A double-blind placebo controlled study to examine effects of sucralfate on paracetamol absorption

Sucralfate (a basic aluminium salt of a disulphated disaccharide) is a safe and effective mucosal protective ulcer healing agent which compares favourably with other antipeptic drugs like cimetidine. Apart from its antipeptic effect, sucralfate is thought to have cytoprotective effects by decreasing the hydrogen ion concentration and forming an adherent and protective chemical complex with proteins at the ulcer site (Nagashima *et al.*, 1980).

Conflicting results have been reported regarding the tendency of concurrent sucralfate administration to reduce the completeness of absorption of other drugs, and the present study was designed to investigate the effects of sucralfate on paracetamol absorption kinetics.

The close correlation between plasma and saliva concentrations of paracetamol (Glynn & Bastain, 1973; Adithan & Thangman, 1982) made it possible to use salivary levels of paracetamol as an index of its absorption.

Six healthy normal volunteers who had fasted overnight took an oral dose of paracetamol (1.0 g) (2 × 500 mg B.P. formulation tablets) concomitant with either sucralfate (1.0 g) (Antepsin) or placebo (1.0 g) and 150 ml water at random, on two different occasions, with at least a 1 week interval. All the subjects were ambulatory throughout the study. Salivary flow was stimulated by chewing on a piece of parafilm for 2 mins (50 mm × 50 mm approx.) and salivary samples were obtained by direct spitting into plastic vials, all subjects having rinsed their mouths thoroughly after taking paracetamol. Samples were collected for 4 h at times, 0, 15, 25, 35, 50, 65, 95, 125, 190, and 240 min, and were stored at −20°C. Prior to analysis, an equal volume of 25% (w/v) trichloroacetic acid was added to each of the samples and vortexed, and later centrifuged at 10,000 *g* for 20 min. The supernatant was then assayed for paracetamol. Paracetamol concentrations were measured by the high performance liquid chromatography method of Howie *et al.* (1977). Paracetamol absorption was assessed from peak concentration, time to peak and the area under the curve (AUC) from the graph of salivary paracetamol concentrations against time at 65 and 125 min using the trapezoidal rule. Statistical significance was tested by using paired Student's *t*-test.

As shown in Figure 1, the highest mean salivary concentrations of paracetamol occurred 15 min after oral ingestion of the drug when given with either sucralfate or placebo, and the mean ± s.e. mean concentrations were 21.6 ± 7.4 μg ml^{-1} and 21.7 ± 8.6 μg ml^{-1} respectively. The mean times for salivary paracetamol concentrations to peak were 26.0 ± 6.4 min with sucralfate and 19.0 ± 4.0 min with placebo. Mean salivary paracetamol concentrations were found to be not significantly different during the time course of the study except at sampling times of 25 min ($P < 0.0025$) due to intra-individual variations. There were no significant differences in AUC at 0–65 min (23.3 ± 3.2 μg ml^{-1} min with sucralfate and 23.3 ± 5.5 μg ml^{-1} min with placebo; $P > 0.499$) and 0–125 min, (36.1 ± 3.1 μg ml^{-1} min with sucralfate and 38.4 ± 7.1 μg ml^{-1} min with placebo; $P > 0.45$), nor in elimination half-life (111.5 ± 16.0 min with sucralfate and 107.9 ± 22.9 min with placebo, $P > 0.40$).

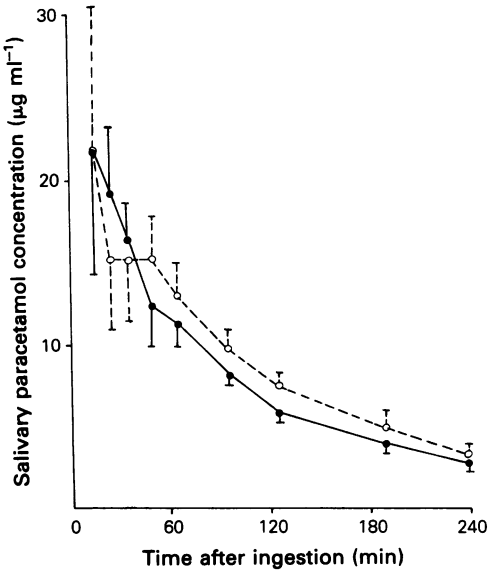

Figure 1 Mean salivary paracetamol concentrations following concomitant ingestion of the drug with either sucralfate (•) or placebo (○) (± s.e. mean).

In this double-blind placebo controlled cross-over study, using salivary levels of paracetamol as an index of its absorption, the concomitant administration of sucralfate did

not seem to have any significant effect on paracetamol absorption. Similar results have been obtained in studies on dogs in which the concomitant oral administration of sucralfate was shown not to affect the absorption of digoxin, quinine, propranolol or aminophylline, although it did reduce phenytoin bioavailability by a third (Lacz *et al.*, 1982). In addition it has been reported that concomitant administration of sucralfate reduces the bioavailability of digoxin in man, but does not do so if given at other times (Giesing *et al.*, 1983). As yet there appears to be no rationale by which those drugs whose absorption is likely to be hindered by sucralfate can be predicted.

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References

Adithan, C. & Thangman, J. (1982). A comparative study of saliva and serum paracetamol levels using a simple spectrophotometric method. *Br. J. clin. Pharmac.*, **14**, 107–109.

Giesing, D. H., Lanman, R. C., Dimmitt, D. C. & Runsen, D. J. (1983). Lack of effect of sucralfate on digoxin pharmacokinetics (abstract). *Gastroenterology*, **84**, 1165.

Glynn, J. P. & Bastain, W. (1973). Salivary excretion of paracetamol in man. *J. Pharm. Pharmac.*, **25**, 420–421.

Howie, D., Adriaenssens, P. I. & Prescott, L. F. (1977). Paracetamol metabolism following overdosage. Application of high performance liquid chromatography. *J. Pharm. Pharmac.*, **29**, 235–237.

Lacz, J. P., Groschang, A. G., Giesing, D. H. & Browne, R. K. (1982). The effect of sucralfate on drugs absorption in dogs. Abstract. *Gastroenterology*, **82**, 1108.

Nagashima, R., Hinohara, Y. & Hirano, T. (1980). Selective binding of sucralfate to ulcer lesion. *Arzneimittel-Forschung*, **30**, 88–91.

Indirect blood pressure measurement during intravenous isoprenaline infusions

Isoprenaline is widely used as an agonist in the investigation of β-adrenoceptors in man. Although the primary focus of isoprenaline testing is on heart rate changes, it is increasingly apparent that simultaneous blood pressure effects may be important. The relative lack of emphasis on this latter parameter has been due to the impossibility of accurate measurement during standardised tests using isoprenaline boluses without direct intra-arterial recording (Cleaveland *et al.*, 1972; George *et al.*, 1972; Arnold & McDevitt, 1983). However, intravenous isoprenaline infusions may allow blood pressure to be recorded at steady-state without intra-arterial puncture. Nevertheless, the potential errors of sphygmomanometry are well recognised (Raftery, 1978). In parallel with a study of vagal reflexes in man (Arnold & McDevitt, 1984), we have recently had the opportunity to compare two possible indirect forms of blood pressure measurement with intra-arterial recording during continuous isoprenaline infusions, pre- and post-atropine.

The details of the methodology are reported elsewhere (Arnold & McDevitt, 1984). In summary, intra-arterial blood pressure was continuously measured (Bell and Howell, 4-422) and recorded (Devices MX4) in eight healthy young subjects. Blood pressure was also measured indirectly on the opposite arm by either a semi-automated Dinamap recorded—Critikon Model 845 (four subjects)—or a Hawksley-Gelman random-zero sphygmomanometer (four subjects). In the latter case, both Korotkoff Phase IV and V for diastolic pressure were recorded where possible.

After a 30 min supine rest, three 8 min infusions of isoprenaline sulphate (1, 2, 4 μg/min) were given, and between each, heart rate and blood pressure were allowed to return to baseline over at least 15–20 min. Atropine sulphate 0.04 mg/kg was then given by slow