The effect of magnesium hydroxide on the oral absorption of ibuprofen, ketoprofen and diclofenac

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- 1 The effect of magnesium hydroxide on the oral absorption of ibuprofen, ketoprofen and diclofenac was investigated in two randomized cross-over studies, both consisting of two phases.
- 2 Single doses of magnesium hydroxide (850 mg) or of water (150 ml) only were given to six healthy volunteers immediately after the ingestion of ibuprofen (400 mg, Study 1), ketoprofen (50 mg, Study 2) or diclofenac (50 mg, Study 2). Plasma drug concentrations were measured up to 24 h.
- 3 Magnesium hydroxide increased the area under the plasma ibuprofen concentration-time curve between 0 and 1 h by 65% ($P < 0.05$) and the peak concentration of ibuprofen in plasma by 31% ($P < 0.01$). The time to peak was shortened by about 0.5 h. The extent of bioavailability of ibuprofen was not increased by magnesium hydroxide.
- 4 Neither the rate nor the extent of absorption of ketoprofen or diclofenac was changed significantly by magnesium hydroxide.
- 5 When rapid onset of the analgesic effect of ibuprofen is required, concomitant ingestion of an antacid, which contains magnesium hydroxide without aluminium, is recommended.

Keywords ibuprofen ketoprofen diclofenac gastrointestinal absorption magnesium hydroxide

Introduction

The evidence for interactions between antacids and nonsteroidal anti-inflammatory drugs is controversial but, according to a recent review (D'Arcy & McElnay, 1987) 'the most likely sequel of interaction would be that the analgesic or antirheumatic effect of the NSAID would be less than expected'. On the other hand, magnesium hydroxide, ingested concomitantly with tolfenamic or mefenamic acid, accelerated greatly and in a dose-dependent manner the absorption of these fenamates (Neuvonen & Kivistö, 1988). Fenamates, like most other anti-inflammatory analgesics, are sparingly soluble in water at gastric pH. However, the absorption accelerating effect of magnesium hydroxide was not shared by aluminium hydroxide.

Rapid absorption is desirable if an immediate analgesic effect is required, for example, in an acute migraine attack. Furthermore, early and high plasma concentrations of anti-inflammatory analgesics may be associated with increased analgesia (Laska *et al.*, 1986).

In the present study the possible accelerating effect of

magnesium hydroxide on the gastrointestinal absorption of ibuprofen, ketoprofen and diclofenac was studied.

Methods

Study design

The investigation comprised two randomized cross-over studies, both consisting of two phases. The interval between the phases was 1 week. The studies were carried out in six healthy subjects, four of whom participated in both studies. The study protocol was approved by the local Ethics Committee and all subjects gave their informed consent.

In Study 1, six women (33 ± 3 years; mean $\pm$ s.e. mean, 66 ± 6 kg) ingested 400 mg ibuprofen (tabs Burana 400 mg, Medipolar, Finland) either with 150 ml water only, or with 150 ml water containing 850 mg

magnesium hydroxide (i.e. 10 ml Milk of Magnesia, Winthrop Laboratories, England).

In Study 2, six women (31 ± 2 years, 63 ± 4 kg) ingested simultaneously 50 mg ketoprofen (caps Orudis, Rhone-Poulenc, Denmark) and 50 mg diclofenac sodium (Trabona enterotabs, Leiras, Finland) either with 150 ml water only, or with water containing 850 mg magnesium hydroxide as in Study 1.

The test drugs were ingested between 07.30–08.00 h on an empty stomach. No food was taken for 3 h from the beginning of the study. Timed blood samples (5 ml) were collected in heparinized tubes at 0, 20 and 40 min, and 1, 1.5, 2, 3, 5, 8 and 24 h after drug ingestion. Plasma was separated within 1 h of sampling. The samples were stored at -20°C until analyzed.

Characterization of absorption

The absorption of the analgesics was characterized by measuring the following parameters: peak plasma concentrations ($C_{\max}$), peak times ($t_{\max}$) and the areas under the plasma drug concentration-time curves from 0 to 1 h AUC(0,1) and from 0 to 24 h AUC(0,24), calculated by the linear trapezoidal rule.

Assay of drugs

Plasma concentrations of racemic ibuprofen (Lockwood & Wagner, 1982), ketoprofen and diclofenac (Kaye *et al.*, 1981) were measured by high performance liquid chromatography, using flufenamic acid as an internal standard. The sensitivity of the methods used was $0.3 \mu\text{g ml}^{-1}$ for ibuprofen and $0.1 \mu\text{g ml}^{-1}$ for ketoprofen and diclofenac. The interassay coefficient of variation for each drug was less than 5% ($n = 8$) at concentrations relevant to the present study.

Statistical analysis

Means $\pm$ s.e. mean are given. The Wilcoxon matched-pairs signed-ranks test was used in the statistical analysis of the results.

Results

Study 1: Ibuprofen

Magnesium hydroxide accelerated significantly ($P < 0.05$) the absorption of ibuprofen. When ibuprofen was

Figure 1 Plasma concentrations of ibuprofen after administration of 400 mg ibuprofen alone (●—●) and together with 850 mg magnesium hydroxide (○—○). Mean $\pm$ s.e. mean data for six subjects (a) and individual data for one subject exhibiting slow absorption during the control phase (b). The asterisk indicates significant differences ($*P < 0.05$) from the control.

taken with magnesium hydroxide plasma ibuprofen concentrations were 50–100% higher ($P < 0.05$) at 20 min, 40 min, 1 h and 1.5 h than when taken without the antacid. The effect of magnesium hydroxide was most pronounced in those subjects who normally had a slow absorption of ibuprofen (Figure 1).

In each of the six subjects the peak of the plasma ibuprofen concentration was higher when ibuprofen was ingested with magnesium hydroxide than without it. On average, the peak concentration was increased by 31%, i.e. from the control value of $32.4 \pm 3.1 \mu\text{g ml}^{-1}$ to $42.4 \pm 3.9 \mu\text{g ml}^{-1}$ ($P < 0.01$). The time to peak plasma ibuprofen concentration was 0.5 h earlier when the drug was ingested with magnesium hydroxide.

The AUC(0,1) of ibuprofen was increased by magnesium hydroxide by 66% ($P < 0.05$, Table 1). There

Table 1 Effect of magnesium hydroxide (850 mg) on the absorption parameters of ibuprofen (400 mg), ketoprofen (50 mg) and diclofenac sodium (50 mg). Magnesium hydroxide was ingested in 150 ml of water immediately after the analgesics. Mean $\pm$ s.e. mean in six subjects

	Ibuprofen +		Ketoprofen +		Diclofenac +	
	water (control)	Mg(OH) ₂ 850 mg	water (control)	Mg(OH) ₂ 850 mg	water (control)	Mg(OH) ₂ 850 mg
$t_{\max}$ (h)	1.5 ± 0.4	0.9 ± 0.06	0.9 ± 0.1	0.8 ± 0.1	1.9 ± 0.3	1.4 ± 0.2
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	32.4 ± 3.1	42.4 ± 3.9^b	6.8 ± 1.0	7.3 ± 0.9	1.8 ± 0.3	1.4 ± 0.2
AUC(0,1) ($\mu\text{g ml}^{-1} \text{ h}$)	15.4 ± 3.2	25.5 ± 3.6^a	3.9 ± 0.7	4.3 ± 0.4	0.2 ± 0.2	0.3 ± 0.1
AUC(0,24) ($\mu\text{g ml}^{-1} \text{ h}$)	173 ± 15.7	179 ± 21.2	13.3 ± 2.5	14.6 ± 3.4	1.9 ± 0.2	1.8 ± 0.2

^{a,b}: significantly ^a($P < 0.05$), ^b($P < 0.01$) different from control

Figure 2 Plasma concentrations of a) ketoprofen and b) diclofenac after combined administration of 50 mg of each drug alone (●—●) and together with 850 mg magnesium hydroxide (○—○). Mean $\pm$ s.e. mean data for six subjects.

was, however, no increase in the total bioavailability of ibuprofen, i.e. AUC(0,24) remained unchanged.

Study 2: Ketoprofen and diclofenac

Neither the peak concentration, peak time nor the areas under the plasma concentration-time curves of ketoprofen or diclofenac were changed significantly by magnesium hydroxide (Table 1). However, the average plasma concentration of diclofenac was about 50% higher at 40–90 min and its peak plasma concentration occurred about 0.5 h earlier when the drug was taken with magnesium hydroxide (Figure 2).

Side effects

Diarrhoea or other gastrointestinal side-effects did not occur when a single 850 mg dose of magnesium hydroxide was taken with ibuprofen, ketoprofen or diclofenac.

Discussion

Not only the extent but also the rate of absorption of an analgesic may be important to its analgesic effect. Thus, in certain clinical conditions there is a need to achieve high plasma analgesic concentrations as soon as possible. The delay in drug action may allow worsening of symptoms to such an extent that the drug is no longer effective,

e.g. in the treatment of an acute migraine attack. An acute migraine attack itself delays gastric emptying and subsequently the absorption of drugs. Slow absorption in association with a short elimination half-life may result in ineffective concentrations of the analgesic.

Laska *et al.* (1986) have shown that there is a linear relationship between serum ibuprofen concentrations during the first 1–2 h after drug ingestion and the degree of pain relief in patients who have had molar extraction. The analgesic effect did not correlate significantly with the dose of ibuprofen ingested. This was due to differences in the absorption rates of the various ibuprofen formulations used. It is well known that the absorption profiles of ibuprofen from different formulations may be significantly different (Källström *et al.*, 1988; Palva *et al.*, 1985).

In the present study the concomitant ingestion of magnesium hydroxide increased the rate of gastrointestinal absorption of ibuprofen but had no significant effect on the absorption of ketoprofen or diclofenac. The effect of ibuprofen absorption was most obvious in those subjects in whom the absorption was slow during the control phase. Magnesium hydroxide has also been shown previously to accelerate the gastrointestinal absorption of tolafenamic and mefenamic acids, but this effect was not shared by other antacids tested. In contrast, aluminium hydroxide retarded the absorption of tolafenamic acid (Neuvonen & Kivistö, 1988).

Ibuprofen and ketoprofen are acidic drugs and are sparingly soluble in water at gastric pH. Elevation of this pH increases their solubility. Milk of Magnesia (10 ml), corresponding to 850 mg magnesium hydroxide, increases the *in vitro* pH of 'gastric acid' to 9.6–9.7. In human volunteers this dose has been shown to elevate intragastric pH to about 7–8 (Tuderman *et al.*, 1979). Thus, increased solubility of ibuprofen at high pH could explain the effect of magnesium hydroxide on its absorption rate.

The absorption of ketoprofen was more rapid than that of ibuprofen, i.e. the peak time averaged 0.9 h. This may be the reason why the effect of magnesium hydroxide on the peak time and peak concentration of ketoprofen was not significant. Diclofenac as its sodium salt is very soluble in water. However, because of the formulation used in the present study diclofenac had the longest peak time during the control phase. There was a tendency to an acceleration of its absorption by magnesium hydroxide but owing to large interindividual variation this effect was not statistically significant. Although an effect of magnesium hydroxide on the absorption of ketoprofen and diclofenac was not evident in the present study, it may become significant when formulations with a slower absorption are used. Furthermore, owing to the small number of volunteers the statistical power of the study was limited to detect small differences.

Aluminium hydroxide and magnesium hydroxide have opposite effects on the absorption rates of fenamates (Neuvonen & Kivistö, 1988). These effects are in agreement with the effects of aluminium and magnesium on gastric emptying rate. The effect of aluminium hydroxide was not studied in the present study, but aluminium has been shown to delay the absorption of ibuprofen when incorporated in the same pharmaceutical formulation (Laska *et al.*, 1986). Furthermore,

an antacid suspension containing both aluminium and magnesium hydroxides did not alter the absorption of ibuprofen (Gontarz *et al.*, 1987).

In conclusion, it has been shown that the gastrointestinal absorption of ibuprofen is considerably accelerated by the concomitant ingestion of magnesium hydroxide. This interaction can be utilized in clinical conditions where a rapid onset of the pharmacological

effect ibuprofen is required. The possibility should also be considered of developing pharmaceutical formulations containing both magnesium hydroxide and ibuprofen.

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References

- D'Arcy, P. F. & McElnay, J. C. (1987). Drug-antacid interactions: assessment of clinical importance. *Drug Intell. clin. Pharm.*, **21**, 607–617.
- Gontarz, N., Small, R. E., Comstock, T. J., Stalker, D. J., Johnson, S. M. & Willis, H. E. (1987). Effect of antacid suspension of the pharmacokinetics of ibuprofen. *Clin. Pharmacy*, **6**, 413–416.
- Källström, E., Heikinheimo, M. & Quiding, H. (1988). Bioavailability of three commercial preparations of ibuprofen 600 mg. *J. int. med. Res.*, **16**, 44–49.
- Kaye, C. M., Sankey, M. G. & Holt, J. E. (1981). A high-pressure liquid chromatographic method for the assay of ketoprofen in plasma and urine. *Br. J. clin. Pharmacol.*, **11**, 395–398.
- Laska, E. M., Sunshine, A., Marrero, I., Olson, N., Siegel, C. & McCormick, N. (1986). The correlation between blood levels of ibuprofen and clinical analgesic response. *Clin. Pharmac. Ther.*, **40**, 1–7.
- Lockwood, G. F. & Wagner, J. G. (1982). High-performance liquid chromatographic determination of ibuprofen and its major metabolites in biological fluids. *J. Chromatogr.*, **232**, 335–343.
- Neuvonen, P. J. & Kivistö, K. T. (1988). Effect of magnesium hydroxide on the absorption of tolfenamic and mefenamic acids. *Eur. J. clin. Pharmacol.*, **35**, 495–501.
- Palva, E. S., Konno, K. & Venho, V. M. K. (1985). Bioavailability of ibuprofen from three preparations marketed in Finland. *Acta Pharm. Fenn.*, **94**, 31–35.
- Tuderman, V., Klinge, E., Krogerus, V. E. & Reijonen, M. (1979). *In vivo* study of certain antacid suspensions commercially available in Finland. *Acta Pharm. Fenn.*, **88**, 63–72.

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