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HYMAN, PHELPS & MCNAMARA, P.C.

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ALAN M KIRSCHENBAUM
DOUGLAS B FARQUHAR
JOHN A GILBERT, JR
JOHN R FLEDER
MARC H SHAPIRO

ROBERT T ANGAROLA
(1945-1996)

700 THIRTEENTH STREET, N.W
SUITE 1200
WASHINGTON, D C 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329

www hpm com

MARY KATE WHALEN
OF COUNSEL

JENNIFER B DAVIS
FRANCES K WU
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MOLLY E CHILDS*

*NOT ADMITTED IN DC

DIRECT DIAL (202) 737-9639

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Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

Dear Sir or Madam:

Enclosed is a supplement to the Ephedra Education Council's submission dated April 7, 2003. In that submission, please replace attachment J, Stephen E. Kimmel, Brief Review Ephedra and Hemorrhagic Stroke Paper, dated January 27, 2003, with the enclosed review, Stephen E. Kimmel, Review of Ephedra and Hemorrhagic Stroke Paper, dated March 31, 2003.

If you have any questions, please feel free to contact me.

Sincerely,

Bryon Powell

Bryon Powell
Legal Assistant

Enclosure

95N-0304

SUP 2

2603 MAIN STREET
SUITE 760
IRVINE, CALIFORNIA 92614
(949) 553-7400
FAX (949) 553-7433

4819 EMPEROR BOULEVARD
SUITE 400
DURHAM, NORTH CAROLINA 27703
(919) 313-4750
FAX (919) 313-4751

COMMENTS ON PROPOSED RULE FOR DIETARY SUPPLEMENTS CONTAINING EPHEDRINE ALKALOIDS; FOOD AND DRUG ADMINISTRATION; HHS [Docket No. 95N-0304]

Review of Ephedra and Hemorrhagic Stroke Paper

Stephen E. Kimmel, MD, MSCE
March 31, 2003

Overview

In a recent analysis of data from a study previously performed to examine the relationship between phenylpropanolamine (PPA) and hemorrhagic stroke (Morgenstern et al. *Neurology* 2003;60:1320135), the investigators measured the association between the use of herbal ephedra-containing products and hemorrhagic stroke. The overall finding was an odds ratio of 1.00. An odds ratio of 1.00 represents no difference in the odds of hemorrhagic stroke among ephedra users versus non-users. Further analyses that divided ephedra into > 32 mg and ≤ 32 mg use on any day in the prior 3 days produced odds ratios of 3.59 and 0.13, respectively.

The purpose of this review is to examine the strengths and limitations of the published study.

Although the strength of the study was the use of a control group against which to compare the cases of hemorrhagic stroke, the authors point out that this study was "not designed specifically to examine *Ephedra*." As such, the study was not appropriately sized or executed in a way to ensure valid results. The potential limitations of the study include both the play of chance and uncontrolled bias.

Study Limitations

The Play of Chance: Sample Size

There were only a total of 7 cases and 12 controls that reported use of an ephedra-

containing product in this study. Among the > 32 mg/day group, there were only 6 cases and 4 controls that reported use of ephedra. These represent very small numbers of exposure. As such, the study was not powered to determine if differences between ephedra users and non-users were due to true differences in effect or simply the play of chance. Here "power" refers to the ability of the study to detect an effect of ephedra. As such, the finding of a 3.6-fold greater odds of hemorrhagic stroke in the > 32 mg/day ephedra group compared with the non-ephedra group (and similarly the odds of 5.83 for *current* use of > 32 mg relative to non-users) could not be distinguished from a chance finding in this study.

Given the limitations of the small sample size, the most precise estimate of effect is that using the whole study population (odds ratio of 1.00, representing no overall effect of ephedra on hemorrhagic stroke risk). However, even this estimate is highly imprecise and therefore is not particularly useful for evaluating the effect of ephedra on hemorrhagic stroke. The authors themselves state that the "most obvious limitation of this study was statistical power."

Other Limitations

Other limitations must also be considered in interpreting this study. These are important to consider in any study, but particularly in this study where the small number of ephedra users would cause even small measurement errors to produce large errors in the estimates of risk. These errors include: recall bias (differences in recall of exposure or dose between those with, versus those without, hemorrhagic stroke), selection bias (selecting controls from a population that is different from that used to identify the cases), uncontrolled confounding (different risk for hemorrhagic stroke between those who use, versus those who do not use, ephedra, unrelated to ephedra), and missing data (on dose, for example).

Conclusions

The present study cannot be used to draw definitive conclusions about an association between ephedra dose and hemorrhagic stroke risk. In fact, the authors of the paper themselves do not draw such a conclusion. They conclude from their study that "*Ephedra* is not associated with increased risk of hemorrhagic stroke, except ***possibly*** [my emphasis] at higher doses." They state only that "the analysis by dose suggests there ***may*** [my emphasis] be an association with use of more than 32 mg/d" but, appropriately, do not try to draw definitive conclusions from their study.

Thus, this study is useful as a "hypothesis-strengthening" study (i.e., one that provides useful information to strengthen the formulation of a hypothesis but does not provide sufficient information to prove or disprove that hypothesis). In order to appropriately test this hypothesis, further studies should be done, designed specifically to address the question of whether ephedra increases the risk of hemorrhagic stroke.