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The absorption of aspirin and paracetamol in patients with achlorhydria

It is generally accepted that the site of absorption of weakly acidic and basic drugs in the gastrointestinal tract is determined by intraluminal pH. According to the pH-partition theory,weak organic acids are rapidly absorbed from the stomach (pH 1–2), and weak organic bases from the small intestine (pH 5·5–6·5). It follows that an increase in gastric pH should reduce the rate of absorption of acidic drugs from the stomach.

Acetylsalicylic acid is a moderately strong acid (pKa 3·5) and its gastric absorption should be pH dependent. Paracetamol is a much weaker acid (pKa 9·5) which is largely unionized at all pH values normally found in the gastrointestinal tract, and its absorption should not be appreciably influenced by changes in gastric pH. Acetylsalicylic acid and paracetamol absorption was therefore studied in achlorhydric and control patients. The groups were comparable for age, weight and sex. [Controls: 3 females, 3 males, mean wt (kg $\pm$ s.d.) 62·5 $\pm$ 13·3, mean age (years $\pm$ s.d.) 56·2 $\pm$ 10·2; achlorhydric patients: 3 females, 3 males, mean wt (kg $\pm$ s.d.) 69·8 $\pm$ 15·2, mean age (years $\pm$ s.d.) 65·2 $\pm$ 4·1]. After an overnight fast, each patient was given 1·5 g paracetamol (Panadol-Bayer) with 50 ml water, and serial plasma samples were obtained for 8 h. Two days later, the same patients were given 900 mg of acetylsalicylic acid (aspirin-Boots) under the same conditions, and samples were taken as before. The subjects were not permitted to walk, eat, drink or smoke for 2·5 h after taking the drugs, nor were they given any other medication on the day of the experiment. The achlorhydric patients had been shown to produce no gastric acid after pentagastrin stimulation (6 μg kg^{-1}); the controls were convalescent with no evidence of diseases associated with achlorhydria. Plasma concentrations of paracetamol were estimated

Table 1. *Mean plasma concentrations of paracetamol and salicylic acid ($\mu g\ ml^{-1} \pm s.d.$) in achlorhydric and control patients.*

Drug	Patients	Hours after ingestion 0·5	1·0	1·5	3·0	5·0	8·0
Paracetamol	Control	25·0 ± 13·0	24·9 ± 9·3	23·6 ± 7·4	14·6 ± 5·2	9·6 ± 5·3	3·9 ± 1·9
	Achlorhydric	23·9 ± 14·8	24·4 ± 10·0	22·4 ± 7·1	15·4 ± 5·8	8·6 ± 3·8	4·0 ± 1·5
Acetylsalicylic acid	Control	13·8 ± 11·9	32·3 ± 11·9	40·5 ± 15·1	47·3 ± 8·5	38·4 ± 3·7	25·2 ± 7·6
	Achlorhydric	19·3 ± 14·6	41·6 ± 12·0	73·8 ± 21·2	60·8 ± 16·8	42·4 ± 10·5	29·6 ± 9·2

by the method of Prescott (1971), plasma salicylic acid concentrations by that of Trinder (1954). The results are shown in Table 1.

As predicted, paracetamol absorption was essentially the same in both groups in respect of peak plasma concentrations and the time taken to reach those concentrations. In contrast, the plasma salicylic acid curves were significantly different. Paradoxically the patients with achlorhydria absorbed the drug more rapidly than the controls. The peak plasma concentrations occurred at 1·5 h in the achlorhydric patients and at 3·0 h in the controls, and the mean plasma concentrations were higher at all times in the former. At 1·5 h the mean plasma concentrations of salicylic acid were significantly higher in the achlorhydric patients than in the controls (73·8 and 40·5 $\mu g\ ml^{-1}$ respectively, $P<0·05$).

There are several possible explanations for these findings. The kinetics of paracetamol absorption depend on the rate of gastric emptying (Heading, Nimmo & others, 1973) and as acetylsalicylic acid is absorbed much more slowly from the stomach than the small intestine (Siurala, Mustala & Jussila, 1969) its absorption is likely to be influenced by the rate of gastric emptying also. The effect of achlorhydria on the rate of gastric emptying is disputed (Halvarsen, Dotevall & Walan, 1973; Brömster, 1969), but the similiarity of the plasma paracetamol curves suggests that the rates of emptying in these groups were similar and that this alone is unlikely to account for the increased rate of acetylsalicylic acid absorption in the achlorhydric patients. Achlorhydria may also be associated with changes in the mucosal surface area, permeability and blood flow, and changes in the volume and viscosity of the gastric secretions, all of which may affect the rate of acetylsalicylic acid absorption, as may pharmaceutical factors such as particle size, tablet formulation, and physicochemical factors such as solubility. The last factor is, in this case, perhaps the most likely explanation for the enhanced absorption of acetylsalicylic acid in the achlorhydric patients in that the solubility of aspirin decreases as the pH is lowered and so its absorption in the controls may have been limited by slower dissolution in the acid gastric contents. Different results may have been observed with other preparations of aspirin. Whatever the explanation, however, these observations provide further evidence of the fallibility of the pH-partition theory in clinical practice.

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