PARACETAMOL ABSORPTION FROM PARAMAX, PANADOL AND SOLPADEINE

Having read the paper by Dougall *et al.* (1983), I would like to make the following points.

1 In the introduction, the authors point out that absorption from an effervescent formulation is more rapid than that from a tablet formulation. However, their paper has compared an effervescent preparation with two tablet formulations, although an effervescent formulation of Paramax is readily available.

2 The paper continues by stating that to accelerate gastric emptying, metoclopramide must be given either before the paracetamol or intravenously. Nonetheless Crome *et al.* (1981), in a study of 12 volunteers, have shown a significant reduction in the time to peak plasma concentration of paracetamol when oral metoclopramide was simultaneously administered.

3 It is further commented by the authors that plasma concentrations of metoclopramide may vary widely after oral administration and the effect of a low oral dose is likely to be unpredictable. However recent work by Ross-Lee *et al.* (1982) demonstrated that orally-administered metoclopramide appeared to enhance the initial rate of aspirin absorption more than the same metoclopramide dose given parenterally. These authors suggested that, following oral administration, earlier drug levels in the intestinal wall were sufficient to activate peristalsis and thus enhance aspirin delivery to the absorptive surfaces of the small intestine.

4 In examining the results from paired comparisons, the Wilcoxon matched-pairs test would have been more appropriate. To obtain a significant result requires at least six pairs of observations, rather than only four. Their approach also needs correcting for the fact that three tests have been performed on each variable. Considering each variable as a separate experiment, to obtain an approximate overall 5% significance level, each paired comparison would have to be performed at a level less than 2%. Re-examined as above, there are no significant differences between any of the results reported, but in view

of the small number of volunteers, neither can it be assumed that there are no differences.

5 In the discussion it is stated that metoclopramide is itself absorbed from the upper small intestine. No reference is given for this statement which has unjustifiably been taken to imply that metoclopramide cannot also be absorbed from the stomach. Further, as mentioned above, there may be local effects.

6 Finally we were particularly surprised that the authors, having chosen to study such a small group of volunteers, extended their comments to the clinical situation. In an acute migraine attack, patients are known to have gastric stasis and consequent impairment of drug absorption (Volans, 1974). The administration of metoclopramide in the parenteral form (Volans, 1975) or the oral form (Ross-Lee *et al.*, 1982) will alleviate the gastric stasis and correct the impairment of drug absorption. The work of Ross-Lee *et al.* (1982) has demonstrated that oral metoclopramide enhanced the speed of absorption of analgesic in patients having a migraine attack, and therefore having gastric stasis. That paracetamol with oral metoclopramide (Paramax) is effective in migraine relief is supported by the clinical observation (Behan, 1982) that, in patients with migraine referred to a neurology clinic, 87% of patients suitable for treatment with Paramax alone obtained good or moderately good symptomatic relief from this therapy.

7 In view of these comments, relating to the limited nature of the observations, it is difficult to understand why the authors have chosen to question the validity of the data submitted to satisfy the regulatory authority on the use of this formulation in patients with migraine.

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