



Phenylpropanolamine and Hemorrhagic Stroke in the Hemorrhagic Stroke Project: A Reappraisal in the Context of Science, the Food and Drug Administration, and the Law

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The report of the Hemorrhagic Stroke Project (HSP), a case-control study of phenylpropanolamine (PPA) was the primary reason that the US Food and Drug Administration (FDA) requested that PPA-containing products voluntarily be withdrawn from the market. In subsequent litigation, scientific information emerged that was not available during the deliberations of the FDA and its advisory committee. Our reappraisal leads us to conclude that chance, bias, and confounding are plausible alternative explanations for the observed findings. Thus, we believe that it is not possible to conclude that there is any valid statistical association between PPA and hemorrhagic stroke, let alone make any judgment of causality. Our reappraisal suggests the FDA's regulatory request may have been premature.

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INTRODUCTION

The Final Report of the Hemorrhagic Stroke Project (HSP) (1), a case-control study, was the primary reason that the US Food and Drug Administration (FDA) (2)

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requested that drug companies voluntarily discontinue marketing products containing phenylpropanolamine (PPA). Dozens of over-the-counter and prescription diet aids, as well as cough and cold remedies containing PPA, were discontinued or reformulated. Shortly thereafter, a prestigious peer-reviewed medical journal (3) took the unusual step of placing the HSP manuscript on their Web site in advance of publication. The enormous medico-legal impact of the HSP provided additional scientific information from the testimony of expert witnesses in the ensuing litigation. While all case-control studies have well-recognized limitations (4), our reappraisal of the HSP reveals numerous additional issues that limit interpretability of the findings and provides valuable lessons from and for scientists, regulators, and lawyers.

The Hemorrhagic Stroke Project (HSP) was a case-control study designed to test whether individuals who consumed PPA had higher risks of hemorrhagic stroke (HS). The HSP recruited men and women from 18–49 years of age from 43 hospitals. Among the criteria for eligibility were the occurrence of a subarachnoid or intracerebral hemorrhage within 30 days prior to enrollment and the absence of a previously diagnosed brain lesion. The HSP used random digit dialing to identify two matched control subjects per patient.

METHODS

The HSP enrolled 702 patients and 1376 control subjects. The HSP examined PPA usage on the 3 days preceding the date of onset of the HS. Overall, the adjusted odds ratio

Selected Abbreviations and Acronyms

HSP = Hemorrhagic Stroke Project
PPA = phenylpropanolamine
FDA = Food and Drug Administration
OR = odds ratio

(OR) for PPA and HS was 1.49 (95% confidence interval, 0.84–2.64; $p = 0.17$). In subgroup analyses by type of PPA-containing drug consumed, the OR was 1.23 (95% confidence interval, 0.68–2.24; $p = 0.49$) for cough/cold remedies, and 15.92 (95% confidence interval, 1.38–184.13; $p = 0.03$) for appetite suppressants. In further subgroup analyses, none of the men used PPA as an appetite suppressant and the OR among women was 16.58 (95% confidence interval, 1.51–182.21; $p = 0.02$). In further analyses, first use was defined as the use of any PPA product within 24 hours and no other uses in the prior 2 weeks. Among first users, all who developed HS ingested cough/cold remedies, not appetite suppressants, the OR was 3.13 (95% confidence interval, 0.86–11.46; $p = 0.08$). Finally, among men, there were no associations between PPA and HS. The HSP investigators concluded that in women, PPA in appetite suppressants, and possibly in cough/cold remedies, is an independent risk factor for hemorrhagic stroke (3).

Chance

This is a large retrospective case-control study of over 700 cases and 1400 controls. But even the most robust and informative overall test of the hypothesis that PPA is associated with hemorrhagic stroke is based on 27 exposed cases and 33 exposed controls, and the test was not statistically significant ($p = 0.17$). While the subgroup finding for women taking PPA as an appetite suppressant is statistically significant, that subgroup is based on just 7 participants (6 exposed cases and 1 exposed control). Among men who reported taking PPA as a cough/cold remedy, based on 19 exposed participants (6 cases and 13 controls), the OR was 0.62 (95% confidence interval, 0.20–1.92; $p = 0.41$) (3). This finding is neither statistically significant so chance is a plausible alternative explanation nor informative as the confidence intervals are wide. In fact, chance would remain a plausible alternative explanation even if the HSP were a randomized, double-blind placebo-controlled trial of PPA. In fact, however, this is a retrospective case-control study with additional concerns about bias, as well as uncontrolled and uncontrollable confounding.

Bias

Selection bias, which refers to the problem of identifying and selecting controls that are similar to cases, is an inherent limitation of all case-control studies and is a major problem

in HSP, because the response rates are low and differential. With respect to cases, 54% identified were considered eligible, and of these, 76% were actually enrolled (3). With regard to controls, even the most optimistic response rate of about 36% is low. In addition, HSP violated accepted random digit dialing methodology (5). Instead of securing a random sample, HSP enrolled the first eligible control who agreed, not recontacting even eligible controls who requested to be called back another time. Moreover, 20% of the nonanswering numbers in one sample were not called back at all or only once, and the callbacks to nonanswering numbers that were done were not spread evenly over days, evenings, and weekends. As a result, for each case, the HSP telephoned on average 151 numbers (range from 3 to 1119) to identify 2.8 eligible persons (range from 1 to 12) for each enrolled control (3). The HSP screening rate is in fact 51.9%, producing an overall response rate of 18.7%. In contrast, studies using random digit dialing generally obtain a response rate of at least 65% (5). There is, therefore, insufficient basis to conclude that HSP's control group is comparable to the cases (4).

Moreover, HSP obtained a much lower prevalence of PPA exposure among its controls than that projected in the protocol based on 3 years of regional data from a PPA market research survey, raising further questions about bias from the low response rate for controls. Although HSP predicted a 0.64% exposure rate for female controls using appetite suppressants (5/750), HSP instead obtained only a 0.1% exposure rate (1/750) (6, 7). Overall, HSP predicted 4.52% of PPA exposures among all controls (62/1376) but only obtained a 2.4% exposure rate (33/1376). Potential controls who had colds may have been reluctant to participate in an interview, but they may have been more likely to use PPA as cough/cold remedy. Similarly, potential controls who were overweight may have rejected an interview on health issues, but they may have been more likely to use PPA as an appetite suppressant. If HSP had obtained the level of PPA appetite suppressant exposure among women controls predicted in the protocol, for example, the adjusted odds ratio for HS would not be the reported 16.58 ($p = 0.02$), but instead, 2.48 (95% confidence interval, 0.65–9.45; $p = 0.18$) (7).

Selection bias was also inherent in the design. For example, HSP admitted a small number of cases based on direct referral of the case by a treating doctor, who might have known the PPA exposure status of the case. The exposure frequency to PPA for these direct-referral cases was 21.4% (3/14) (8, 9). In contrast, the exposure frequency to PPA among all cases was 3.8% (27/702) (3). Thus, cases enrolled by direct referral were 5.5 times more likely to be exposed to PPA than were the entire case series. An additional concern about selection bias was the apparent prior knowledge of the physician that each of the exposed cases they referred had

taken PPA, raising the possibility that they had been referred not just because they had hemorrhagic stroke, but also because they were exposed to PPA (9).

Recall bias, which refers to the problem of subjects who have had a bad outcome or event being more likely to recall an exposure to a drug, may also be present in HSP because cases were asked about their PPA use prior to their catastrophic event, whereas controls were asked about their use before a day chosen in the last 7 days. Thus, cases are likely to have over-reported PPA use compared to controls. The HSP investigators concluded a lack of recall bias because they reasoned that, on the one hand, cases were more likely to recall the exposure, but on the other, controls had a shorter recall period (3). In fact, each of these is a separate source of bias that is not quantifiable. In addition, noncomparability was substantial, since far more controls (44) were interviewed by telephone than cases (3) (1).

Blinding of interviewers is important in case-control studies to minimize systematic differences in the ascertainment of exposure. The HSP protocol stated that the interviewers would be blinded to the study hypothesis (6), but the HSP “gave up on that requirement early on in the study” (10). Indeed, in its final report, HSP stated that “HSP interviewers were not blinded to the case-control status of study subjects and some were aware of the study purpose” (1). One interviewer from Ohio and another from Connecticut have subsequently said that they saw a copy of the protocol in which PPA was mentioned and understood that one objective of the study related to PPA and hemorrhagic stroke before they began any interviews (11, 12). Of the numerous interviewers at the four sites, four of the six exposed appetite suppressant cases were enrolled by only two interviewers from Ohio, one of whom has stated that she knew the study hypothesis (8, 11, 13). One case (11) reported PPA ingestion 84 hours prior to her stroke, which one of the HSP investigators described as “in violation” (8). This case was, nonetheless, included, even though neither of her controls was matched on race, and one of her controls was interviewed outside the permitted time period (8).

Moreover, in at least one of the four sites, the participants were not blinded to the hypothesis. Specifically, the informed consent signed by all participants at Rhode Island Hospital stated in large capital letters underlined at the top of the cover page, “CASE CONTROL STUDY OF PPA AND HEMORRHAGIC STROKE” (10). One exposed female case of hemorrhagic stroke (also a plaintiff) reported that she was informed before the interview that the study was designed to evaluate PPA and stroke in young women (14). In fact, in Rhode Island, the exposure rate for cases (3.03%) was nearly three times the rate of that for controls (1.03%), while the site with the next greatest difference in case exposure rate over control exposure rate had a case exposure rate only approximately one and

a half-times higher (3.10% case exposure vs. 2.00% control exposure) (15). The possibly biased overestimate of the observed exposure to PPA in cases, combined with the possibly biased underestimate of the observed exposure to PPA in controls, especially in small samples, leads to a probably biased overestimate of the odds ratio.

During the study, moreover, because of difficulties in data collection on PPA use within the past 7 days, the first-use definition was changed by extending from 7 to 14 days the period prior to PPA ingestion during which no PPA may have been taken. As a result, one control who used PPA as a cough/cold remedy was excluded. The rationale for this change in first use definition of a clear period from 7 to 14 days reduces the biologic plausibility of the finding because of the short half-life of PPA (9). If, by contrast, the clear period had been changed from 7 to 2 days, consistent with a recommendation from HSP’s Scientific Advisory Board, the adjusted matched odds ratio for the association of women’s first use of PPA is 1.75 ($p = 0.32$) rather than 3.13 ($p = 0.08$), which was the ratio published by HSP, and for all study subjects’ first use is 1.66 ($p = 0.32$), as compared to 3.14 ($p = 0.06$) published by HSP (7).

Confounding

In the HSP, uncontrolled confounding was present because multivariate analyses included only race, history of hypertension (not current levels of systolic and diastolic blood pressure), education, and current cigarette smoking (not amount currently smoked). Rather than control for all confounders, the HSP included only those variables as confounders that changed the matched odds ratio estimate by 10% or more (3). Moreover, education is an important confounder in these data. Although the HSP reported the breakdown of its subjects according to three levels—not a high school graduate, high school graduate, and attended college or college graduate—the HSP only controlled for education based on two levels: high school graduate or not. A three-level approach, however, results in an odds ratio of 2.62 ($p = 0.15$) for women’s first-use of PPA, rather than the published odds ratio of 3.13 ($p = 0.08$). Moreover, using education as a continuous adjustment variable based on years of study completed results in an odds ratio of 2.00 ($p = 0.32$) for women’s first-use of PPA (7). The methodologies employed, therefore, underestimate both the nature and the number of confounders controlled.

Uncontrollable confounding is present, most notably in the subgroup analyses of women using PPA for appetite suppression, where the findings are based on six exposed cases and one exposed control. Three of the major and independent risk factors for hemorrhagic stroke are hypertension, cigarette smoking, and heavy alcohol consumption (16). Among the six cases were several who were hypertensives,

smokers, or heavy drinkers of alcohol (9, 15). The single control, however, was not hypertensive, a smoker, or a drinker of alcohol. In such circumstances, it is most common to exclude cases with confounding variables not represented in the control series. If this is done, then, as noted by an HSP investigator, in the subgroup of women there is no association between PPA used as an appetite suppressant and hemorrhagic stroke (8). Furthermore, when the sample size in any cell is less than five, an exact method should be used to control confounding, but instead, HSP investigators used an approximate large sample method whose underlying assumptions are likely to have been violated (15).

CONCLUSION

The PPA litigation led to the discovery of importantly relevant scientific information not available to the US FDA or to its advisory committee, which further increases the likelihood that chance, bias, and confounding remain plausible alternative explanations for the observed findings in HSP. Thus, it is not possible to conclude that there is a valid statistical association between PPA and hemorrhagic stroke, let alone make a judgment of a causality. Interestingly, regarding silicone breast implants, the FDA's regulatory action led to emotional trauma among those with implants and contributed to litigation that caused the bankruptcy of a major consumer products company (17). The current totality of scientific evidence regarding silicone breast implants, however, is far more reassuring than alarming (18–23). With regard to PPA, our reappraisal indicates that the FDA's regulatory action, based on the results of HSP, may have been premature.

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