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Effect of sucralafate and antacids on the bioavailability of sulpride in humans

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Summary

The effect of two anti-ulcer drugs, sucralafate and an antacid, containing aluminum and magnesium hydroxide on the bioavailability of another anti-ulcer drug, sulpride, was studied. Using a latin-square design, six healthy male volunteers participated in the trials. Concomitant administration of the antacid or sucralafate with sulpride significantly (ANOVA, $P < 0.01$) reduced its extent of bioavailability, as measured by total urinary excretion in 48 h. A therapeutic dose of sucralafate decreased the oral bioavailability from $31 \pm 8.4\%$ to $18.6 \pm 4.4\%$, a 40% reduction. A therapeutic dose of the antacid decreased the oral bioavailability from 31 ± 8.4 to $20.9 \pm 4.5\%$, a 32% reduction. There was no change in the rate of urinary excretion and hence no change in biological half-life of sulpride. When the antacid or sucralafate were given 2 h before sulpride, the extent of bioavailability reduction was about 25%.

The interaction between sulpride and the other two anti-ulcer drugs is thought to be due to binding or complexation resulting in interference with the gastrointestinal absorption of sulpride. This interaction is expected to be clinically significant and it is recommended that if these drugs are used concurrently, sulpride should be given 2 h before and not with or after the antacid or sucralafate.

Introduction

Drug therapy of peptic ulcers aims to achieve relief of pain, healing and prevention of recurrences.

Antacids, in adequate doses, remain the basis of management of acid-peptic

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diseases. Antacids reduce hyperacidity and help to relieve ulcer pain. Intensive antacid therapy was also found to speed the rate of healing of peptic ulcers (Texter and Jordon, 1979). Antacids containing aluminum and magnesium hydroxide are most commonly prescribed.

Sucralafate, basic aluminum sucrose sulfate, is a recently introduced drug promoted for the treatment of peptic ulcer. Sucralafate is not an effective antacid. Its protective action appears to be a local one. After initial contact with gastric acid, sucralafate loses its aluminum ion, yields a multivalent anion, and forms a highly condensed viscous mass which binds preferentially to the ulcer site. This cytoprotective barrier protects the ulcer from the potential ulcerogenic properties of acid, bile and pepsin. Sucralafate also interacts directly with pepsin and bile (Nagashima, 1981; McGraw and Caldwell, 1981).

Sulpride is a benzamide derivative with potent antidopaminergic properties and like other dopamine blockers, the drug is an effective anti-emetic agent and has antipsychotic activity. Sulpride has frequently been used in ulcer patients. It is said to be particularly valuable in stress ulceration after head trauma and neurological disease (Abrahamsson and Dotevall, 1979). Sulpride and antacids were used together and this regimen was compared to cimetidine for the treatment of benign gastric ulcer. The antacid–sulpride regimen was found very effective in healing gastric ulcer with a healing rate that was at least as effective as that obtained with cimetidine (Mihas and Mihas, 1981).

Sulpride–antacid combination was also used in the treatment of duodenal ulcers. Sulpride was found to have a minor but definite synergism with antacids (Lam et al., 1979).

Because the concurrent administration of antiulcer drugs is a common practice, the present study was designed to evaluate the effect of the concomitant use of sucralafate or antacids and sulpride on the bioavailability of the later drug.

Materials and Methods

Materials

Sulpride (base) powder, lot no. 80/37 and Dogmatil capsules (sulpride, 50 mg), lot no. 292 were kindly supplied by Delagrange Labs., Paris, France. Carafate (sucralafate, 1 g/tablet) tablets, control no. P2114 (Marion Laboratories, Kansas City, MO, U.S.A.) and Simeco suspension (an antacid, each 5 ml containing: aluminium hydroxide 215 mg, magnesium hydroxide 80 mg and simethicone (activated dimethicone) 25 mg) were purchased. Methanol, spectral grade (Merck, Darmstadt; chloroform, UV grade (BDH Chemicals, Poole, U.K.); glacial acetic acid (BDH Chemicals, Poole, U.K.) were used as reagents in the assay procedure.

Bioavailability studies

A latin-square design was used. Six healthy male volunteers participated in the trials. Their average age (years) and body weight (kg) were 35 and 65, respectively.

The volunteers were instructed not to take any drug one week before and during the trials.

A wash-out period of at least one week ensured complete drug elimination before the next trial. A complete physical examination including urine analysis, blood chemistry profile was given before trials. Each subject ingested a dose of 100 mg of sulpride (two capsules), after an over-night fast, according to the trial design shown in Table 1. Food was not allowed for 3 hours after dosing.

A urine sample was collected at the time of drug administration (0 h), ensuring complete emptying of the bladder, and at hourly intervals for the first 8 h, then at various intervals up to 48 h. Water was ingested to maintain adequate urine flow. The pH of urine was monitored during the collection period.

Method of analysis

A high-pressure liquid chromatography (HPLC) method was used (Alfredsson et al., 1979), after modification. The instrument was a Waters (Bedford, MA, U.S.A.) model 6000 delivery system equipped with an automatic sample injector WISP model 710B (Waters, U.S.A.), a fluorescence detector model 420C (Waters) set at an excitation wave-length of 254 nm and emission at 337 nm, and a recorder (Philipps PM 8251 single pen recorder). The column was stainless steel (30 cm × 4 mm i.d.) packed with microparticulate silica (10 μm) C_{18} bonded with octadecyl silane.

The mobile phase consisted of methanol (30%), double-distilled water (69%), and glacial acetic acid (1%). To compensate for erratic loss of the compound during the extraction procedure a standard curve in urine was made with every run. To a 2-ml urine sample about 0.2 ml conc. ammonia solution was added. The sample was extracted twice with each of 10 ml of chloroform. An 18 ml aliquot of the chloroform layer was transferred to a tube, the chloroform was evaporated to dryness in vacuum at 60°C. The residue in the tube was dissolved in 1 ml of the mobile phase. Standard curves were prepared by adding known amounts of sulpride solution (dissolved in the mobile phase) to 2 ml of the urine sample obtained at 0 h. The range for the standard concentrations of sulpride were 5–30 μg/ml.

TABLE 1

BIOAVAILABILITY STUDY OF SULPRIDE

Subject	Treatment number		
	1	2	3
SH	A	B	C
HM	C	A	B
AH	B	C	A
SB	C	A	B
WG	B	C	A
GM	A	B	C

Treatment code: A, drug taken alone; B, drug taken 0.5 h after the administration of 1 g sucralafate tablet; C, drug taken with 30 ml antacid.

Results and Discussion

The total amounts of sulpride excreted in the urine after 48 h when the drug was taken: (i) alone; (ii) after 0.5 h (to allow for tablet disintegration) of one sucralafate, 1 g/tablet; and (iii) concurrently with an average dose of the antacid, are shown in Table 2. This presents a measure of the extent of bioavailability of sulpride under the above conditions. The cumulative amount of the drug excreted in the urine at various time intervals are plotted in Fig. 1.

TABLE 2

TOTAL URINARY EXCRETION OF SULPRIDE IN 48 h AFTER ORAL ADMINISTRATION OF 100 mg SULPRIDE CAPSULES WITH AND WITHOUT THE OTHER ANTI-ULCER DRUGS

Subject	Total excreted (mg)		
	Treatment A *	Treatment B *	Treatment C *
SH	34.0	22.9	24.0
HM	42.0	16.2	26.5
AH	25.3	14.4	13.9
SB	22.8	15.9	17.8
WG	23.1	16.6	21.2
GM	39.0	25.3	22.2
Mean ± S.D.	31.0 ± 8.4	18.60 ± 4.4	20.9 ± 4.5

* See Table 1 for details of treatment regimen.

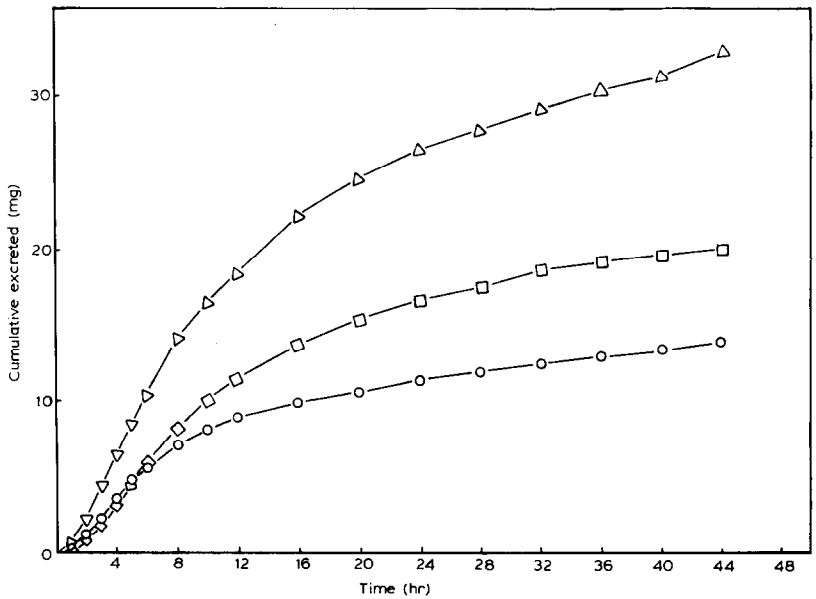

Fig. 1. Mean cumulative amount of sulpride excreted in urine after oral administration of 100 mg capsules (average of 6 subjects). △, control: ○, with sucralafate; □, with antacid (see text for dosage).

Sulpride is excreted, more than 95%, in the unchanged form. The extent of sulpride bioavailability, expressed as percentage of the dose administered, was on the average 31% (S.D. ± 8.4, Table 2.). This value is within the range previously reported. Kleimola et al. (1976) reported the 48-h urinary excretion of sulpride in humans as approximately 30% of a 100 mg dose. Using labelled sulpride, Imondi et al. (1978) reported an average urinary recovery of 40 ± 14% of the dose in 48 h following oral administration of capsules.

The rate of elimination of sulpride was uniformly rapid in each subject. Of the total amount recovered in urine, 83% was collected during the first 24 h and 95% had been excreted within 36 h after administration of the drug (Fig. 1). A similar pattern was previously observed by Imondi et al. (1978). The rate of urinary excretion is plotted on a semilogarithmic scale in Fig. 2. Maximum urinary excretion rate was obtained at 5–7 h. The biological half-life of sulpride was determined from the slope of urinary excretion rates by linear regression analysis of urinary excretion rate (mg sulpride excreted unchanged per hour) versus time from 8 h to 36 h. The biological half-life was found to be 10.0 ± 2.7 (S.D.) h (Table 3). This value is in close agreement with previous reported values of 10.5 ± 3.3 h calculated from the slope of plasma levels following oral administration (Wiesel et al., 1980). A half-life of sulpride of about 9–10 h has also been published (Kleimola et al., 1976).

When sulpride was administered with a therapeutic dose of sucralafate (1 g) the extent of bioavailability was significantly reduced (ANOVA, $P < 0.01$). The total amount of drug excreted in 48 h was lowered from 31 ± 8.4% to 18.6 ± 4.4% (Table 2). This represents a 40% reduction in bioavailability. However, the rate of urinary excretion of sulpride (Fig. 2) and the biological half-life (Table 3) did not change.

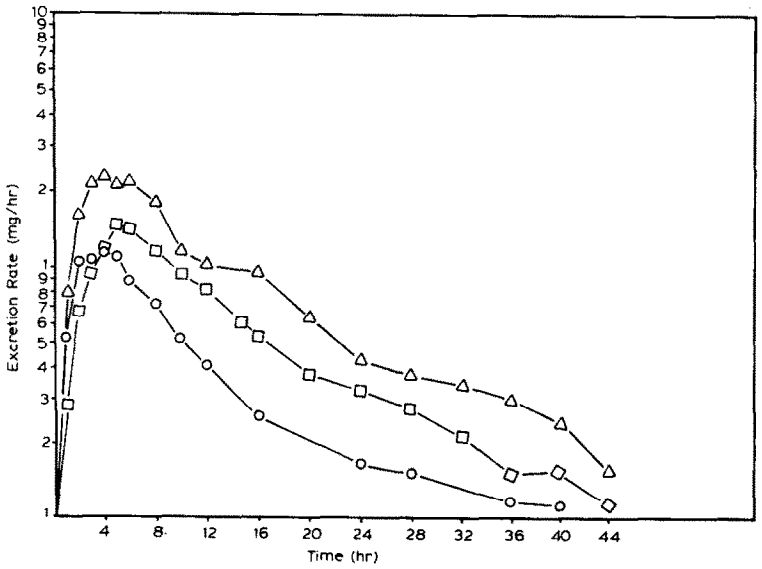

Fig. 2. Mean urinary excretion rate of sulpride after oral administration of 100 mg sulpride capsules (average of 6 subjects). △, control; ○, with sucralafate; □, with antacid (see text for dosage).

TABLE 3

BIOLOGICAL HALF-LIFE OF SULPRIDE AS DETERMINED FROM URINARY EXCRETION AFTER ORAL ADMINISTRATION WITH AND WITHOUT THE OTHER ANTI-ULCER DRUGS

Subject	Biological half-life ($t_{\frac{1}{2}}$, h).		
	Treatment A *	Treatment B *	Treatment C *
SH	11.8	14.7	10.0
HM	6.3	6.6	6.8
AM	13.9	14.4	12.4
SB	10.6	8.7	10.9
WG	7.9	8.3	11.4
GM	9.3	9.2	7.0
Mean ± S.D.	10.0 ± 2.7	10.5 ± 3.7	9.8 ± 2.3

* See Table 1 for details of treatment regimen.

The administration of a therapeutic dose of the antacid (30 ml) with sulpride also resulted in a significant decrease in bioavailability (ANOVA, $P < 0.01$). The total amount of drug excreted was reduced from 31 ± 8.4% to 20.9 ± 4.5% of the administered dose, representing a 32% reduction in bioavailability. Again, there was no significant change in the rate of urinary excretion and the biological half-life (Fig. 2, Table 3).

Two more experiments were carried out where either sucralafate (treatment D, Table 4) or the antacid (treatment E, Table 4) were given 2 h before sulpride to two subjects. These treatments resulted in reduction of bioavailability in each of the subjects. The extent of bioavailability reduction was approximately 25%, not as pronounced as when the drugs were given concurrently.

An additional experiment was carried out where sucralafate was given 2 h after sulpride to one subject. As expected, there was no change in bioavailability when this regimen was followed.

Both sucralafate and the antacid are non-absorbable anti-ulcer drugs. Their significant reduction of sulpride bioavailability, on concurrent administration, seems to be the result of their interference with the gastrointestinal absorption of this drug.

TABLE 4

TOTAL URINARY EXCRETION OF SULPRIDE IN 48 h AFTER ORAL ADMINISTRATION OF 100 mg CAPSULES UNDER DIFFERENT CONDITIONS [a]

Subject	Total excreted (mg)		
	Treatment A	Treatment D	Treatment E
SH	34.0	–	22.5
GM	39.0	27.2	30.5
WG	23.1	18.7	–

[a] Conditions – Treatment A, drug taken alone; Treatment D, drug taken 2 h after the administration of 1 g sucralafate tablet; Treatment E, drug taken 2 h after the administration of 30 ml antacid.

This is further evidenced by the facts that the rate of elimination and hence the biological half-life of sulpride was found to be essentially the same (Table 3) in the presence and absence of the antacid or sucralafate.

The urine pH varied between 5.5 and 6.5 during all treatments. The administered dose of the antacid did not change urinary pH. The mechanism of interaction between sulpride and the antacid or sucralafate is probably a complexation or adsorption of the drug to those two anti-ulcer drugs. Sucralafate and the antacid can also form a viscous barrier within the gastrointestinal tract resulting in decreased absorption of sulpride.

Regardless of the mechanisms of this interaction, the reduction in bioavailability of sulpride on concurrent administration with sucralafate or the antacid, or when the drug was given 2 h after, is expected to be clinically significant. It is recommended that if the drugs are used concurrently, sulpride should be given 2 h before and not with or after these two other anti-ulcer compounds.

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References

Abrahamsson, H. and Dotevall, G., Pharmacological and clinical aspects of some drugs used in peptic ulcer treatment. Scand. J. Gastroent., 14 (1979) 117–120.

Alfredsson, G., Sedvall, G. and Wiesel F.A., Quantitative analysis of sulpride in body fluids by high performance liquid chromotography with fluorescence detection. J. Chromotogr., 164 (1979) 187–193.

Imondi, A.R., Alam, A.S., Brennan, J.J. and Hagerman, L.M., Metabolism of sulpride in man and rhesus monkeys. Arch. Int. Pharmacodyn., 232 (1978) 79–91.

Kleimola, T., Leppanen, O., Kanto, J., Mantyla, R. and Syvalahti, F., Spectrofluorometric method for quantiative determination of sulpride in human plasma and urine. Ann. Clin. Res., 8 (1976) 104–110.

Lam, S.K., Lam, K.C., Lai, C.L., Yeung, C.K., Yam, Y.C.L. and Wong, W.S., Treatment of duodenal ulcer, with antacid and sulpride. Gastroenterology, 76 (1979) 315–322.

McGraw, B.F. and Caldwell, E.G., Sucralafate. Drug Intell. Clin. Pharm., 15 (1981) 578–580.

Mihas, A.A. and Mihas, T.A., A controlled trial of an antacid sulpride regimen and cimetidine in the treatment of benign gastric ulcer. Gastroenterology, 80 (Part 2) (1981) 1232.

Nagashima R., Development and characteristics of sucralafate. J. Clin. Gastroent., 3 Suppl. 2 (1981) 103–110.

Texter, E.C. and Jordon, H.J., General Principles of Drug Therapy for Disorders of the Gastrointestinal Tract. In Wang, R.I.H. (Ed.), Practical Drug Therapy, Lippincot, Philadelphia, 1979, pp. 303–326.

Wiesel, F.A., Alfredsson, G., Ehrnebo, M. and Sedvall, G., The pharmacokinetics of intravenous and oral sulpride in healthy human subjects. Eur. J. Clin. Pharmacol., 17 (1980) 385–391.