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July 31, 1992

Paula Botstein, M.D.
Acting Director
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research
1520 Standish Place Room 217
Rockville, Maryland 20855

Dear Dr. Botstein,

I have carefully reviewed the materials you and Mr. Shernam have sent regarding the use of phenylpropanolamine (PPA) containing diet compounds and subsequent adverse cardiovascular outcomes. It was an interesting exercise to review the data, but I do not feel the hypothesis can be assessed with existing data.

It is my opinion that the reports in the medical literature and to the FDA, along with the biological plausibility of a possible association due to the pressor effect of PPA, indicate the need for a population based case-control study of PPA use and intracranial bleeding. It is also my opinion that the analyses prepared by the FDA, and reports in the current medical literature, do not support or refute a possible association. There are too many limitations to the data. These concerns are discussed more specifically in the summary that follows.

My research group completed a population based study of subarachnoid hemorrhage and oral contraceptives, Principle Investigator William Longstreth, MD, (206) 223-3251. 150 cases and 300 controls were interviewed. Unfortunately the question on diet pills was included in a list of other stimulants. They found relative risks of 12 for use of stimulants in the week before the ever. I have attached the paper (see pages 9 and 15) which will appear in Stroke this fall, and the questionnaires and show cards. I talked to Dr. Longstreth about the need for specific data on over-the-counter diet pills. He is considering contacting the patients who answered yes to the stimulant question, or their surrogates if they are deceased, in order to clarify the exposures to facilitate an analysis of over-the-counter diet preparations.

In addition, NICHD is currently funding two studies, Principal Investigators David Siscovick MD (206) 223-8050, Seattle, and Diane Petiti MD and Gary Friedman MD (415) 987-2124, Kaiser Permanente Oakland, to evaluate oral contraceptives and cardiovascular events. Dr. Siscovick has agreed to add specific questions on PPA related drugs including as timing, use patterns, and dosage in relation to CVA events.

Thank-you for the opportunity to review this interesting potential problem. If you have other specific questions or if I can clarify any of my comments, please feel free to call me.

Sincerely,

Janet R. Daling

Janet R. Daling, Ph.D.

Mayo Clinic Rochester, Minnesota 55905 Telephone 507 284-2511

August 3, 1992

Department of Health Sciences Research
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Section of Health Services Evaluation
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Mr. Robert Sherman
Office of OTC Drug Evaluation
Federal Drug Administration, HFD-814
7520 Standish Place, Room 217
Rockville, MD 20855

RE: OTC Trac No. 206-12

Dear Mr. Sherman:

This is in response to your letter of June 22, 1992 and concerns your request that I assist the Agency by commenting on your evaluation and risk assessment of phenylpropanolamine (PPA) used in over-the-counter weight control drug products. I have reviewed the material that you sent with special attention to the reports that were generated from the Epidemiology Branch noted in your letter. I shall respond to the questions in your letter by reference to the identification of the questions in your letter.

1. The Epidemiology Branch reports of April 30, August 6, and December 26, 1991 do adequately describe the data and methods used to evaluate the occurrence of stroke and hypertensive episodes related to the use of PPA for weight control. The data and methods do not support the conclusions that were reached.

   a. The reasons are clear and I believe are valid for focusing on adverse drug experience reports to FDA's spontaneous reporting system and in the medical literature. I believe it is appropriate not to use data from the Poison Control Centers and the Drug Abuse Warning Network.

   b. (1) I believe it is appropriate to focus on use of PPA for weight control because of the combination drugs that are used for cough-cold preparations

      (2) The estimated incidence rate of intracerebral hemorrhage in young women of 1 per 10,000 person years is reasonable from the literature cited. It would not include subarachnoid hemorrhage (SAH), but SAH may not be an issue. In the population of Rochester, Minnesota, in the 40-year period from 1945 through 1984 the rates for intracerebral hemorrhage gradually decreased in each decennial period through 1974 but increased in the 1975-1984 decennium. This is similar in all age groups and for all types of stroke except subarachnoid hemorrhage, so it would not seem to put a focus on young persons or on intracerebral hemorrhage.

      The numbers used in the various scenarios cited are interesting but are largely speculative. The percent of reporting is the key along with the expected rate of intracerebral hemorrhage. It is also key to have a clear understanding of the number of persons that are exposed and, in spite of the numbers cited, I do not have much confidence about that knowledge. The number of days of exposure for an individual

cycle of treatment may well be appropriate for the average user. In my opinion, a 10% reporting rate would be believable because of the serious nature of most intracerebral hemorrhages.

c. The findings described in Parts 1-4 of the April 30 report are clearly presented.

d. The conclusion from the analysis of the report to the SRS and the literature suggesting that PPA diet pills increased the risk of stroke is not warranted from the data that are presented. The conclusion is not warranted primarily because of the lack of reliable information. I agree that it is not feasible to test the hypothesis of an association between PPA weight control product and cerebral hemorrhage by a clinical trial or by a cohort study because of the low event rate. I also believe that a case-control study in this circumstance would be an unsatisfactory approach. It would have to include a large number of cases and some kind of assurance that the knowledge regarding exposure was equally satisfactory for the cases and the controls. I believe that would be doubtful since the cases are much more likely to recall some possible association with an event or drug than are the controls, and particularly so after any delay in trying to obtain the information.

In my opinion, it would be better to do an external comparison but with clear knowledge of exposure by tracking through computerized pharmacy records. I am not sure that this is possible for an over-the-counter drug that does not require prescription, but it would seem to me to be the reasonable way to obtain even adequate information on exposure.

(1) The observation of a possible effect of an excessive dose seems to me to be irrelevant and more in the category of poisoning and probably is not relevant to the issue at hand.

(2) The observation that most stroke cases follow the first dose may be relevant but I think it is difficult to judge that point as it might have a different implication to a patient because of the recent beginning of a new drug than it would be otherwise. The evidence that tolerance is rapidly developed in terms of blood pressure response is not particularly helpful because it is not clear what happens if the patient is not taking the drug for 1 or 2 or more days during a course of treatment. I agree, therefore, that it may be a consequence of reporting bias and the drug relationship to this first day effect is not convincing.

(3) I do not believe the ratio comparison is a very useful control for possible reporting bias.

(4) The reasons noted on page 8 of the April 30 report for a difference in reporting stroke following use of weight control preparations and cough-cold products seems to me to be plausible.

(5) I have already commented on this issue earlier in this letter for both the first day scenario and the other scenarios.

(a) I reviewed the discussion in the December 26, 1991 report of the differences between Dr. Jolsen's cases and those of the Non-Prescription Drug Manufacturers Association (NDMA). I do not believe the NDMA report provides any convincing information that there is not an added risk from PPA.

(b) It is best not to include gross overdoses, but it seems to me the analysis could be done both ways.

(c) I find the 10% reporting scenario most convincing which would allow me to guess that the relative risk is close to 1, but I must emphasize that it is a guess and that the information to make this judgment is inadequate. I believe it is entirely possible that a full pressor response might occur after skipping one day, but that needs to be tested.

(d) I have already indicated that I believe that the 10% reporting rate seems to be reasonable for a severe adverse event, such as intracerebral hemorrhage.

I believe that I have covered all of the relevant points in responding to your queries.

Sincerely,

Jack P. Whisnant

Jack P. Whisnant, M.D.

JPW/dj