Phenylpropanolamine and the hemorrhagic stroke: A new search for the culprit

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Phenylpropanolamine (PPA) is a nonselective adrenergic receptor agonist and norepinephrine reuptake inhibitor[1] that was widely available as popular over-the-counter (OTC) cold and flu medications. Accumulated experience for over 70 years had established the position of PPA as the most frequently used amongst all sympathomimetics in OTC cold and flu preparations, with over six billion doses consumed annually.[2]

Based primarily on the Final Report of the Hemorrhagic Stroke Project (HSP) released on May 2000,[3,4] the Food and Drug Administration (FDA) had concluded that there is an association between PPA and hemorrhagic stroke. In November 2000, the FDA formally recommended that PPA not be considered safe for the OTC use and asked the drug manufacturers to voluntarily discontinue marketing any products containing PPA.[5] As a consequence, in most countries, all of OTC and prescription diet aids, as well as cough and cold remedies containing PPA, were discontinued or reformulated with another decongestant. Ephedrine and pseudoephedrine were the mostly used substitutes as they share the pharmacological properties of PPA and are approximately similar in potency except that PPA causes less central nervous system stimulation.[1]

As a senior practicing physician, I totally agree with FDA decision concerning the total prohibition of PPA in appetite suppressants and in any OTC product.

But I am in favor of allowing some of the cold and sinusitis preparations to be available as registered ethical products to be brought only with prescription and used under medical supervision with watchfulness for the dose and any drug interactions.

This suggestion is not biased by the interest of any manufacturing company rather than based on logical and worthy to debate reasons.

The first one is based on the long history of success in all markets, as a first choice decongestant in cold and flu preparations, passing the test of time for over 70 years.

The second reason was based on the level of evidence that we can draw from the report of the HSP.[4] This evidence could in my view justify only banning the PPA in any OTC preparations, because the OTC status is fraught with more misuse and less vigilance in drug contraindications, interactions, and accurate dosage for different weights and conditions.

Overall, there was no statistically significant difference in the prevalence of the use of products containing PPA as a chemical substance (in any indication, form, frequency or duration of exposure) between the total hemorrhagic stroke group and the total control group.

In addition, cold and flu remedies containing PPA failed to have an association with hemorrhagic stroke in all subjects, men and women subgroup comparisons.

The association was significant only in the very *small sub-*

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subgroup comparison among the women (seven subjects) who took appetite suppressants.

This statistically drawn perplexity can be explained according to the following argument. The two groups were obviously unmatched with regard to many important risk factors. The group of patients had a significantly higher prevalence of numerous known independent risk factors for hemorrhagic stroke.[6] These included family history of hemorrhagic stroke (unadjusted odds ratio (OR) = 1.85), history of hypertension (OR = 2.46), cigarette smoking (OR = 2.38), regular alcohol use (OR = 2.09), nicotine (OR = 17.86), caffeine (OR = 2.51), and recent cocaine use (OR = 11.95). These were in addition to other confounding variables such as lower educational level, lower socioeconomic status, and higher rate of black race in the patients group.

The significantly higher rates of consumption of alcohol and other drugs particularly cocaine, caffeine, and nicotine could indicate not only multiple higher independent risk factors for hemorrhagic stroke in the patients group but also substantial difference in psychological vulnerability, behavioral, biological, or genetic propensity to multidrug abuse between groups.[7-10]

These vulnerability factors could even be more linked with the behavior/act of self-administration of OTC appetite suppressants particularly of the adrenergic receptor agonist class. Being an easy to buy OTC adrenergic agonist that shares many neurochemical properties with cocaine,[11,12] PPA, especially in monocomponent appetite suppressants (unlike the multicomponent cold mixtures), could have been preferably used by patients as an agonist substitution/replacement for withdrawal symptoms or craving for cocaine.[11,12] Agonist replacement is a known phenomenon in drug abusers that is even used in therapy.[11]

Therefore, if there was a true association of the stroke with PPA "as a substance or a chemical molecule" it should had been found statistically significant in the larger whole sample analysis (which fits more with the precalculated minimal sample size for detection of association with least type I and II statistical errors).

The estimated sample size, power, and the 0.05 one-tailed level of significance were based on an assumed 0.50% exposure rate to PPA in the control group. Therefore comparison would not be proper in the appetite suppressant subgroup that were represented by only one subject in the control group (0.073% exposure rate). With this very low exposure rate and marginal level of significance, the probability of committing type I error (rejecting true null hypothesis) would be very high, particularly in the presence of many confounding variables.

With this in mind, the author here analyzes "as a proof" only one of the many confounding variables, the recent cocaine intake, which is a confirmed risk factor for hemorrhagic stroke. It was more prevalent in the whole sample than PPA in appetite suppressants (14 vs. 7 subjects) with an unadjusted bivariate odds ratio of 11.95 which is fairly higher than that calculated for any use of PPA during the 3 days window in the whole groups' analysis (OR = 1.63), in the all women analysis (OR = 2.12), in all men analysis (OR = 0.9), and even in appetite suppressant subgroup analysis (OR = 11.85). Taking the history of cocaine intake in recruited subjects in a shorter window (one day) than that for PPA, would not even allow for proper adjustment for the confounding effects of drug interaction or tendency for abuse/substitute in the multivariate logistic model.

Lastly, 3 and 5 years after they had released the final report of the HSP, the same group of investigators published two papers[13,14] based on new analyses from the same original data of the HSP and confirming my viewpoint.

The first one published in 2003, titled "Major risk factors for aneurysmal subarachnoid hemorrhage (SAH) in the young are modifiable."[13] Its objective was to determine the environmental risk factors for aneurysmal SAH based on cases and controls among the HSP.

They concluded that aneurysmal SAH is largely a preventable disease among the young and middle-aged because the adjusted OR for the association with risk for aneurysmal SAH was high for family history of hemorrhagic stroke (OR = 3.83) and current cigarette smoking (OR = 3.73). Other significant independent risk factors included hypertension, lean body mass, less than a high school education, heavy alcohol (≥2 drinks daily), caffeine (≥5 drinks daily), exposure to marijuana, caffeine (in pharmaceuticals), and nicotine (in pharmaceuticals). The bivariate OR for the association with risk for aneurysmal SAH was highest for exposure to cocaine in the last 3 days before the index date (OR = 24.97; $P = 0.0001$), while PPA exposure failed to be a significant independent risk factor with a bivariate (OR = 1.15; $P = 0.87$).

To complete the picture they had made a new analysis for the data of the second type of hemorrhagic stroke "intracerebral hemorrhage (ICH)" from the original HSP cases and controls in their second paper published in 2005.[14] They reported that the independent risk factors for ICH included hypertension (adjusted OR = 5.71), diabetes (adjusted OR = 2.40), menopause (adjusted OR = 2.50), current cigarette smoking (adjusted OR = 1.58), alcoholic drinks ≥ 2/day (adjusted OR = 2.23), caffeinated drinks ≥ 5/day, and caffeine in drugs (adjusted OR, 3.55). Again, PPA exposure failed here also to be a significant independent risk factor with a bivariate (OR = 2.17; $P = 0.25$).

The third reason is based on my long experience confirmed with a historical cohort analysis comparing efficacy and

tolerability of cough and cold preparations containing PPA to those containing pseudoephedrine/ephedrine. I reviewed all records of children below 12 years old that had presented to our outpatient clinic during the past 15 years with severe nasal and sinus congestion. Although it is just a real-life practice observation and not a comprehensive controlled study, I can claim that at least in my practice there was no significant difference with regards frequency of reported adverse effects. They were few and non-serious apart from an insignificant trend to higher frequency of irritability, nervousness, and sleeplessness in ephedrine/pseudoephedrine treated children. Regarding efficacy, we observed faster and more effective relief of nose and sinus distressing symptoms in PPA-based therapy.

To test the external validity of this observation, a personal communication with a group of pediatricians and ENT consultants was conducted. The majority reported higher level of satisfaction with the overall efficacy and tolerability of products containing PPA than ephedrine/pseudoephedrine when prescribed prudently with dosage based on body weight. They reported also that they missed the higher decongestant efficacy of PPA based cold and sinus products especially in irritable sleepless children, with distressed breathing due to severe rhinosinusitis with nasal obstruction and sinus congestion.

How an association of a serious event such as "stroke" could not be clearly verified among trillions of doses given for over 70 years of heavy use mainly as therapy in cough/flu. Any drug could be a poison if misused, even through its expected type-A-pharmacological effects.

A high dose of any sympathomimetic taken by abusers is expected to lead to hypertension and stroke or cardiac arrhythmia. That is why there is a section of warning in a drug leaflet and in the summary of product characteristics (SPC).

I totally agree with FDA decision concerning the prohibition of PPA in all appetite suppressants and in any OTC product. However, I am in favor of allowing some of the cold and sinusitis preparations to be available as registered ethical products, to be bought only with prescription and used under medical supervision and caution for the dose and any drug interactions.

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