In the revised form, correct analysis confirmed the bioequivalence previously claimed by the authors.

Conclusions

Attention needs to be drawn to situations of the kind described above, since, although reanalysis according to proper operating guidelines salvaged the trials, the sponsors involved in these cases wasted considerable time and in some cases lost opportunities. I conclude that operators involved in this kind of trial should study and follow the appropriate guidelines before selecting the type of pharmacokinetic and statistical analysis to be carried out.

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Letter to the Editor

It May Be the Caffeine in Extra Strength Excedrin that is Effective for Migraine

FREDERICK C. STRONG III*

Department of Chemistry, Bucknell University, Lewisburg PA 17837, USA

It was announced in the US Federal Register for June 16 that a meeting of the Nonprescription Drugs Advisory Committee would be held on July 15 to hear presentations and discuss data submitted regarding New Drug Application 20–802, Excedrin Extra Strength, 250 mg paracetamol, 250 mg aspirin and 65 mg caffeine, for the pain of migraine (Friedman 1997). A description of the test procedure and results was given by the director of one of the three studies (Lipton 1997). The meeting was held and approval is currently pending.

Research that I have carried out indicates that the effective ingredient for migraine in Excedrin may be the caffeine. I suffer from migraine-type headaches, which I believe to be vascular in nature. My migraines are caused by numerous foods and food components. This was confirmed by a double-blind test using tyramine hydrochloride. I see auras on average twice a month, which is a classical sign for migraine.

I have used every non-prescription analgesic on the US market for my headaches, including aspirin, paracetamol, ibuprofen, ketoprofen, naproxen sodium, Excedrin and aspirin-free Excedrin; only the last two have been effective. I have also tested caffeine alone (100 mg) in the form of Nodoz; it too is effective. Since the other two ingredients of Excedrin alone (aspirin and paracetamol) have no effect, I concluded that the reason the two versions of Excedrin are effective for my headaches is that they contain caffeine.

I therefore undertook a study of the analgesic properties of caffeine in a single human subject, namely me. In an experiment, my blood was analysed every hour following a single 100-mg dose of pure caffeine. After two and a half hours, I consumed 250 mg monosodium glutamate in 90 g ricotta cheese. A headache began five and a quarter hours after the dose of caffeine; this is the period of effectiveness of 100 mg caffeine.

Assuming first-order kinetics for the decay of caffeine in blood (Renner et al 1984), the blood concentrations were used to extrapolate an initial caffeine value of 3·82 mg mL^{-1}, with the value at the start of the headache being 1·97 mg mL^{-1}. The half-life was calculated to be 5·48 h.

I found a 50-mg dose to have no effect on my headaches. This agrees with the results of Laska et al (1984) of 10 000 patients taking analgesics containing caffeine as an adjuvant. A minimum of 60 mg caffeine was required for effective results. The adult dose for Excedrin recommended by the manufacturer as an analgesic provides 130 mg caffeine (two caplets).

Because of the relatively long half-life of caffeine in the blood, I also observed that if a headache returned after taking caffeine, an additional 50-mg dose was sufficient to maintain the analgesic effect for another two hours. Keeping the dose low then avoided causing nervousness and usually did not prevent me sleeping.

I conclude the unique effectiveness of caffeine is that, unlike other analgesics I tested, it is a vasoconstrictor (Rall 1985).

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* Formerly: Professor Titular, Department of Food Science, State University of Campinas, Brazil.