LETTER TO THE EDITOR

Acetylsalicylic acid, paracetamol and caffeine combination in headache

Dear Sir Use of fixed-combination medications is controversial for several reasons. Amongst them is the inflexibility of the combination, which may be inappropriate for some users, especially against subjective and variable symptoms such as headache. There is also the uncertainty usually present as to whether the combination of medications is superior in efficacy to each of its constituents given alone in the same or perhaps higher doses. It can be expected that side-effects of the constituents will summate, whether or not efficacy does.

Diener et al. (1) made a sterling 5-year effort to investigate these issues in respect of the fixed combination of acetylsalicylic acid (500 mg), paracetamol (400 mg) and caffeine (100 mg) in acute headache treatment. They went beyond the regulatory requirement, which is to show superior efficacy of the combination over each separate constituent in the same dose as in the combination; they compared the combination with the usual higher dose when used alone (1000 mg) of each of acetylsalicylic acid and paracetamol as well as with caffeine (100 mg). The combination was indeed found superior on all reported efficacy end-points, with a small penalty in the incidence of adverse reactions.

The outcome of this study has potential value for vast numbers of people worldwide. Both acetylsalicylic acid and paracetamol are on the World Health Organization's essential medicines list for migraine, although good evidence supports only the former. If they work better together and with caffeine, this needs to be known. There are, however, some aspects of this experiment that raise small but important questions. Clarification would help in knowing whether its conclusions stand or need confirming.

First is the selection of patients. I understand the intention to enter patients with headache (migraine or tension-type) for whom non-prescription analgesic therapy alone was a reasonable choice. Why, then, exclude patients whose usual choice of treatment was such analgesics in effervescent formulation? This is generally the better formulation for oral analgesia in migraine, if not in tension-type headache. Furthermore, it is the widely preferred formulation for acetylsalicylic acid in Germany. Was there bias against acetylsalicylic acid, since its users, presumably happy with it, were preferentially excluded?

Second is the choice of primary end-point: time to 50% pain relief. Whilst the study claims to have complied with the International Headache Society guidelines on clinical trials (2, 3), in this very important respect it did not. The explanation given—that it combines pain relief and time to its onset into a single end-point—is not convincing. Conventional end-points such as responder rates at 1 and 2 h do this job just as well and are widely accepted. 'Response' in this trial could have been defined as pain reduction by 50%, given that pain at baseline (>30 mm on 100-mm visual analogue scale) may not always have been moderate to severe. These end-points were actually included amongst the secondary efficacy measures, but they are not reported (although the others are). In the primary end-point adopted, the difference between the combination and the least efficacious of the analgesic components (paracetamol) was 16 min, but the estimate of time to 50% relief was arrived at by extrapolating linearly between observations an hour apart. This procedure makes assumptions about the course of pain relief that are not generally tenable: many observers note step-wise decrements in pain, sometimes interrupted by increments. Superiority of the combination is widely expressed across all reported end-points, so why this primary end-point and what did those not reported show?

Third is the formulation of supplies delivered by Boehringer Ingelheim, in matching tablets, which were presumably not commercially available preparations. I believe the kinetics of acetylsalicylic acid in particular are crucially dependent upon formulation, especially particle size. Were C_{max} and T_{max} within the ranges for standard preparations? This is important for external validity of the conclusions and their extrapolation to routine care.

Statement of interests

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References

1 Diener HC, Pfaffenrath V, Pageler L, Peil H, Aicher B. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalalgia 2005; 25:776–87.
2 International Headache Society Committee on Clinical Trials. Guidelines for trials of drug treatments in tension-type headache. First edition. Cephalalgia 1995; 15: 165–79.
3 International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in migraine: second edition. Cephalalgia 2000;20:765–86.

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