International Journal of Pharmaceutics, 34 (1987) 189–196
Elsevier

IJP 01156

Research Papers

Adsorption of ketoprofen and bumadizone calcium on aluminium-containing antacids and its effect on ketoprofen bioavailability in man

F.A. Ismail, N. Khalafallah and Said A. Khalil

Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria (Egypt)

(Received 8 July 1986)
(Accepted 28 July 1986)

Key words: Ketoprofen; Bumadizone calcium; Antacid; Interaction; Bioavailability

Summary

The present study reports the adsorption of ketoprofen and bumadizone calcium, two non-steroidal anti-inflammatory drugs, on three aluminium-containing antacids. The type of aluminium antacid, the initial drug concentration and the pH of the medium were found to influence drug adsorption. At pH 3–4, binding of both drugs to aluminium hydroxide and dihydroxyaluminium sodium carbonate indicated co-operative adsorption, while adsorption profiles of bumadizone calcium on aluminium glycinate suggested a constant partitioning pattern. pH (1–8) adsorption profiles for ketoprofen and bumadizone calcium binding to aluminium hydroxide and dihydroxyaluminium sodium carbonate passed through a maximum in the pH range 3.5–4.5. Antacid dissolution during the adsorption runs was also investigated at different pH values. The effect of coadministration of ketoprofen and aluminium hydroxide on the bioavailability of ketoprofen was investigated in healthy volunteers. Urine was collected for 24 h following drug administration and samples were analyzed by HPLC for ketoprofen and its conjugates. The urinary excretion data indicated a decrease in drug bioavailability upon coadministration with aluminium hydroxide.

Introduction

Drug interactions involving antacids continue to be of interest both clinically and in research. One challenging aspect of these interactions is their non-consistant effects on drug efficacy as evident from the numerous reports of the effect of antacids on drug bioavailability. Results reported in these studies have ranged from no effect on drug absorption (Spahn and Mutschler, 1985; Reed and Schwartz, 1984), to decreased or delayed absorption (Tobert et al., 1981; Naggar et al., 1978). At the same time, though less frequently, some studies have reported acceleration of drug absorption upon coadministration with antacids (Lucarotti et al., 1972; Rivero-Calimlim et al., 1971). As a result extrapolation of data from one drug to another cannot be advocated and prediction of the possible consequences of concomitant antacid intake on drug efficacy is mere speculation.

The study of drug–antacid interactions becomes more important for drugs prescribed in combination with antacids. Animal studies have indicated an inhibitory effect of antacids on lesions of the gastric mucosa caused by non-steroidal anti-inflammatory drugs (Tsurumi et al., 1979), suggesting that administration of antacids with these drugs may reduce gastrointestinal side ef-

Correspondence: N. Khalafallah, Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt.

fects and intolerance. Theophylline is also recommended to be administered with antacids for patients at risk of upper gastrointestinal bleeding (Foster et al., 1979). Similarly, anticholinergics and ulcer-healing drugs are often administered with antacids in modern therapeutics.

The present study reports the interaction of aluminium-containing antacids with ketoprofen and bumadizone calcium, two acidic non-steroidal anti-inflammatory drugs known to cause gastrointestinal irritation. Both in vitro and in vivo data are reported.

Materials and Methods

The drugs used were kind gifts from the suppliers: ketoprofen, Alexandria Pharmaceutical Co., Alexandria-Egypt; bumadizone calcium, BYK Gulden, Pharmazeutika, Konstanz, F.R.G.; declofenac sodium, Swisspharma S.A.A.; diflunisal, Merck Sharp & Dohme Research Lab., U.S.A.; Fentiazac, Wyeth Laboratories, Taplaw, Maidenhead, Berks. Profenid Capsules [1], manufactured by Alexandria Pharmaceutical Co., Alexandria-Egypt, under licence from Rhone Poulenc, Paris-France, batch no. 910016, were purchased locally. The antacid powders used were aluminium hydroxide, B.P.; dihydroxyaluminium sodium carbonate (DHASC), Warner-Lambert Co., Morris Plains, NJ, U.S.A.: aluminium glycinate, B.P.; magnesium trisilicate, B.P., Paul Lohmann, F.R.G.; and light kaolin, B.P. All antacid powders were sieved (mesh size 100 μm), dried at 120°C for 3 h, and stored in air-tight bottles. Dialysis bags used were Spectrapor membrane tubing, M.W. cutoff 12,000–14,000, Spectrum Medical Industries, LA.

Adsorption study

Equilibrium adsorption runs were carried out in 100 ml glass stoppered conical flasks containing 50 ml of 0.005–0.1 N HCl. Aliquots of a methanolic solution of each drug were added to give an initial concentration range below the saturation solubility of each drug, determined in the present study. The methanolic content in the medium did not exceed 5%. Five hundred mg of antacid powder were added to each flask. The flasks were shaken horizontally at 37°C for 18 h, a length of time found necessary for equilibrium, and the contents were filtered through Whatman no. 1 filter paper. Filtrates were measured for pH and were analyzed spectrophotometrically at appropriate wave lengths.

Because of a filtration problem in the case of colloidal aluminium hydroxide suspension, adsorption runs with this antacid were carried out using dialysis bags filled with 10 ml of the medium. The bags were suspended in 40 ml of the medium in conical flasks together with 500 mg of the antacid and different concentrations of each drug. At equilibrium, the bags were removed, blotted dry and the contents read spectrophotometrically. Adsorption results recorded are the average of duplicate runs.

Solubility determination

Equilibrium drug solubility data were obtained in water and in 0.1 N HCl. Excess drug was shaken with the medium in vials at 37°C for 24 h. Filtrates were analyzed spectrophotometrically. Solubility data were also obtained for the aluminium antacids. The extent of antacid dissolution during the adsorption runs was determined at adsorption equilibrium by measuring the concentration of aluminium ions released in the medium by a tritrimetric method (Vogel, 1961). Standards were prepared using aluminium chloride solution, 0.01 M.

Bioavailability study

Five informed volunteers, 3 males and 2 females participated in this study. Their ages ranged from 23 to 40 years, and their weights from 52 to 65 kg. The study was carried out in a random cross-over manner. Each volunteer received two treatments one week apart. In treatment A, one profenid capsule was swallowed in the morning with 200 ml of water after an overnight fast. The volunteers abstained from eating for a further 4 h post-drug administration. Urine was collected at 0, 1, 2, 3, 4, 6, 8, 12 and 24 h following drug intake; volume and pH of each urine sample were recorded before

[1] Containing 50 mg of ketoprofen.

freezing the sample pending analysis. Treatment B was identical to A except that the drug was administered with 1 g of aluminium hydroxide powder suspended in 100 ml of water followed by drinking another 100 ml of water.

Urine samples were analyzed for ketoprofen (free and conjugated) by an HPLC method (Bannier et al., 1980) following extraction. The extraction procedure (Populaire et al., 1973) involved initial alkaline hydrolysis of the drug conjugates followed by a cleansing extraction step with diethyl ether (analytical grade, Prolabo-Paris) in alkaline medium. The drug was then extracted from acid medium with ethyl acetate (Reidel-De Haën, Seezle, Hannover, F.R.G.) which was evaporated, and the residue reconstituted in mobile phase. Ten μl were injected onto a reversed-phase column (Perkin-Elmer RP-8 column). The mobile phase, consisting of 0.025 M phosphate buffer, pH 3.0, containing 50% acetonitrile (acetonitrile for chromatography, E. Merck, Darmstadt), was pumped at flow rate of 1.3 ml/min. UV detection was carried out at 264 nm. Bumadizone calcium was used as internal standard, 20 μg being added to each urine sample and standard (1 ml each) before extraction. Retention times were 6.5 and 11 min for ketoprofen and internal standard, respectively. Recovered standards were prepared by spiking control (drug free) urine with ketoprofen to cover a concentration range of 10 to 50 μg/ml and processing them with the test samples. Recovery values were 87.5% for ketoprofen and 58.8% for internal standard. These recovery values were obtained by comparing peak heights of standards prepared in urine with peak heights of direct-on-the-column injection of the same amount of ketoprofen and internal standard. Inter-day coefficients of variation determined at 4 concentration levels, ranged from 13,3% at a concentration level of 10 μg/ml to 0.13% at a level of 100 μg/ml with a mean of 6.38% $\pm$ 5.97 (S.E.).

Results

In vitro data

Equilibrium drug solubility data at 37°C indicated that only ketoprofen and bumadizone calcium showed appreciable solubility in water at pH 1.4 (15.3 and 22.4 mg%, respectively). Fentiazac solubility value did not exceed 1.0 mg% while declofenac sodium and diflunisal showed negligible solubility at this pH. Only a slight increase in solubility was observed for all drugs at pH 4. Because of the limited aqueous drug solubility, the capacity of antacids to reduce the effective drug concentration in aqueous medium could only be investigated for ketoprofen and bumadizone calcium. Among the antacids tested, only aluminium-containing ones showed interaction with these two drugs.

The adsorption profiles of ketoprofen and bumadizone calcium on the three aluminium antacids tested at pH 4 are shown in Figs. 1 and 2. Plotting x/m as a function of C_{eq} permitted identifying the adsorption class as suggested by Giles and coworkers (Giles et al., 1960). Based on the resulting initial slope, adsorption of both drugs on aluminium hydroxide and DHASC could be identified as an S class of adsorption, where the more solute that was adsorbed, the easier it appeared

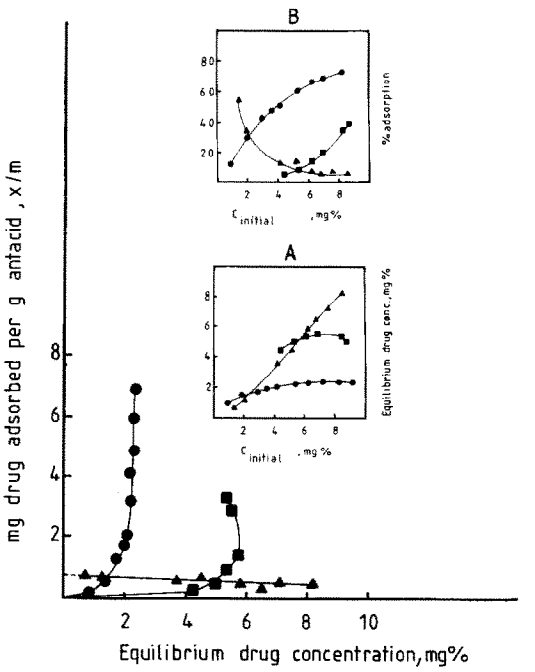

Fig. 1. Adsorption of ketoprofen on 1% w/v of aluminium hydroxide (●), dihydroxyaluminium sodium carbonate (■), and aluminium glycinate (▲) at pH 4 and temperature 37°C.

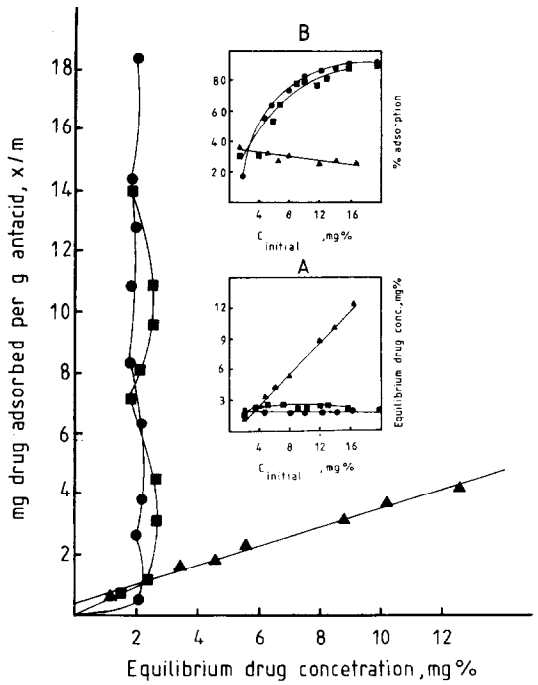

Fig. 2. Adsorption of bumadizone calcium on 1% w/v of aluminium hydroxide (●), dihydroxyaluminium sodium carbonate (■), and aluminium glycinate (▲), at pH 4 and temperature 37°C.

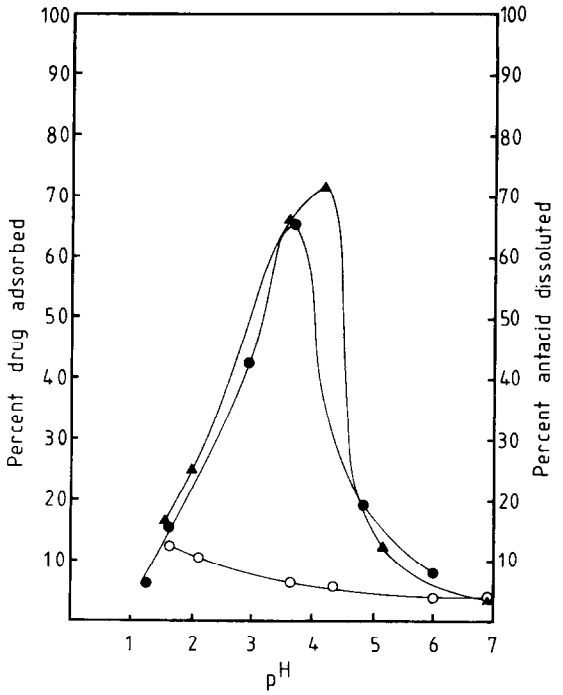

Fig. 3. pH–adsorption profile for ketoprofen (●) and bumadizone calcium (▲) on aluminium hydroxide. The open circles (○) denote the extent of antacid dissolution during the adsorption run.

for additional amounts to become fixed on the adsorbent. Adsorption by both these antacids resulted in drug depletion from the medium such that a constant and low equilibrium drug concentration was maintained in spite of the rising initial concentration, particularly in the case of aluminium hydroxide (insert A in Figs. 1 and 2). This adsorption pattern has previously been identified as co-operative adsorption (Giles et al., 1960), to describe the side-by-side association between adsorbed molecules believed to be vertically oriented. The adsorptive power of aluminium glycinate for both drugs was much poorer under the conditions of the study. Changes in x/m as a function of C_{eq} suggested a C class of adsorption in the case of bumadizone calcium (Fig. 2); this pattern also being known as a constant partitioning adsorption one (Giles et al., 1960). The effect of these two different adsorption patterns on the percent drug adsorbed is shown in insert B of Figs. 1 and 2.

Adsorption data for ketoprofen and bumadizone calcium on aluminium hydroxide and DHASC were generated over a pH range of 1.25–8.0 at a constant initial drug concentration of 10 mg%. Aluminium hydroxide adsorption profiles were found to pass through a maximum at pH 3.7 and 4.2 for ketoprofen and bumadizone calcium, respectively (Fig. 3). Corresponding maxima in the case of DHASC were 4.25 and 4.5 (Fig. 4). Superimposed on the pH–adsorption profiles in Figs. 3 and 4 are the pH–solubility profiles of the antacids used. Slight but expected increases in antacid solubility occurred with increasing medium acidity. The relative shapes of each pair of drug adsorption and antacid solubility curves indicated that while the slight increase in antacid dissolution, as the medium became more acidic, may have partially contributed to the decreased adsorption observed over a pH range of 1–4,5, the decreased drug adsorption beyond pH 4.5 could not be attributed to changes in antacid solubility.

TABLE 1

CUMULATIVE URINARY EXCRETION OF KETOPROFEN OBTAINED AFTER THE ADMINISTRATION OF A 50 MG CAPSULE TO FASTING VOLUNTEERS WITH WATER (TREATMENT A) AND WITH 1 G OF ALUMINIUM HYDROXIDE POWDER IN WATER (TREATMENT B)

Time, h	Cumulative amount of ketoprofen excreted in urine, mg											
	Treatment A						Treatment B					
	Volunteers						Volunteers					
	NK	FI	MA	EH	GM	Mean (±S.E.)	NK	FI	MA	EH	GM	Mean (±S.E.)
1	3.41	4.50	7.33	4.43	2.10	4.35 (0.77)	5.18	1.15	4.25	3.53	7.6	4.34 (0.94)
2	19.41	9.70	18.32	16.93	16.04	16.08 (1.52)	15.83	4.00	9.86	9.29	14.50	10.70 (1.88)
3	28.19	17.79	26.66	24.50	23.15	24.06 (1.60)	23.13	7.07	17.57	14.05	18.98	16.16 (2.41)
4	34.00	25.07	29.25	30.00	26.19	28.90 (1.41)	27.09	12.55	21.67	18.88	21.90	20.42 (2.12)
6	40.00	30.65	32.55	34.00	28.78	33.20 (1.71)	33.28	17.63	27.40	22.00	24.01	24.86 (2.35)
8	41.83	32.61	34.00	36.20	30.37	35.00 (1.75)	35.87	20.96	28.25	24.13	25.96	27.03 (2.25)
12	44.26	35.90	37.32	38.10	31.49	37.41 (1.84)	37.46	24.00	29.90	25.92	27.06	28.87 (2.10)
24	45.87	39.22	38.30	39.91	32.55	39.17 (1.90)	38.81	27.77	31.14	27.24	27.68	30.43 (1.95)
Mean % excreted at 24 h (±S.E.)						78.34% (3.80)						60.86% (3.91)
						$t^a = 5.92$, $P < 0.005$						
Mean peak excretion rate (mg/h) (±S.E.)						12.30 (2.24)						7.44 (0.83)
						$t = 5.93$, $P < 0.005$						

[a] Paired Student's *t*-test.

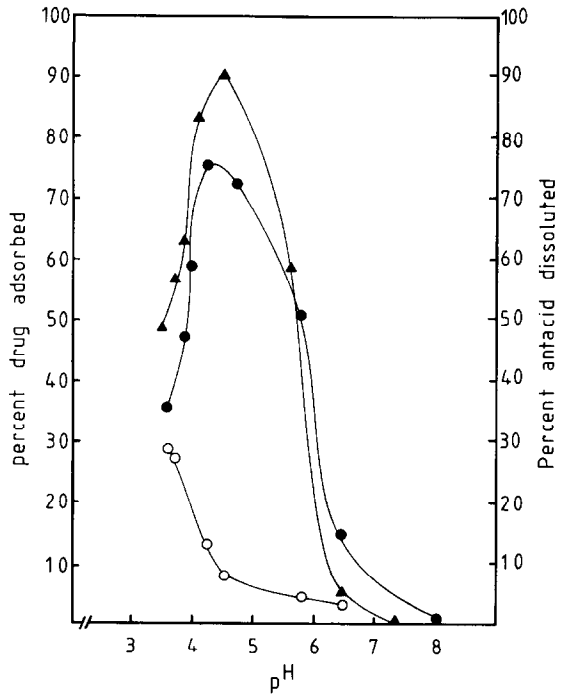

Fig. 4. pH–adsorption profile for ketoprofen (●) and bumadizone calcium (▲) on dihydroxy aluminium sodium carbonate. The open circles (○) denote the extent of antacid dissolution during the adsorption run.

In vivo data

Table 1 provides the cumulative urinary excretion data obtained for the 5 volunteers administered treatments A and B. The percent drug excreted, both free and as conjugates, in treatment A ranged from 65.1 to 91.7 of the administered dose, with a mean of 78.34%. Upton and coworkers (Upton et al., 1980), reported excretion of 73.7 ± 6.4% of a 50 mg oral dose of ketoprofen, in the form of conjugates over a 6-h period in 5 volunteers. Administration of ketoprofen with aluminium hydroxide in the present study resulted in a decrease in the amount of drug excreted in each of the 5 volunteers (Table 1). The average percent drug excreted dropped from 78.34% in treatment A to 60.86% in treatment B. the difference was found to be statistically significant (Table 1). Excretion rate profiles were consistantly lower in treatment B compared to A (Fig. 5). No effect of antacid on ketoprofen elimination was anticipated based on the observed lack of difference between

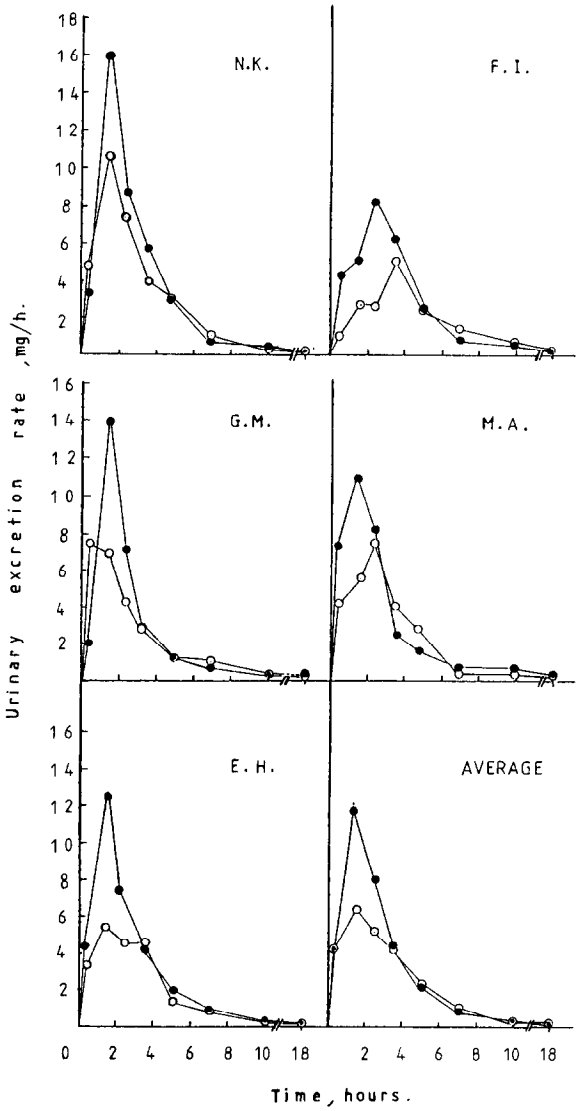

Fig. 5. Urinary excretion rate of ketoprofen following the administration of 50 mg of ketoprofen to volunteers with 1 g of aluminium hydroxide (○) and without antacid (●).

treatment A and B in urine pH, and the fact that ketoprofen is almost completely excreted as glucoronide which is not likely to be affected in its elimination by urinary pH changes. Furthermore, antacids through elevating urine pH, if they cause a rise in urinary pH, are expected to increase the excretion of acidic drugs by supressing tubular passive reabsorption. This permits the conclusion that the observed decrease in drug excretion in

treatment B resulted from a decrease in drug bioavailability as a result of coadministration with the antacid.

Discussion

The present study has looked into ketoprofen and bumadizone calcium interaction with aluminium antacids. Both the in vitro and in vivo data obtained indicated that an interaction does take place. The pattern of the in vitro drug uptake pointed to drug adsorption on the surface of the antacid particles. Aluminium antacids have been found to bind a variety of substrates including anions of incompletely dissociated acids (Bowden et al., 1973), pepsin (Sepelyak et al. 1984) and drugs such as oral hypoglycaemics (Naggar and Khalil, 1980; Said and Abdullah, 1981) and anticholinergics (Blaug and Gross, 1965; Khalil and Moustafa, 1973).

The adsorption of ketoprofen and bumadizone calcium on aluminium hydroxide and DHASC indicated co-operative adsorption and was found to be pH-dependent. Maximum adsorption occurred between pH 3.5 and 4.5, which points to electrostatic attraction as an important factor in the binding of these two drugs to the antacid surface. Similar pH–adsorption profiles were reported for pepsin on aluminium hydroxide (Sepelyak et al., 1984) and anions of incompletely dissociated acids on metal oxides (Bowden et al., 1973). It can be reasoned that aluminium hydroxide with a reported zero point charge of 8.5 (Schott, 1977) will be positively charged while ketoprofen and bumadizone calcium with reported pK_a values around 5 (Wallis and Simkin, 1983; Seebald and Førth, 1977) will be negatively charged in the pH range studied ($pH < 8$), resulting in electrostatic attraction. The negative charge on the drug will decrease as the medium acidity increases leading to reduced electrostatic attraction and declining pH–adsorption profiles from pH 4.5 to 1.5 (Figs. 3 and 4). Beyond pH 4.5, the antacid surface becomes less positive at a rate possibly greater than the rate of dissociation of the drug resulting in the downward pH–adsorption profiles above pH 4.5.

While drug binding to the antacid surface appeared to be the dominant event in the in vitro study, other factors may have contributed in vivo. For instance, antacids may affect drug bioavailability by altering stomach pH. For acidic drugs administered in solid dosage form, an increase in stomach pH will enhance drug dissolution and will increase drug dissociation which exert opposite effects on drug bioavailability. Furthermore, aluminium antacids, through yielding aluminium ions in acid medium, are recognized to delay gastric emptying rate (Hurwitz and Sheehan, 1971), a factor known to influence the rate and possibly extent of drug absorption. The aluminium hydroxide powder used for the in vitro and in vivo study was of the slowly dissolving type, and hence no appreciable effect on gastric emptying rate was anticipated in this study.

In conclusion, based on the results obtained in the present study, the practice of administering ketoprofen with antacids to alleviate its irritating effect in the stomach should be viewed with caution as many of the antacid preparations contain aluminium hydroxide. A decrease in ketoprofen bioavailability is a likely event in this therapeutic combination.

References

Bannier, A., Brazier, J.L., Ribon, B. and Quincy, C., Determination of ketoprofen in biological fluids by reversed-phase chromatography. *J. Pharm. Sci.*, 69 (1980) 763–765.

Blaug, S.H. and Gross, M.R., In vitro adsorption of some anticholinergic drugs by various antacids. *J. Pharm. Sci.*, 54 (1965) 289–294.

Bowden, J., Bolland, M., Posner, A. and Quirk, J., Generalised model for anion and cation adsorption at oxide surfaces. *Nature (London)*, 245 (1973) 81–83.

Foster, L.J., Trudeau, W.L. and Goldman, A.L., Bronchodilator effects on gastric acid secretion. *J. Am. Med. Assoc.*, 241 (1979) 2613–2616.

Giles, C.H., MacEwan, T.H., Nakhwa, S.N. and Smith, D., Studies in adsorption. Part XI. A system of classification of solution adsorption isotherms and its use in diagnosis of adsorption mechanisms and in measurement of specific surface areas of solids. *J. Chem. Soc.*, (1960) 3973–3993.

Hurwitz, A. and Sheehan M.B., The effects of antacids on the absorption of orally administered pentobarbital in the rat. *J. Pharmacol. Exp. Ther.*, 179 (1971) 124–131.

Khalil, S.A. and Moustafa, M.A., In-vitro-adsorption of some drugs on antacids. *Pharmazie*, 28 (1973) 116–118.

Lucarotti, R.L., Colaizzi, J.L., Barry III, H. and Poust, R.I., Enhanced pseudoephedrine absorption by concurrent administration of aluminium hydroxide gel in humans. *J. Pharm. Sci.*, 61 (1972) 903–905.

Naggar, V.F., Khalil, S.A. and Gouda, W., Effect of concomitant administration of magnesium trisilicate on GI absorption of dexamethasone in humans. *J. Pharm. Sci.*, 67 (1978) 1029–1030.

Naggar, V.F. and Khalil, S.A., In vitro antidiabetics–antacid interactions. *Pharmazie*, 35 (1980) 412–416.

Populaire, P., Terlain, B., Pascal, S. Decouveleare, B., Lebreton, G., Renard, A. and Thomas, J.-P., Dosage de l'acide (benzoyl-3 phényl)-2 propionique ou kétoprofène dans les milieux biologiques. *Ann. Pharm. Franc.*, (1973) 679–690.

Reed, R.C. and Schwartz, H.J., Lack of influence of an intensive antacid regimen on theophylline bioavailability. *J. Pharmacokin. Biopharm.*, 12 (1984) 315–331.

Rivera-Calimlim, L., Dujovne, C.A., Morgan, J.O., Lasagna, L. and Bianchine, J.R., Absorption and metabolism of L-DOPA by the human stomach. *Eur. J. Clin. Invest.*, 1 (1971) 313–320.

Said, S.A. and Abdullah, M.E., Effect of antacids on activity of oral hypoglycemics. *J. Pharm. Sci.*, 70 (1981) 621–624.

Schott, H., Relationship between zero point charge and solubility product for hydroxides and polyvalent cations. *J. Pharm. Sci.*, 66 (1977) 1548–1550.

Seebald, H. and Forth, W., Determination of ^{14}C-bumadizone and ^{14}C-phenylbutazone in the systemic blood, the blood of the portal vein, the intestinal lymph and the bile of cats after intrajejunal administration. *Arzneim.-Forsch./Drug Res.*, 27 (1977) 804–809.

Sepelyak, R.J., Feldkamp, J.R., Moody, T.E., White, J.L. and Hem, S.L., Adsorption of pepsin by aluminium hydroxide. 1: Adsorption mechanism. *J. Pharm. Sci.*, 73 (1984) 1514–1517.

Spahn, H. and Mutschler, E., The influence of aluminium hydroxide on the bioavailability of feprazone. *Arzneim.-Forsch./Drug Res.*, 35 (1985) 167–169.

Tobert, J.A., DeSchepper, P., Tjandramaga, T.B., Mullie, A., Buntinx, A.P., Mesinger, M.A.P., Huber, P.B., Hall, T.L.P. and Yeh, K.C., Effect of antacids on the bioavailability of diflunisal in the fasting and postprandial states. *Clin. Pharmacol. Ther.*, 30 (1981) 385–389.

Tsurumi, K., Kyuki, K., Hayashi, M. and Fujimura, H., Study on combination of nonsteroid anti-inflammatory drug with antacid. 1. Influence of antacids on gastric lesions induced by anti-inflammatory agents. *Oyo Yakuri*, 17 (1979) 1061–1068 (Engl.).

Upton, R.A., Buskin, J.N., Williams, R.L., Holford, N.H.G. and Riegelman, S., Negligible excretion of unchanged ketoprofen, naproxen and probenicid in urine. *J. Pharm. Sci.*, 69 (1980) 1254–1257.

Vogel, A.I., *Quantitative Inorganic Analysis Including Elementary Instrumental Analysis*, 3rd Edn., Longmans, Ch. IV, 1961, p. 436.

Wallis, W.J. and Simkin, P.A., Antirheumatic drug concentrations in human synovial fluid and synovial tissue. Observations on extravascular pharmacokinetics. *Clin. Pharmacokin.*, 8 (1983) 496–522.