Letters to the Editor

Limitations of Acetaminophen, Aspirin, and Caffeine in Alleviating Migraine

The conclusions of Lipton et al1 that the combination of aspirin, acetaminophen, and caffeine was highly effective for the treatment of migraine headache symptoms requires further comment. They acknowledge in their “Patients and Methods” section that the most severely disabled segment of migraineurs was excluded. However, they do not tell us what percentage of the potential population was excluded for this reason. In a previous article2 by the first 2 authors of the current study, severe disability was identified in 50% of migraineurs who had been diagnosed by a physician and 25% of migraineurs who had not been previously diagnosed.

The lack of relapse data is surprising in any study of an acute headache treatment and is a major limitation of this study.

I would suggest the conclusion should be limited to say that, for migraineurs who are not usually severely disabled, the combination of aspirin, acetaminophen, and caffeine produces significant headache relief for up to 6 hours.

Finally, while the authors emphasize the “excellent safety profile” of the medication, they neglect to mention that caffeine-containing combinations are particularly prone to causing drug rebound headache.3 Most experts on headache would limit the use of these combinations to 2 days per week. The availability of this combination over-the-counter, with aggressive advertising from the manufacturer, is likely to lead to a significant increase in the “unrecognized epidemic”4 of drug rebound headache.

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In reply

We thank Maizels for his letter. We agree that our results cannot be generalized to the most severely disabled segment of patients with migraine. We deliberately excluded those migraine sufferers whose attacks usually required bed rest or who vomited 20% or more of the time to define a migraine population for whom nonprescription medication would be most appropriate. We estimate that the most severely disabled segment of migraine sufferers who was excluded from our studies encompassed about 30% of the overall migraine population. These patient selection criteria were stressed in the abstract, “Patients and Methods” section, and in the “Comment” section to be sure that readers would understand our design and the reasons for it. We thank Maizels for reemphasizing this key point.

Maizels comments on the lack of “relapse” or “recurrence” data, often defined as the proportion of patients who achieve headache response (no pain or mild pain) at 2 hours and redevelop moderate or severe pain over the subsequent 22 hours. We agree that recurrence data are important. The present studies were designed to address acute treatment effects over 6 hours. Follow-up studies will address recurrence.

When we described the “excellent safety profile” of study medication, we were commenting on the results of the acute treatment trials in our article. We were not attempting to provide general practice guidelines or to review the literature on rebound headache. We agree that dosing of all analgesics (prescription and nonprescription) should be limited in patients with migraine to reduce the risk of analgesic rebound headache.1

Finally, Maizels suggests that the availability of over-the-counter migraine products will exacerbate the problem of rebound headache. Of course, nonprescription analgesics (including a combination product of acetaminophen, aspirin, and caffeine) have long been widely available and widely used for migraine. In fact, almost two thirds of migraine sufferers in the United States treat with over-the-counter medication to the exclusion of prescription drugs.2 Until the recent approval of Excedrin Migraine (a combination product of aspirin, acetaminophen, and caffeine), all nonprescription medication use for migraine was off-label. We believe that controlled clinical trials provide consumers and health care providers with the information they need to make appropriate treatment choices. We also believe that appropriate medication labeling as well as professional and consumer education about appropriate use should reduce, not increase, the “unrecognized epidemic” of drug rebound headache.

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Critical Illness Myopathy, Steroids, and Cytochrome P450

Critical illness myopathy is a poorly understood, but increasingly recognized clinical syndrome that characteristically occurs in the intensive care unit among patients who have been treated with multiple drugs (particularly neuromuscular-blocking agents and antibiotics) and high-dose steroids.1-6 This rapidly progressive myopathy is characterized by muscle fiber atrophy and/or necrosis, often selectively affecting type 2 myofibers (Figure). Steroids are potent inducers of some forms of cytochrome P450.7 Recent studies8 suggest that cytochrome P450 is associated with skeletal muscle sarcoplasmic reticulum. Induction of cytochrome P450 and the consequent formation of reactive intermediates in the metabolism of some compounds result in the activation of calcium-release channels.9 Critical illness myopathy may result from steroid induction of cytochrome P450 associated with sarcoplasmic reticulum. The consequent production of reactive intermediate metabolites of other drugs given in the setting of critical illness then causes pathologic activation of calcium-release channels in sarcoplasmic reticulum and consequent muscle injury. The differences between muscle fiber types in calcium handling may account for the preferential involvement of type 2 muscle fibers in both steroid myopathy7 and critical illness myopathy.

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Correction

Error in Figure. In the article titled “Neuropsychiatric Assessment of Patients With Hyperkinetic and Hypokinetic Movement Disorders” by Litvan et al published in the October 1998 issue of the ARCHIVES (1998;55:1313-1319), the red arrows showing inhibitory neurons on figures 2 and 3 should have been yellow, as indicated in the figure legend.