Sherman

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT - 5 1992

FROM: Medical Officer, HFD-733

TO: Director, Monograph Review Staff, HFD-810

THROUGH: Acting Director, Division of Epidemiology and Surveillance, HFD-730

10-5-92

SUBJECT: Consultants' reviews of the Epidemiology Branch's safety reports concerning phenylpropanolamine

This memorandum is in response to your request for a summary of the reviews of the PPA Epidemiology Branch reports by Drs. Daling, Whisnant and Kittner as well as an analysis of the feasibility of studying PPA diet preparations and cerebrovascular accidents using case-control methodology. The questions and responses have been summarized in an attempt to accurately reflect the consultants' views in a concise way.

1. Do the Epidemiology Branch reports of April 30, August 6, and December 26, 1991, adequately describe the data and methods used to evaluate the occurrence of cerebrovascular accidents (CVAs) and hypertensive episodes related to the use of PPA for weight control? Do the data and methods support the conclusions reached?

a. Introduction to the April 30, and August 6, reports - Are the reasons clear and valid for focusing on adverse drug experience (ADE) reports to FDA's Spontaneous Reporting System (SRS) and in the medical literature , and not using data from Poison Control Centers (PCCs) and the Drug Abuse Warning Network (DAWN)?

All three reviewers agree that the focus should be on SRS data and not data from PCCs or the DAWN.

b. Methods - Is the approach described in parts 1-5 of the April 30 report reasonable? Please consider the following points:

1) Proportional analyses of CVA with PPA weight control products compared to PPA cough/cold products and all other drugs.

Drs. Daling and Kittner both had reservations concerning the proportional analyses. Dr. Daling stated "It is difficult for me to consider the comparison

of PPA diet/cough preparations to all other drugs as appropriate....A comparison of PPA diet with PPA cough medications is plagued with the same problems...." Dr. Kittner states "the strokes per usage analysis is a relatively weak source of evidence... [and] the strokes per total adverse drug reaction analysis is an even weaker source of evidence." The views of Dr. Whisnant on this issue are not clearly stated in his response.

2) Comparison of the number of reported CVAs in PPA weight control product users to the number expected by chance.

Estimated incidence rate of hemorrhagic stroke in women age 15-44

Drs. Daling and Kittner both felt that the estimate used for the expected rate of hemorrhagic events (1/10,000 person years) may be too high. Dr. Daling felt the estimate may be too high because most of the women with events fall into the younger years of the age range. In addition, Dr. Kittner points out that if one were to consider only intracerebral hemorrhage then the expected rate would be reduced by approximately one-half. A reduction of the expected rate would increase the observed to expected ratios. Dr. Whisnant felt that the rate of 1/10,000 person years for intracerebral hemorrhage is reasonable from the data cited. Dr. Whisnant supports his estimates with data from Rochester, Minnesota from 1945 through 1984.

Reporting rate estimates

In Dr. Whisnant's opinion a 10% reporting rate seemed reasonable. Dr. Kittner believed that the reporting rate is likely to be less than 5% based upon a study of adverse drug reaction reporting practices of Maryland physicians. Dr. Daling felt that the reporting rate is probably higher than 10% due to the unexpected nature of the event.

First dose effect

Drs. Kittner and Daling both felt that a first dose effect may be biologically plausible. Dr. Kittner is firm in this belief and felt it is unwise to assume that the clustering of cases occurring after the first dose is due to reporting bias. However, Dr. Daling points out other explanations for the observation that most CVA cases follow the first dose. For instance she states that: the first dose may be more likely to be in excess of the recommended dose, perhaps many people only take a first dose, there may be an interaction between the indication for use and the blood pressure effects of PPA (i.e., the blood pressure effects may be more pronounced in someone who has reduced their caloric intake or is fasting).

Excess dose

Dr. Whisnant felt excess dose was an irrelevant issue and such cases should be categorized as poisoning. Dr. Daling was unclear as to FDA's role regarding the issue of overdose. Both felt that analyses could be done that were stratified by dose. Dr. Kittner believes that any drug taken for its intended effect should be included as an adverse reaction.

Inclusion of not otherwise specified reports as first day reports

Dr. Daling and Dr. Kittner both feel that inclusion of all cases with duration not specified in the "first day" analyses is not justified. Dr. Kittner points out that only 2 of the 14 cases included in scenario C fall into the category of not specified and would not appreciably effect the results.

Most persuasive scenario

Drs. Daling and Kittner found scenario C to be most persuasive. Dr. Whisnant did not choose among the four scenarios but did make the comment that "[t]he numbers used in the various scenarios cited are interesting but are largely speculative."

c. Results - Are the findings described in parts 1-4 of the April 30 report clear?

All the reviewers felt that the findings were clearly presented.

d. Discussion - Please comment on all critical aspects of the discussion.

Dr. Daling does not agree that the analyses presented in the reports prepared by the Epidemiology Branch, the review of case histories, or the medical literature suggest that PPA diet pills increase the risk of CVA other than to indicate an area in need of study. Specific problems with the data cited by Dr. Daling include: the select voluntary nature of the collection of adverse events; the total lack of knowledge about underreporting; and the lack of information on confounders and adjustment for confounders. Dr. Daling states that "the existence of the case reports to the FDA and those appearing in the literature indicate that a careful population-based case-control study is warranted."

Dr. Whisnant's position is similar to that of Dr. Daling, namely that the suggestion of an increased risk of CVA with PPA diet pills is not warranted because of a lack of reliable information. Dr. Whisnant has reservations concerning the conduct of a case-control study because of the large number of cases required and the possibility of biased recall of PPA diet pill use among the cases and controls (i.e., cases are more likely to recall a drug than are the controls). Dr. Whisnant would prefer a study design making use of computerized pharmacy records. However, he goes on to state that this may not be feasible if over-the-counter drugs are not included in the database.

Dr. Kittner appears to be in agreement with the conclusion reached in the April 30 Epidemiology Branch report that there is a suggestion that PPA diet pills increase the risk of CVA. Dr. Kittner bases this conclusion on the concurrence of the three types of analyses presented, the specificity of the relationship, the presence of first dose and excess dose effects, and the high degree of biologic plausibility. Dr. Kittner agrees with the need for further studies to resolve the uncertainties of the available data and that a case-control study design would be most suitable.

The feasibility of a case-control study examining a possible association of PPA diet preparations and CVA to a large extent depends upon the sample size needed to detect a difference in exposure to PPA diet preparations between cases and controls. Dr. Yi Tsong, Division of Biometrics, has prepared tables estimating sample size based on the following assumptions:

Probability that if the two samples differ this reflects a true difference in the two populations (confidence level). This will be set at 95%.

Probability that if the two populations differ, the two samples will show a significant difference (power). This will be set at 80%.

The number of controls per case - This will be set at 4.

The expected frequency of exposure in the control group - To estimate this exposure the assumptions for scenario C will be used (women < 44 years and 6,000,000 consumers per year). There were 58.4 million women between the ages of 15 - 44 in 1989 based upon data from The Bureau of the Census, Current Population Reports. Therefore the expected exposure frequency for a woman in this age group during anytime in one year would be approximately 10%. However if we assume that a patient is only at increased risk of experiencing a CVA while taking a PPA diet preparation (i.e., risk period = exposure period) and we assume two sixteen day courses per year, the probability that a control is exposed on any given day of the year is 32 days / 365 days X 10% = 0.88%. Likewise if only the first day of each course is felt to be relevant the probability that a control is exposed on any given day of the year is 2 / 365 X 10% = 0.055%.

Determination of an odds ratio that is considered to be of clinical-regulatory significance - Estimation of sample size will be determined for odds ratios ranging from 2 to 10. Based on the two risk periods described in the above paragraph, the sample size for the odds ratios of 2 and 4 are:

	2 day risk period		32 day risk period	
	Cases	Controls	Cases	Controls
Odds Ratio = 2	24,422	97,688	1,533	6,212
Odds Ratio = 4	4,112	16,488	265	1,060

A complete sample size table with calculations of odds ratios from 2 to 10 is attached (Attachment 1).

The estimation of the true exposure prevalence to PPA diet preparations used in the sample size calculations above may be an overestimate based on data provided to FDA on the use of PPA diet preparations from the Case-Control Surveillance Study of the Slone Epidemiology Unit (Attachment 1). Among 8,396 adult women less than 49 years of age admitted to the hospital for illnesses and conditions judged not to be related to use of weight control drugs, only 64 (0.76%) reported recent use (within one year) of a PPA diet preparation.

If we apply a rate of 1 hemorrhagic CVA/10,000 person years to the 58.4 million women aged 15-44 then we would expect approximately 6,000 cases in the U.S. in this age group per year. Therefore to detect an odds ratio of two would require identifying 25% of all incident U.S. cases in one year.

Aspects other than sample size also need to be considered in the feasibility of using case-control methodology to study this issue. Recent cases will have to be identified and interviewed in order to obtain accurate information with respect to use of PPA diet preparations and other possible risk factors (e.g., medications, illicit drugs, alcohol use, smoking history). In many instances surrogates will have to be interviewed due to the patients incapacitation or death. An appropriate control group will have to be identified. A detailed case definition and extensive network of reporters (hospitals, physicians, medical examiners) will need to be established to identify incident cases.

In conclusion, using case-control methodology to study this issue would be difficult because of the low prevalence of exposure to PPA diet preparations and because of the logistic problems presented in identifying and interviewing appropriate numbers of cases and controls. This is especially true if an odds ratio of two or lower is felt to be clinically significant. Limitations of using FDA's cooperative agreements with HMO data include limited sample size and the non-formulary status of PPA diet preparations.

Joel Freiman, MD, MPH

CC:
HFD-100 Temple
HFD-110 Fenichel, Buehler
HFD-700 Anello
HFD-800 Botstein
HFD-814 Cothran, Sherman
File: DRU 1.7 Phenylpropanolamine, CHRON

Attachment 1

SAMPLE SIZE REQUIREMENT FOR PPA CASE-CONTROL STUDY
TWO-SIDED TEST FOR COMPARISON OF TWO PROPORTIONS
TESTING ODDS RATIO = 1

Power= 0.8 N_ratio= 4 Type_I= 0.05

B_grnd Rate	Relative Risk	Study Attr Risk	Odds Ratio	No. of controls	No. of cases	No. in Total
.00055	2.00	.0005494	2.00	97688	24422	122110
.00055	3.00	.0010982	3.00	30764	7691	38455
.00055	4.00	.0016464	4.00	16448	4112	20560
.00055	5.00	.0021940	5.00	10800	2700	13500
.00055	6.00	.0027409	6.00	7896	1974	9870
.00055	7.00	.0032873	7.00	6168	1542	7710
.00055	8.00	.0038331	8.00	5032	1258	6290
.00055	9.00	.0043783	9.00	4236	1059	5295
.00055	10.00	.0049229	10.00	3648	912	4560
.00880	2.00	.0086465	2.00	6212	1553	7765
.00880	3.00	.0171434	3.00	1972	493	2465
.00880	4.00	.0254946	4.00	1060	265	1325
.00880	5.00	.0337039	5.00	700	175	875
.00880	6.00	.0417747	6.00	516	129	645
.00880	7.00	.0497106	7.00	404	101	505
.00880	8.00	.0575150	8.00	332	83	415
.00880	9.00	.0651910	9.00	280	70	350
.00880	10.00	.0727419	10.00	244	61	305

Attachment 2

Send us a copy of questionnaire

Report to the FDA on use of phenylpropanolamine-containing appetite suppressants in data from the Case-Control Surveillance Study of the Slone Epidemiology Unit

April 19, 1991

Lynn Rosenberg, Sc.D.
Slone Epidemiology Unit
1371 Beacon Street
Brookline, MA 02146

Here ask for each drug by indication and a long list.

In response to the request of the FDA for data on utilization of phenylpropanolamine-containing appetite suppressants (PPA), we examined data from our Case-Control Surveillance Study.

In the Case-Control Surveillance Study, our nurse-interviewers administered standard questionnaires to adult patients under the age of 70 years who were admitted to participating hospitals for any of a wide variety of illnesses. Data were recorded on demographic variables, medical history, and habits (such as cigarette smoking). History of use of medications was elicited by questions concerning over 40 indications, which included "diet/weight control." For each episode of drug use, the drug name, dates of use, duration, and frequency were recorded. Over 60,000 patients have been interviewed since the inception of the study in late 1976; of patients approached for an interview, 4 percent refused to participate.

For present purposes, we selected from the total pool of interviewed subjects those who had been admitted to participating hospitals located in Boston, New York, Philadelphia and Baltimore from 1977 through 1991. These centers have accounted for over 80 percent of all patients. We selected 15,687 relatively "healthy" patients who had been admitted for illnesses and conditions that we judged not to be related positively or inversely to the use of weight control drugs: traumatic injuries or orthopedic disorders (5541 patients), and infections, hernias and a variety of other illnesses (10,146 patients.)

For the analyses of PPA use, we searched the entire data base and identified all PPA-containing appetite suppressants that had been reported by brand name by at least one patient -- these are listed in Table 1. Virtually all had been reported for the indication "diet/weight control." The most commonly used appetite suppressant was Dexatrim, reported in 72 percent of episodes of PPA use; the next most commonly reported drug was Super Odrinex, reported in 10 percent of episodes. The prevalence of PPA use was similar in the two major diagnostic categories: patients admitted for trauma or orthopedic disorders, and patients admitted for other conditions.

As shown in Table 2, 1.3 percent of subjects reported having ever used PPA; ever use was relatively constant over the period 1980-1981 through 1990-1991. Recent use of PPA (within the previous year) was reported by 0.5 percent of subjects; the prevalence of recent use was highest in the years 1980 through 1983 and declined thereafter.

As shown in Table 3, use of PPA was more common among women than men: 1.8 percent of women had ever used PPA and 0.4 percent were recent users, compared

with 0.4 percent and 0.1 percent, respectively, of men. The prevalence of use was greatest at young ages. Among women, 3.7 percent of those under age 30 had used PPA, compared with 0.4 percent of women aged 60-69; the corresponding percentages for recent use were 1.7 percent and 0.1 percent.

Table 4 gives ever and recent use of PPA according to body mass index (kg/cm^2). Ever use increased with increasing body mass index, from 1.0 percent in subjects with body mass index less than 24, to 1.5 percent for body mass index 24-27, and 1.9 percent for body mass index 28 or more. Adjustment for age, sex, and interview year changed these percentages slightly. The percentage of recent users was 0.5 percent in each of the three body mass index categories; these proportions were little altered by adjustment for age, sex, or interview year.

Table 5 gives ever use of PPA according to history of selected conditions that might be contraindications for use: history of admission to hospital for myocardial infarction, history of elevated serum cholesterol, history of drug-treated hypertension, history of drug-treated diabetes mellitus, history of thyroid disease (as indicated by history of a thyroid condition or use of an antithyroid drug or thyroid hormone), history of depression (as indicated by history of depression or use of an antidepressant drug). Ever use of PPA was reported by 1.9 percent of subjects with a history of depression compared with 1.3 percent of all subjects. The slightly higher prevalence of use in subjects with a history of depression was not diminished by control for age, sex, or interview year. For subjects with the other conditions considered, the prevalence of ever use was less than in the overall group.

It should be borne in mind that the time sequence of PPA use and the occurrence of the condition, such as diabetes mellitus, are unknown in Table 5: that is, the diabetes mellitus might have occurred after use of PPA. In Table 6, data are given for recent use of PPA according to history of conditions that might be contraindications to PPA use. In this instance, it can generally be assumed that the condition preceded the use of PPA. For all the conditions considered except a history of depression, the prevalence of PPA use was 0.3 percent or less, compared with 0.5 percent in the overall group. Among subjects with depression, based on 4 users, the prevalence was 0.5 percent.

Thus, in general it appears that persons with conditions that are contraindications to PPA use tended to use PPA less frequently than other persons.

Table 7 gives the prevalence of ever and recent use of PPA according to cigarette smoking and alcohol use. In drinkers, the prevalences of ever use (1.9%) and recent use (0.6%) were slightly greater than in the overall group; these differences were diminished by allowance for interview year. Ever and recent use did not differ among smokers (within the previous year) and nonsmokers; this was also the case when smokers were divided according to whether they smoked less than 25 cigarettes per day or at least 25 per day. Thus, in these data PPA use was not materially related to tobacco or alcohol use.

Table 1

PPA-containing appetite suppressants reported by subjects in the Case-Control Surveillance Study

Acutrim
Appedrine
Bio-Slim T
Control
Dexatrim
Dexatrim 15
Dexatrim Extra Strength Caffeine-Free
Dexatrim Caffeine Free
Dex-A-Diet Caffeine Free
Dietac Pre-Meal Diet Aid Tablets
Dietac Pre-Meal Diet Aid Drops
Dietac 12 Hour Diet Aid Caps
Diet-Trim
Full Stop
Grapefruit Diet Plan/C Diadax
Hungrex/C PPA
Panamine
Prolamine
Super Odrinex

Table 2

Ever use and recent use (within the previous year) of PPA-containing weight control drugs

Year	No.	PPA use			
		Ever		Recent	
		No.	(%)	No.	(%)
1977-1979	5535	9	(0.2)	3	(0.1)
1980-1981	1987	41	(2.1)	22	(1.1)
1982-1983	2234	57	(2.6)	23	(1.0)
1984-1985	2370	32	(1.4)	10	(0.4)
1986-1987	1610	35	(2.2)	11	(0.7)
1988-1989	1138	17	(1.5)	2	(0.2)
1990-1991	813	17	(2.1)	0	(0)
TOTAL	15618	208	(1.3)	71	(0.5)

Table 3

Ever use and recent use of PPA-containing weight control drugs according to sex and age

Sex			Age (years) <30	30-39	40-49	50-59	60-69	Total
Female								
Total no.			2081	3008	3307	1337	1005	6548
PPA use:	Ever	no.(%)	76(3.7)	61(2.0)	40(1.2)	9(0.7)	4(0.4)	190(1.8)
	Recent	no.(%)	36(1.7)	15(0.5)	13(0.4)	0(0)	1(0.1)	65(0.4)
Male								
Total no.			1027	1172	892	955	903	4949
PPA use:	Ever	no.(%)	4(0.4)	9(0.8)	3(0.3)	1(0.1)	1(0.1)	18(0.4)
	Recent	no.(%)	1(0.1)	2(0.2)	2(0.2)	1(0.1)	0(0)	6(0.1)

Table 4

Ever use and recent use of PPA according to body mass index

Body mass index (kg/cm^2)	No.	PPA use			
		Ever		Recent	
		No.	(%)	No.	(%)
<24	7187	73	(1.0)	33	(0.5)
24-27	5059	75	(1.5)	23	(0.5)
28+	3141	60	(1.9)	15	(0.5)

Table 5

Ever use of PPA–containing weight control drugs
according to conditions that are contraindications for use

Condition	No.	Ever used PPA	
		No.	(%)
Total subjects	15687	208	(1.3)
History of myocardial infarction	253	1	(0.4)
History of elevated serum cholesterol	790	7	(0.9)
History of diabetes mellitus	375	3	(0.8)
History of hypertension	1808	4	(0.2)
History of depression	739	14	(1.9)
History of thyroid disease	942	11	(1.2)

Table 6

Recent use of PPA-containing weight control drugs according to conditions that are contraindications for use

Condition	No.	Recent PPA use	
		No.	(%)
Total subjects	15687	71	(0.5)
History of myocardial infarction	253	0	(0)
History of elevated serum cholesterol	790	2	(0.3)
History of diabetes mellitus	375	0	(0)
History of hypertension	1808	0	(0)
History of depression	739	4	(0.5)
History of thyroid disease	942	1	(0.1)

Table 7

Ever use and recent use of PPA-containing weight control drugs according to cigarette smoking and alcohol use

			PPA use	
			Ever	Recent
		No.	No. (%)	No. (%)
Nonsmoker		8958	117 (1.3)	39 (0.4)
Smoker		6565	91 (1.4)	32 (0.5)
Alcohol use:	Regular*	7300	122 (1.7)	42 (0.6)
	Occasional	5762	59 (1.0)	25 (0.4)
	None	2256	16 (0.7)	4 (0.2)

*At least 4 days a week.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 2, 1992

FROM: Charles Anello, Sc.D., Acting Director
Office of Epidemiology and Biostatistics (HFD-700)

SUBJECT: Phenylpropanolamine (PPA) MEETING 9/1/92

TO: Joel Freiman, M.D., Acting Chief
Epidemiology Branch

Two issue arose from the PPA meeting yesterday which require Epidemiology Branch input.

1) The three consultants do not fully agree on the review of the material provided relating to phenylpropanolamine and adverse cardiovascular events. In order to decide on the next course of action, we need a detailed point-by-point summary of the three expert opinions and points of disagreement. DES was asked to prepare their summary and to draft a letter asking for further responses to see if the differences, if any, could be resolved.

2) The second issued concerns the proposed case control study. Two of the three experts say a case control study is possible and the other says would be difficult to interpret. What are the key elements of the design and size of study? What is Epi's opinion? How would such a study be designed? Could Epi do such a study using our Cooperative Agreements or contracts? Could we advise industry on how to prepare the study? Could we utilize already planned studies in this arena?

   Could Shapiro or a multi-record linkage study using all or HMO's work?

The precise wording of the FR Notice will depend, in part, on Epi's response. Thus, The Division of OTC Products would like a response by 9/2//92.

Charles Anello

Charles Anello, Sc.D.

Copies:
HFD-100/Botstein/Temple
HFD-700/Chron/File:PPA
HFD-730/Johnson
HFD-800/Gilbertson
evh:September 2, 1992

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November 17, 1992

Paula Botstein, M.D.
Activity Director
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research
7520 Stardish Place, Room 217
Rockville, Maryland 20855

RE: OTC Trac No. 210-09

Dear Dr. Botstein,

Thank you for the opportunity to review the responses of the 2 other consultants, Drs. Jack Whisnant and Janet Daling, as well as the FDA's Epidemiology Branch's sample size estimates for a case-control study.

Dr. Whisnant, Dr. Daling and I are in agreement with the FDA Epidemiology Branch Reports on April 30, August 6, and December 6, 1991 in suggesting that further epidemiologic studies are needed to resolve the uncertainties in available data regarding the stroke risk associated with phenylpropanolamine (PPA) use. We all agree that the data does not permit the conclusion that PPA is safe. Dr. Whisnant shares the concern expressed in your October 21, 1992 letter regarding sample size, and he also expresses concern regarding the potential for information bias in a case-control study.

Recall or information bias is a potential drawback of all case-control studies. Yet, the public health has been advanced by the application of case-control methodology in many areas of inquiry. For example, the demonstration of a stroke risk from oral contraceptives was first accomplished by case-control studies and later confirmed by follow-up studies.

I believe that your interpretation of the sample size projections lead you to overly pessimistic conclusions regarding the feasibility of a case-control study. I agree that a sample size adequate to detect a relative risk of 2 (N=1553) would be impractical, particularly within a 1 year time frame. However, a multi-year study involving several centers with the capability of case-ascertainment over large populations should make detection of a relative risk of 3 (N=493) attainable.

In summary, available evidence does not permit the conclusion that this over-the-counter medication is safe, nor will this longstanding controversy be resolved without additional new data. I continue to believe that a case-control study is the method most likely to provide quantitative information on the stroke risk associated with PPA use. In lieu of such a study, a rational alternative would be to withdraw PPA from its over-the-counter status.

I hope these comments are useful to your efforts to reach a scientific consensus on the safety of PPA.

Sincerely,

Steven J. Kittner, M.D., M.P.H.
Assistant Professor of Neurology,
Epidemiology and Preventive Medicine

SJK:mef

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Division of Public Health Sciences
Weiss/Daling Studies (MP 381)

November 16, 1992

Paula Botstein, M.D.
Acting Director
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Botstein:

Thank you for sending the reviews of Dr. Jack P. Whisnant and Dr. Steven J. Kittner on your evaluation and risk assessment of phenylpropanolamine (PPA) use and subsequent occurrence of stroke and hypertensive episodes. I do not think my review and that of Dr. Whisnant differ substantially. Although this agreement extends for most of Dr. Kittner's review, he appears to be more convinced that a causal relationship exists. And, although I agree with his line of reasoning stated on Page 8 of his review, I still think that deriving conclusions from adverse drug reports is a tenuous exercise.

Case-control studies of subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke are difficult to conduct; with careful design and evaluation they illicit worthwhile data as evidenced by the enclosed paper by Longstreth et al. This study was conducted by my research team, and you can review the methodology and the evaluation of the responses from surrogates.

The first question to answer in considering the case-control methodology is whether you are convinced that only the first day/dose of use poses any risk. In suggesting a case-control study, I did not consider this to be proven. I agree then Dr. Whisnant that the stroke case may be more likely to report an event connected with a drug used for the first time. In fact, I think that it is <u>likely</u> this bias exists. At the very least, I do not think you have data to refute this possibility. For this reason I think a 32-day risk period should be considered. I <u>do agree</u> with the power/sample size calculations presented in your letter and the conclusion that assessing a two-day risk period is not feasible.

I have enclosed a copy of a paper describing a case-crossover design. This method is designed for studying transient effects of an exposure. Only cases are used. It does assume that the cases are accrued in an unbiased manner.

I hope these comments are helpful to you. Please call me if you have further questions.

Sincerely,

Janet R Daling

Janet R. Daling, Ph.D.

JRD:csb
Enclosures (2)
cc: Robert Sherman ✓