. If you read this and were to substitute any anticoagulant, i.e., heparins, it wouldn't offend me to have that kind of advisory out there. So, I guess I would be for that, but I would like to see a lot more data supporting it.

DR. HORLOCKER: I actually do not think that we should extend the labeling because I feel that by doing so, we're saying that that risk is equivalent with these other drugs, and I just don't think we've seen the same problem because we've been educated on how to manage both the anticoagulant effect as well as regional anesthetic techniques in patients that receive warfarin and intravenous heparin. So, I would not put a boxed warning. I think that they need warnings, as other members have mentioned, but I would not put it to the same degree as the

low molecular weight heparins which are difficult to manage because we can't monitor their effect, and they have such a long half-life.

Dr. Rhode. Oh, I'm sorry.

MS. CURLL: That's okay. No, I don't think they need the same type of labeling.

DR. HORLOCKER: Dr. Rhode.

DR. RHODE: It strikes me that there's even less data here, so I would say no.

DR. WOOD: I would say no. The data is not there. I think if you look back to what we did for bupivacaine we said the same thing. There was a boxed warning for bupivacaine but let's see what's going to happen with bupivacaine before we do it. So, I would agree.

DR. HORLOCKER: Members of the FDA --

DR. TALARICO: No. I was just noticing the fact that Coumadin is contraindicated for patients with spinal anesthesia, and yet it seems to be the most widely used anticoagulant. So, that I find a little bit difficult.

Second, I think we are confusing a little bit starting Coumadin for thromboprophylaxis and the patient being coumadinized. If a patient is on Coumadin and has to

have a hip replacement, that patient will be at risk no matter what. But obviously if the Coumadin is started the day after surgery and takes three more days to reach the appropriate INR, by then all the manipulations will be over and the risk will be minimal. But there is some risk nevertheless with the Coumadin.

DR. REVES: But, see, in their insert they already say it's contraindicated. I mean, you can't be more direct than that.

DR. TALARICO: True, but then we are contraindicating something that's off label. We are making it a boxed warning for something that's off label.

DR. HORLOCKER: Dr. Talarico, are you happy then with what the discussion is? Are you happy with the way the voting is? Do you need us to get more elaborate or do you want a formal show of hands?

DR. TALARICO: No. I think it's fine. I think we get the message that we do have to expand the boxed warning with more information, give more data on the cases reported, probably include some information about the drug pharmacology, and that will obviously depend from one labeling to another because each drug is somewhat different.

DR. HORLOCKER: Yes. Would you like to make a

comment?

DR. MAGNANI: I think everybody is agreed here that we undoubtedly need a black boxed warning. For me there's a paradox. The same patients who require the spinal anesthesia, the neuraxial anesthesia are also largely the same ones who need anticoagulant treatment. They're usually the very old, the very weak, and the ones who are likely to be more bedridden. So, the physician has to be helped somehow to make a decision as to how he's going to work out this tradeoff.

Now, of course, the paralysis is catastrophic but so is a fatal PE. I think this is the thing we have to keep in mind because we're all concerned with safety, but we also have to be concerned with efficacy. And I would disagree that things like stockings and aspirin are equivalent in these very high risk patients to the low molecular weight heparins and perhaps heparinoids and even heparin itself.

If we follow Dr. Horlocker's argument, what do we do with the new compounds if we don't include unfractionated heparin and we don't include oral anticoagulants in some way? I admit they have a warning, so perhaps that is more excusable, but if we don't include unfractionated heparin, what are we going to do with the

new things that come along which have absolutely no incidence because they've hardly ever been tested? How are you going to treat those? Put them automatically in a black box, or are you going to leave them outside until you get a case? Because I think that also has to be taken into account.

DR. HORLOCKER: Yes.

DR. DeVANE: Philip DeVane, Wyeth-Ayerst.

Could I just ask for clarification on the vote? Because polling the voting members, I thought the answer to the last question was no.

DR. HORLOCKER: Dr. Somers, you have the formal count. It's a split, though, between the two drugs. We'll have to tally them up separately.

DR. DeVANE: Is everybody voting?

DR. HORLOCKER: The guests and FDA do not vote. There are only eight votes. There are five noes.

DR. DeVANE: And there were five noes.

DR. HORLOCKER: Yes.

In summary then, I think what this committee has decided to advise the FDA is that we do need additional expansion of our boxed label warning to include more patient data, that describes the patients that have developed spinal hematomas, and perhaps some

pharmacokinetic/pharmacodynamic data that will help assess when it's safe to place and remove a catheter. Also, we have voted to not extend the boxed label warning to other anticoagulant drugs.

Is there anything else that anybody on the committee would like to say?

(No response.)

DR. HORLOCKER: I'd like to thank you all for the opportunity to serve you. It has been an experience and an educational one at that. Thank you very much for your support.

We're adjourned.

(Whereupon, at 2:06 p.m., the committee was adjourned.)