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

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SUBJECT: **Review of study protocol, final study report and raw data regarding the incidence of hemorrhagic stroke associated with the use of phenypropanolamine.**

TO: Charles Ganley, M.D., Director,
Division of OTC Drug Products, HFD-560

PID # D 000487

Executive Summary

This consult is in response to a request from the Division of OTC Drug Products, HFD-560, to review the study report entitled "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of the Hemorrhagic Stroke Project", the study protocol and raw data submitted by Yale University. It was designed to test the association between hemorrhagic stroke in young people and use of phenylpropanolamine-containing products, a signal generated from studying case reports in our spontaneous reporting system. Our overall conclusion is that this study was well designed and executed. The case-control design was best suited for this study since the outcome under investigation was rare. All reasonable steps were taken to minimize bias and confounding. The study demonstrated a statistically significant increased risk of hemorrhagic stroke among both appetite suppressant users and first time users of PPA as a cough/cold remedy.

OPDRA concludes that the study provides compelling evidence of increased risk of hemorrhagic stroke in young people who use PPA-containing appetite suppressants. This finding, taken in association with evidence provided by spontaneous reports and case reports published in the medical literature, leads us to recommend that these products should no longer be available for

over-the-counter use.

The Yale investigators also found a statistically significant association between first time PPA use in cough/cold remedies and hemorrhagic stroke. OPDRA considers this association to be as important as that for use of PPA as an appetite suppressant. FDA continues to receive spontaneous reports of hemorrhagic stroke with high-dose cough/cold remedies. Some reports indicate that only one dose was administered. The doses of PPA delivered in cough/cold preparations overlap those delivered in appetite suppressants, and there is evidence to suggest that the risk of hemorrhagic stroke may be higher with PPA doses at or above 75 mg/day. OPDRA concludes that high-dose PPA cough/cold remedies are associated with an increased risk of hemorrhagic stroke. These high doses may be achieved by exceeding the recommended labeled dose of the low-dose products. OPDRA therefore recommends that PPA-containing cough/cold remedies should no longer be available as over-the-counter products.

Introduction

This consult is in response to a request from the Division of OTC Drug Products, HFD-560, to review the study report entitled "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of the Hemorrhagic Stroke Project", the study protocol and raw data submitted by Yale University, as well as comments on the Hemorrhagic Stroke Project Report, May 24, 2000, provided by the CHPA Phenylpropanolamine Working Group. We were also requested to provide an update of cases of hemorrhagic stroke associated with phenylpropanolamine (PPA) use, reported to the Agency's Adverse Event Reporting System (AERS) since the end of January 1991, the date of the last review.

The body of this memorandum contains the review of the study protocol and final report. Appendix A contains an update of cases of hemorrhagic stroke in AERS along with information on background incidence rates of hemorrhagic stroke. Appendix B contains a response to CHPA's comments, in the form of a consult to OPDRA prepared by Dr. Yi Tsong from the Office of Biostatistics.

Review of Study Protocol and Report

The Yale study demonstrated an increased risk of hemorrhagic stroke associated with PPA use. The investigators found the increase in risk of hemorrhagic stroke to be statistically significant among appetite suppressant users and first time users of PPA as a cough/cold remedy. Observational studies, particularly case-control studies, are potentially subject to a number of biases, and this case-control study is no exception. However, the hallmark of a good case-control study is that these biases are anticipated and measures instituted in the design and analysis stages to minimize them to the greatest extent possible. In reviewing the design and analysis of this study we will attempt to examine potential biases and the measures taken to minimize them. We will also report on additional analyses undertaken by us to test the consistency of the data and the

results.

Study Objectives
The objectives were clearly identified and articulated, and were threefold:
1) To estimate the association between PPA and hemorrhagic stroke among men and women aged 18 – 49 years;
2) To estimate the association between PPA and hemorrhagic stroke by type of PPA exposure among the same target population;
3) Among women aged 18-49 years to estimate (a) the association between first use of PPA and hemorrhagic stroke and (b) the association between PPA in appetite suppressants and hemorrhagic stroke.

We must point out that from the Agency's point of view, the third hypothesis [parts (a) and (b)] was the most important, as this was generated from studying case reports in our spontaneous reporting system as well as those reported in the published literature (Heidi Jolson, 1991) and was the main stimulus for the performance of this study. It is therefore pertinent that these were the hypotheses that were found to be statistically significant.

Case Definition
Strict diagnostic criteria were developed to ensure accurate identification of hemorrhagic stroke cases in the target population. Both clinical and diagnostic criteria had to be met. Clinical criteria included signs and symptoms consistent with hemorrhagic stroke. Diagnostic confirmatory criteria were either CT scan or MRI or lumbar puncture in the absence of CT scan or MRI. One of the investigators confirmed the disease status by reviewing the medical records of suspected cases, without knowledge of the exposure status of the cases. This served to minimize **misclassification bias** among cases.

Inclusion/Exclusion Criteria
These were clearly defined for both cases and controls, again minimizing **misclassification.**

Exposure Definition/Ascertainment
Exposure was clearly defined and an exposure window was identified. Ascertainment of exposure was undertaken by trained interviewers. It was not possible to blind interviewers as to case/control status. To minimize potential **interviewer bias**, interviewers were randomly assigned to cases or controls, and questions were asked about multiple medications, thus blinding them to the exact exposure under study. In addition, subjects were only classified as "definitely exposed" if the exposure was confirmed by one of several methods outlined in the protocol. Both cases and controls were interviewed in-person. The location of in-person interviews was determined by the subject's preference. Cases were interviewed either in hospital (majority) or at home. Controls were interviewed at home, physician's office, or other convenient location. Since the choice of the location of the interview was based on the subject's preference and convenience, it is highly unlikely that the location of the interview would be related to the use of PPA. Forty-four of the 1376 controls and three of 703 cases preferred to complete the interview by telephone. Since telephone interviews only were conducted on a very small fraction of cases and controls,

any bias due to differences in ascertainment methods should be minimal, and would be expected to be non-differential with respect to the interviewing methods.

Opportunity of Exposure

Since the use of PPA might be seasonal, to ensure that cases and controls had an equal opportunity of exposure, controls were identified and interviewed within 30 days of the index date (e.g., date of stroke) of their matched case subject. Controls were also matched to cases for day of the week and time of day of the stroke. This matching strategy ensured the probability of exposure to any medication or other covariates (e.g., alcohol drinking or cigarette smoking) was similar between cases and controls since their use could vary by time and by day of the week.

Recall Bias

Recall bias reflects the greater likelihood of cases to recall events prior to or surrounding the event of interest, in this case, the stroke. Several strategies were used to minimize recall bias. First of all, case subjects were interviewed within a short period of the index day (mean 13 days, range 0 – 30 days). Another strategy to minimize recall bias was to obtain information on **all** medications used, and by the use of date prompts, such as birthdays or dates of other significant events. For the purpose of ascertainment of PPA exposure, a focal time for controls was established as one of the 7 days prior to their identification as controls. The focal time was matched with the day and time of day of the matched case's focal time – the time of onset of symptoms that led the cases to seek medical care. This was another method of ensuring that controls were able to recall the events accurately (a short period to the event). Further, by making the "exposure opportunity" the same for cases and controls for those variables that could vary by time of day, and day of the week, the potential for **information bias** was also minimized. Information bias refers to differences in data quality and completeness based on the method used to obtain the information.

Independence of Association of Exposure to Cases or Controls

Assessment of exposure was independent of the selection of cases and controls. It is unlikely that participation in the study was related to PPA use. First, more than 85% of cases were identified from 3 sites which enrolled nearly all of the acute care hospitals in their geographic location. Second, the reason why most eligible non-participants did not participate in the study was that for logistic reasons the interviewer was not able to contact these case subjects within 30 days after the stroke, as specified in the protocol. There is virtually no possibility that the interviewers' inability to contact these individuals on time was related to the use of PPA, as the exposure status of the cases was unknown. For controls, although we do not have any information on how many eligible controls refused to participate, nor what was the overall response rate, there is no reason to believe that PPA use was related to participation of controls.

Selection Bias

A potential bias in case-control studies is selection bias. This may occur when groups of patients are selected into the study for whom risk of disease is different from that of the whole group with the disease. The possibility of selection bias exists in this study because the most severe cases

were excluded, i.e., those who died, were unconscious or unable to speak up to 30 days after the stroke. This was considered by the investigators in the planning stage but was weighed against the exposure misclassification error that would result from the use of proxy interviews for these cases. Sample calculations were done and the results indicated that the error from proxy interviews greatly exceeded that from any potential selection bias that might result from excluding cases that were unable to speak. The investigators also calculated that the impact of exposure misclassification error introduced by proxy respondents would have been so great as to render the study incapable of detecting an odds ratio as great as 10. In other words, there would have been no point in conducting the study. In order to determine the impact of excluding these cases on the estimate of the odds ratios we would have to assume that PPA use was related to the survival or severity of a stroke, and we have no reason to believe that this is true.

Selection of Controls

The authors attempted to identify 2 controls per case by using random digit dialing. This was a good strategy for two reasons. First, the controls were chosen completely at random; second, the controls were population-based, so that the results are generalizable to the source population from which the cases and controls were drawn. To ensure comparability between cases and controls with respect to some of the risk factors (possible confounders), attempts were made to enroll controls that were matched with cases on gender, age, race (black, other), and telephone exchange (surrogate for socioeconomic status). Although matching increases the complexity of a study, in case-control studies, it is considered an excellent method for efficient controlling of the confounding variables analytically. Although matching was largely successful, matching on race and educational level was slightly unequal between cases and controls. The authors further controlled for these inequalities by adjustment during analysis. Since the use of PPA might be seasonal, and to ensure that cases and controls had an equal opportunity of exposure, controls were identified and interviewed within 30 days of the index date of their matched case subject. Finding matching controls seems to have been difficult as the average number of phone calls dialed to find matches for each case was 150.

Temporal Precedence Bias

To ensure that the exposure preceded the onset of stroke, the authors used detailed accounts of subjects' onset of symptoms in relation to diagnosis. This information was used to establish a focal time as previously described. The focal time refers to the time of onset of symptoms that led the patients to seek care. Only medication use prior to the focal time was considered relevant to the study question. Since headache may be a symptom of stroke, the authors also examined the "alternate focal time" on the estimate of effect measurement to rule out the possibility of temporal precedence bias. The "alternate focal time" represented the earliest possible time that intracerebral bleeding could have occurred and the onset of sentinel headache was chosen as the "alternate focal time". Sub-analyses using the "alternative focal time" yielded estimates of the odds ratio that were similar to that found with the original focal time, leading the investigators to conclude that temporal precedence bias in this study was minimal or not present.

Misclassification Bias

The investigators reduced the possibility of misclassification of exposure (PPA use) by using a

highly structured questionnaire. Events such as birthdays, holidays, and special events were used as memory aids. The authors also verified each of the reported medications by asking the subjects to present the actual container of the reported medication or by picking out reported brand-name medications from a book containing photographs (Product Identification Book). Verification for medication use in the 3-day window prior to the focal time was 96% and 94% for cases and controls respectively. This verification was another method of reducing misclassification of PPA use. Additionally, the authors conducted two more steps to further ensure that the possibility of exposure misclassification error was reduced to an absolute minimum. One, they only considered the "definite" and "possible" exposure responses in the analyses. Two, they compared the use of other non-prescription medications between cases and controls to ensure that the cases did not systematically have greater recall of the use of any medications as a reason for their recent stroke. Based on their analysis, there was no evidence of recall or misclassification bias.

Sample Size

An essential step in the design of case-control studies is conducting sample size and/or power calculations to ensure the study is large enough to detect a difference if one really exists. Considerations are given to the rarity of the outcome and of the exposure, as well as to cost and time constraints. The authors did this in the protocol. They took into account the rarity of hemorrhagic stroke in young people, the problem of finding matched population controls and the prevalence of PPA exposure in the population. They set up surveillance systems to detect as many cases of stroke as possible, and estimated how long the study would take. However, historical records indicate that the Agency was concerned that the study might be underpowered to detect an association since the original sample size calculation was based on an odds ratio of 5 for an association between hemorrhagic stroke and first use of PPA. We must point out that the odds ratio of 5 was not determined by any public health or clinical considerations, but on practical considerations related to time and cost constraints. As often happens in epidemiologic studies in the field, the investigators encountered practical problems including difficulties in recruiting controls, which contributed to the study taking longer than expected. Despite this, it should be noted that this is a particularly large prospective case-control study, the largest ever conducted on hemorrhagic stroke. In spite of the Agency's initial reservations about inadequate sample size and power, the study still identified an association between PPA use and hemorrhagic stroke in the 3-day period following initial use, the time period of greatest concern and suspicion.

Statistical Analysis

Exposure Variables

As outlined in the study protocol, the authors examined two exposure-windows for PPA use: one was defined as "the index day prior to the focal time and the preceding three calendar days", the other was defined as PPA use on "the index day prior to the focal time or on the preceding calendar day". In other words, the first exposure window included the three days prior to the stroke date and the second window – defined as *current use* - included the day preceding the stroke. If the latter exposure occurred without any use of PPA during the preceding two-week

period, that exposure was referred to as *first use*. *Not-first use* is current use with other use in the two-week period before the index date.

Covariates
The investigators collected a large amount of information on risk factors for stroke by interviewing study participants. The confounding effect of these variables was assessed analytically. The three most important risk factors: race (black or non-black), history of hypertension, and cigarette smoking, were included in the multivariate analysis (basic adjusted model). The confounding effect of the other covariates was examined if adding any of them to the basic model altered the odds ratio estimate by 10%. High school education was the only covariate determined to change the odds ratio by at least 10%.

Statistical Method
Appropriately, the conditional logistic regression model was used for calculating both unadjusted and adjusted odds ratios, since the study had a matched design. Since the number of exposures was small particularly for analysis of appetite suppressant and first use, the authors calculated the confidence interval of unadjusted odds ratio based on an exact method. For the purpose of statistical testing, the authors reported only the lower limit of the one-sided 95% C.I. as pre-specified in the protocol.

Additional Statistical Analyses of Raw Data Conducted by OPDRA

Potential Confounding by Hypertension and Other Factors
Hypertension is the single most important risk factor for a stroke, followed by smoking, body weight and alcohol consumption. Life-style changes may lower hypertension and thus the risk for stroke. Therefore, past history of hypertension may not be reflective of the hypertension status of an individual at the time of a stroke. This misclassification of hypertension status could result in residual confounding. Let us therefore examine the possible effects of this residual confounding on the results of the study. First, the odds ratio for appetite suppressant use is 15.92, a substantial increase in risk. Its very magnitude makes it difficult to explain by confounding alone. Second, in order for a variable to be a confounder, the variable must in some way be associated with the exposure. There is very little evidence to support the view that PPA use/non-use is related to hypertension. Since the labels of PPA-containing products advise that PPA use should be avoided in hypertensive persons, the association of PPA use with hypertension should be negative. Such a negative association would result in biasing the result towards no association (OR=1) if the confounding factor is not controlled for. Thirdly, in addition to the steps taken by the investigators, we examined this further ourselves by additional analyses restricted to subjects without a past history of hypertension as described earlier, and the results did not change materially, thereby providing additional evidence that confounding by hypertension is not present.

We analyzed education and body mass index (BMI) as continuous rather than categorical variables, and again the OR remained largely unchanged. At our request, the Yale investigators

explored the possible impact of cigarette smoking and alcohol consumption in a more detailed way. The following is an excerpt from their report.

With regard to cigarette smoking*: "The following measures of cigarette smoking were examined for their effects on all PPA-stroke associations: Current cigarette smoker (yes/no); average number of cigarettes per day smoked in 3-day exposure period (continuous variable); average packs per day smoked in 3-day exposure period (<1, 1, 2+); cigarettes smoked in 3-day exposure period (any vs. none); average number of cigarettes per day smoked in prior 6 months (continuous variable); average packs per day smoked in prior 6 months (<1, 1, 2+). Odds ratios for PPA and stroke were essentially unchanged by inclusion of any of these quantitative measures of smoking."*

With regard to alcohol consumption: *"The following measures of alcohol consumption were examined for their effect on all PPA stroke associations: Any positive response to history of alcohol abuse screening questions; 3 or more positive responses to history of abuse questions; average number of drinks per day in 3-day exposure period (continuous variable); average of more than 2 drinks per day in 3-day exposure period (yes/no); average number of drinks per week in prior 6 months (yes/no). Odds ratios for PPA and stroke were essentially unchanged by inclusion of any of these measures of alcohol consumption and final adjusted models were reported without adjustment for alcohol use."*

In summary, the investigators examined the impact of all important confounding factors on the estimates.

Dose Response

The investigators examined the association between current PPA dose and risk for hemorrhagic stroke. Among 21 exposed control subjects, the median current dose of PPA (i.e., the total amount taken on the index day or preceding day) was 75 mg. The adjusted odds ratio was higher for current doses above 75 mg than for lower doses. Among first dose users, four of eight cases and two of five controls were exposed to > 75 mg of PPA.

Given that 75 mg is contained in a single dose of many over-the-counter long-acting PPA cough/cold remedies, and that recommended adult dosing is every 12 hours or 150 mg/day, OPDRA further evaluated the association between risk of hemorrhagic stroke and a range of current PPA doses. Exploratory analyses suggest that there may be an increased risk of hemorrhagic stroke with labeled doses at or above 75 mg/day; dose-ordering of odds ratios was seen.

Sparse Data Bias

The small number of exposed subjects (i.e., PPA users) limits the power of the study and may also result in sparse data bias, particularly for the results for appetite suppressant and first use of PPA. In order to examine the impact of sparse data bias, we conducted three sensitivity analyses. The results are displayed in Table 1. In each case we changed the exposure status of only one subject. In the first analysis, we changed the status of one case subject from non-exposed to

exposed while his/her matched control remained non-exposed. The odds ratio for PPA in appetite suppressants and first time PPA use changed from 15.92 to 20.31 and from 3.14 to 3.45, respectively. In the second analysis, we changed the status of one control subject from non-exposed to exposed, while his/her matched case remained exposed. The odds ratio of PPA in appetite suppressants and first use of PPA changed from 15.92 to 14.42 and from 3.14 to 3.07, respectively. In the third analysis, we changed the status of one control subject from non-exposed to exposed, while his/her matched case remained non-exposed. Under this condition, the odds ratio of PPA in appetite suppressants and first use of PPA changed from 15.92 to 7.29 and 3.14 to 2.27, respectively. We consider these scenarios unlikely because great care was taken to avoid misclassification error, such that changes in excess of 10% are highly improbable. **The association of appetite suppressants and first use of PPA still remains even under these conditions.**

Further, we examined the impact of moving two control subjects from a non-exposed to an exposed status. This analysis was only employed for matched pairs in which both cases and controls were non-exposed. Under this condition, the odds ratio of hemorrhagic stroke associated with PPA in appetite suppressants changed from 15.92 to 3.22 and the odds ratio of stroke associated with first use changed from 3.14 to 2.1. Again, even under this extremely unlikely condition, the association of PPA containing products with hemorrhagic stroke remains. We interpret this to mean that the association between appetite suppressant and first use of PPA with hemorrhagic stroke cannot be completely explained by the sparse data bias alone.

Discussion

This epidemiologic case-control study was designed to test specific hypotheses generated by analysis of spontaneous reports received by the Agency from 1977 to 1991. These reports strongly suggested an association between hemorrhagic stroke and use of high-dose PPA as an appetite suppressant. Additional evidence of an association was suggested for use of PPA as a cough/cold remedy. Most of the reports were associated with first use of these products. Domestic reports of stroke in women aged 10-59 years topped the list of drugs with reports of stroke in this population in the Agency's adverse event report database (SRS). Additional details regarding these reports are summarized in Dr. Tsong's review in Appendix B.

An updated search of spontaneous reports of hemorrhagic stroke in the 18-49 year age group in the Agency's adverse event reporting database (encompassing 1991 – 2000) revealed 16 additional cases, thirteen occurring in women. In all cases, the suspect drug was a long-acting preparation containing 75 mg of PPA per unit dose. Of eleven cases for which the indication of use was provided, ten reported an indication for respiratory symptoms. Further clinical details are provided in Appendix A.

Case reports in the literature are consistent with spontaneous reports received by the Agency in suggesting a possible association of PPA use and hemorrhagic stroke.

The study conducted by Yale University was well designed and executed and its findings merit serious attention. The strengths of the study lie in the clarity of its objectives, the meticulous adherence to sound epidemiology practices in its design and execution, and the consistency of the findings, regardless of the analytic methods. Its only limitation was in the power and sample size, which we discussed earlier. That the study was nevertheless able to find a consistent association between PPA use and hemorrhagic stroke, particularly in women, attests to its overall high quality.

The case-control design was best suited for this study since the outcome under investigation was rare. All reasonable steps were taken to minimize bias and confounding. Quality control measures were built into the design. Analysis was appropriate for the type of study. For the sub-sets of PPA use as an appetite suppressant and of first time PPA use as a cough/cold remedy, the association was statistically significant and was most striking in women.

Conclusion

The Yale study was a well-designed case-control study with prospectively defined endpoints and appropriate statistical analyses. Study conduct and analyses of results were done according to protocol. Specific conclusions of OPDRA follow.

Appetite Suppressants. In the Yale study, for the association between hemorrhagic stroke and PPA use in appetite suppressants within the three-day exposure window, the adjusted odds ratio was 15.92 (lower confidence limit=2.04, p=0.013). For the association between PPA in appetite suppressants and risk for hemorrhagic stroke among women, the adjusted odds ratio was 16.58 (lower confidence limit=2.22, p=0.011). OPDRA believes that the weight of evidence from this epidemiologic case-control study taken together with spontaneous reports and reports in the published literature strongly suggests that PPA use as an appetite suppressant is associated with hemorrhagic stroke.

Cough/Cold Remedies. In the Yale study, for the association between hemorrhagic stroke and PPA use in cough/cold remedies within the three-day exposure window, the adjusted odds ratio was 1.23 (lower confidence limit=0.75, p=0.245). For first time PPA use among women, the adjusted odds ratio was 3.13 (lower confidence limit=1.05, p=0.042). All first dose PPA use involved cough/cold remedies. We note that the lower odds ratio encountered with first time PPA use represents a wide range of doses of PPA in the different preparations (e.g., 6.25 – 75 mg/dose).

We consider the association with hemorrhagic stroke for cough/cold remedies as important as that for use of PPA as an appetite suppressant. FDA continues to receive spontaneous reports of hemorrhagic stroke with high-dose PPA cough/cold remedies in recent years. Some reports indicate that only one dose was administered. The doses of PPA delivered in cough/cold preparations overlap those delivered in appetite suppressants, and there is evidence to suggest that the risk of hemorrhagic stroke may be higher with PPA doses at or above 75 mg/day. We conclude that high-dose PPA cough/cold remedies are associated with an increased risk of

hemorrhagic stroke. These high doses may be achieved by exceeding the recommended labeled dose of the low-dose products.

Recommendations

OPDRA recommends that over-the-counter use of PPA as an appetite suppressant be reevaluated in light of its strong association with hemorrhagic stroke. We recommend that PPA-containing appetite suppressants should no longer be available as over-the-counter products.

OPDRA recommends that over-the-counter use of PPA as a cough/cold remedy be reevaluated in light of its positive association with hemorrhagic stroke. Although the odds ratio is less than that for PPA-containing appetite suppressants, nonetheless it is clearly positive and statistically significant. In addition, there was suggestive evidence for a dose-related increase in the risk of hemorrhagic stroke. Thus, the lower magnitude odds ratio with cough/cold remedies may well be explained by diluting the effects of high-dose PPA products with low-dose PPA products. In light of the potential for high dose exposure from use of ***any*** of the PPA-containing cough/cold remedies, we recommend that PPA-containing cough/cold remedies should no longer be available as over-the-counter products. The use of PPA-containing cough/cold remedies in the US population is undoubtedly greater than the use of PPA-containing appetite suppressants, so the public health implications of safe dosing for this indication are far-reaching.

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Table 1. Sensitivity Analyses for Addressing Bias due to Sparse Data

	First Time PPA Use (Odds Ratio and 95% C.I.)	Appetite Suppressants (Odds Ratio and 95% C.I.)
From original study report	3.14 (0.96 – 10.28)	15.92 (1.37 –184.12)
One case subject moved from non-exposed to exposed while his/her matched control remained non-exposed	3.45 (1.09 – 10.96)	20.31 (1.95 – 212.26)
One control subject moved from non-exposed to exposed while his/her matched case remained exposed	2.07 (0.93 –10.15)	14.42 (1.16 –178.09)
One control subject moved from non-exposed to exposed while his/her matched case remained non-exposed	2.27 (0.73 – 7.15)*	7.29 (1.14 –46.31)**

*We repeated this analysis 10 times, the average point estimate was 2.6

**We repeated this analysis 10 times, the average point estimate was 6.9

(Note: Cases and controls were not matched on exposure)

Appendix A

Update on Cases of Hemorrhagic Stroke Associated with PPA Use in AERS

On July 17, 2000, AERS was queried for cases reported since February 1, 1991, in association with PPA-containing medications, using the SOC (System Organ Class) term Nervous system disorders and the PTs (preferred terms) cerebrovascular accident NOS, hemorrhagic stroke, intracranial hemorrhage NOS, subarachnoid hemorrhage NOS, and intraventricular hemorrhage NOS. This yielded reports of 37 US cases. Images were printed and reviewed for accuracy, duplications and retrieval of relevant information. Cases of vascular malformations and aneurysms were excluded, as also were cases over age 49 years, cases of cerebrovascular accidents due to thrombosis or infarction, or reports with no indication in the narrative or elsewhere of intracranial hemorrhage.

The results are summarized in Table 1 A. After exclusions as listed above there were 16 unduplicated cases of hemorrhagic stroke reported in the 18-49 age group. The age range was 18-47 years, with a median of 35 years. Thirteen cases were female and three male. In all cases, the suspect drug was a long-acting preparation containing 75 mg of PPA per unit dose. There were 4 deaths, all in females, two due to overdose. The diagnosis of hemorrhagic stroke was confirmed in 10 cases by CT scan or autopsy. In 10 of the 11 cases for whom an indication for use was provided, the indication was for respiratory symptoms. Information on duration of treatment was provided for 8 cases and ranged from a single dose to 7 days, with a median of 48 hours. The time to onset after the last dose was only stated in 6 cases and ranged from 1-2 hours to less than 24 hours, with a median of 4 hours. One case had a past history of hypertension and another a past history of a previous infarct associated with complicated migraine.

Background Incidence of Hemorrhagic Stroke in Young People

Sacco and colleagues reported that the average annual age-specific incidence of all strokes for ages 20-44 years was 20 per 100,000 population (1). They estimated that 23% of these were hemorrhagic (intracerebral hemorrhage 17%, subarachnoid hemorrhage 6%). Combining these estimates would give an average annual incidence of hemorrhagic stroke in the 20 – 44 age group of 4.6 per 100,000 per year. This estimate is consistent with that of Petitti and colleagues who reported the incidence of hemorrhagic stroke in women of childbearing age (15-44 years) as 5.2 per 100,000 (C.I.= 4.7-6.1) (2). The background incidence will be used to assess the public health impact of the risk of hemorrhagic stroke with PPA use in young people.

References

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