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Effect of dosage form, food, and an anticholinergic drug on the bioavailability of sulpiride

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Summary

The oral bioavailability of 3 different dosage forms of sulpiride (Dogmatil), as measured by total 48-h urinary excretion, was studied in 6 healthy male volunteers. Administration of 200 mg of the drug as capsules, tablets and syrup resulted in mean absorptions of 31%, 26% and 20%, respectively. The bioavailability from the syrup was significantly less (ANOVA, $P < 0.05$) than that from capsules. Coadministration of food or an anticholinergic drug, propantheline bromide, with the syrup increased the mean bioavailbility of the drug to about 26%. The results suggest that the delay in gastric emptying and intestinal transit time due to food or propantheline bromide allows for a better site-specific absorption of sulpiride from the intestine.

Introduction

The orthopramide drug sulpiride is used in disorders of the upper gastrointestinal tract and is also prescribed as a psychotropic agent. The pharmacokinetics of sulpiride after oral and i.v. administration in the rat and the dog was studied, and marked species difference in the systemic bioavailability of oral sulpiride was reported (Segura et al., 1976). Using urinary excretion data in dogs, Alam et al. (1980) reported that the bioavailability from capsules was equivalent to that of the hydrochloride solution, while bioavailability from tablets varied according to manufacturing source.

Kleimola et al. (1976) reported no significant differences in oral bioavailability in humans between either two brands of sulpiride tablets or between two brands of sulpiride liquid preparations. The same authors also reported that oral bioavailability from sulpiride liquid preparations was significantly less than bioavailability from tablets and capsules. The pharmacokinetics of i.v. and oral sulpiride in healthy human subjects was studied, and oral bioavailability from tablets was reported to be low and variable (Wiesel et al., 1980).

The above studies suggested that formulation factors play a significant role in the oral bioavailability of sulpiride. The present study was designed to assess the effect of different dosage forms on the oral bioavailability of sulpiride supplied by the same manufacturer. The effect of food and an anticholinergic drug (propantheline bromide) on

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the bioavailability of sulpiride from solution dosage form was also studied, in an attempt to explain the unexpectedly low bioavailability of this form compared to solid dosage forms.

Materials and Methods

Materials

Sulpiride (base) powder, lot No. 80/37; Dogmatil capsules (Sulpiride 50 mg) batch No. 141, Dogmatil tablets (Sulpiride 200 mg) batch No. 783, and Dogmatil syrup (Sulpiride 5 mg/ml) batch no. 041 were kindly supplied by Delagrange Labs., Paris, France. Pro-Banthine tablets (propantheline bromide, 15 mg) batch No. 001 was purchased. All reagents used in the assay procedure were spectral grade.

Bioavailability studies

A latin-square design was followed. Six healthy male volunteers, capable of informed consent, participated in the trials under medical supervision. Their average age was 35 years, and average body weight was 65 kg. The volunteers were instructed not to take any drugs one week before and during the trials. A wash-out period of at least one week ensured complete drug elimination before the next trial.

Each subject ingested a dose of 200 mg of sulpiride (one tablet, 4 capsules or 40 ml of syrup), after an overnight fast according to a trial design previously reported (Gouda et al., 1984). Food was not allowed for 3 h 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 allowed freely to maintain adequate urine flow.

Effect of food

Four volunteers participated in the trial. Using

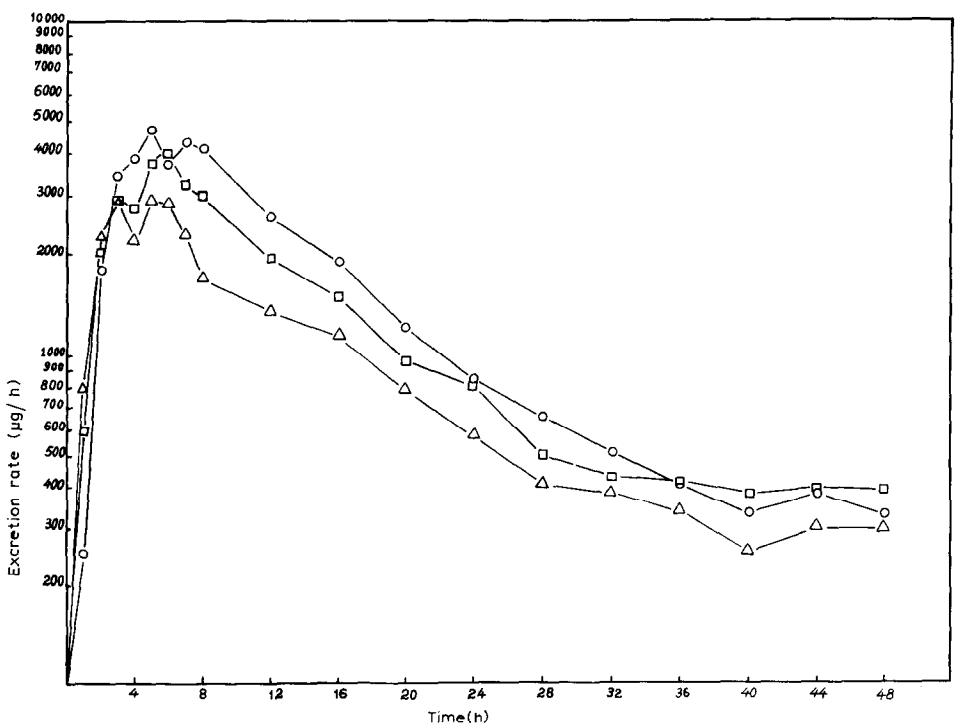

Fig. 1. Mean urinary excretion rate of sulpiride after administration of 200 mg of different dosage forms (averages of 6 subjects). ○, Capsules; □, tablet; △, syrup.

a cross-over design, each subject ingested 40 ml (200 mg) of Dogmatil syrup in one trial (after an overnight fast) and one week later, the same dose was given after a standard breakfast composed of bread, cheese and jam.

Effect of propantheline bromide

Four volunteers participated in the trial. Following a cross-over design, each subject ingested 40 ml of Dogmatil syrup after an overnight fast, and one week later, the same dose was given half an hour after the ingestion of two 15-mg propantheline bromide tablets.

Method of analysis

A high-pressure liquid chromatography (HPLC) method, previously reported, was used (Gouda et al., 1984).

Results and Discussion

Sulpiride is excreted, more than 95%, in the unchanged form (Imondi et al., 1978). The rate of urinary excretion of sulpiride after administration of the capsules, tablets and syrup is shown in Fig. 1. The elimination pattern was similar to a previous report (Gouda et al., 1984). The biological half-life, as determined from urinary excretion rate, was similar for all 3 dosage forms. Mean value of 9.5 ± 2.0 (S.D.), 10.0 ± 2.0 and 11.4 ± 2.4 h were obtained for the capsules, tablets and syrup, respectively. Previously reported values ranged from 9 to 10.5 h (Gouda et al., 1984; Wiesel et al., 1980; Kleimola et al., 1976).

The cumulative amounts of the drug excreted in the urine at various time intervals are plotted in Fig. 2. The bioavailability of sulpiride, as measured by total urinary excretion after 48 h, from capsules, tablets, and syrup is shown in Table 1. Bioavailability of sulpride from Dogmatil capsules was, on the average, about 31%. The same value was obtained in a previous study (Gouda et al., 1984) for the bioavailability following administration of a 100-mg dose of sulpiride from the same brand of capsules. Kleimola et al. (1976) reported a value of 30% following the administration of a different brand of capsules containing 100 mg of the drug while Imondi et al. (1978) reported a range of 27–52% following the administration of 100 mg of labelled sulpiride as capsules.

Bioavailability of sulpiride from Dogmatil tablets in the present study was slightly less (26%) than that from capsules (Table 1). The bioavailability, determined from combined plasma and urine data, was reported to be 27% following administration of 100 mg Dogmatil tablets (Wiesel et al., 1980). After comparing the bioavailability of sulpiride from two brands of tablets, Dogmatil and Sulpiril tablets, Kleimola et al. (1976) reported 48-h urinary excretions of 26% and 30%, respectively, of the total 200 mg oral dose. The non-significant decrease in bioavailability from

TABLE 1

Total urinary excretion of sulpiride in 48 h after oral administration of the 3 different dosage forms containing 200 mg sulpiride each

Subject	Total excreted (mg)		
	Capsule	Tablet	Syrup
SH	63.3	47.2	39.0
HB	44.0	26.0	20.0
AA	78.0	74.6	54.5
SB	47.0	32.4	27.0
WG	62.7	60.8	46.8
GM	72.0	73.0	56.0
Mean ± S.D.	61.2 ± 13.4	52.3 ± 20.5	40.5 ± 14.7

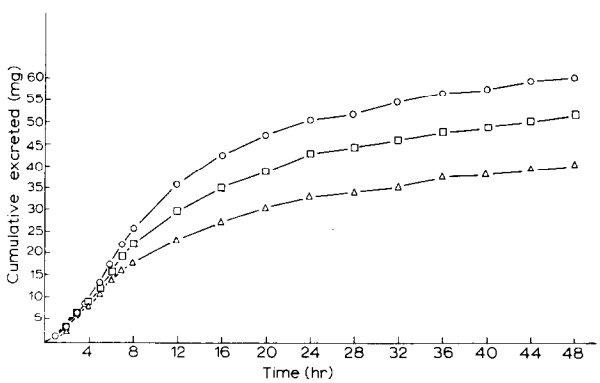

Fig. 2. Mean cumulative amount of sulpiride excreted in urine after oral administration of 200 mg of different dosage forms (averages of 6 subjects). ○, Capsules; □, tablet; △, syrup.

TABLE 2

Total urinary excretion of sulpiride in 48 h after administration of 40 ml (200 mg) Dogmatil syrup with and without food

Subject	Total excreted (mg)	
	Control (without food)	With food
A	39.0	54.5
B	31.5	58.3
C	54.4	56.5
D	53.8	44.8
Mean ± S.D.	39.7 ± 10.3	53.5 ± 6.0

TABLE 3

Total urinary excretion of sulpiride in 48 h after administration of 40 ml (200 mg) Dogmatil syrup with and without propantheline (30 mg)

Subject	Total excreted (mg)	
	Control (without propantheline)	With propantheline
E	42.0	48.5
F	53.0	66.2
G	37.3	49.1
H	35.0	51.1
Mean ± S.D.	41.8 ± 8.0	53.7 ± 8.4

the tablet form observed in this study as compared to capsules is in accordance with general expectation (Gibaldi, 1984).

Bioavailability of sulpiride from the syrup dosage form was 20% significantly less (ANOVA, $p < 0.05$) than that from capsules. Kleimola et al. (1976) compared the bioavailability of two different brands of sulpiride liquid preparations, Dogmatil syrup and Sulpiril mixture, and reported values of 18% and 17% of a 100 mg oral dose, respectively. The low bioavailability of the syrup dosage form as compared to capsules is not what one would generally expect.

Oral bioavailability of sulpiride in humans was reported to be low (Wiesel et al., 1980). However, consideration of formulation factors affecting bioavailability usually favor solutions over solid dosage forms. Alam et al. (1979) studied the bio-

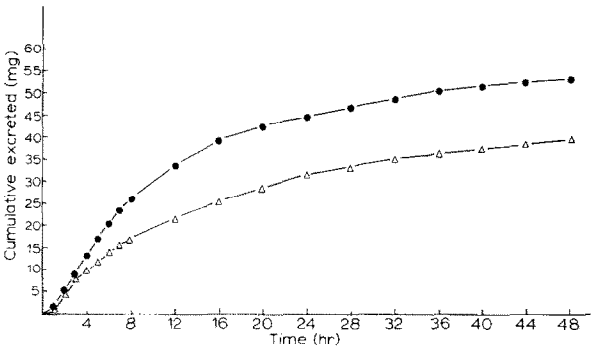

Fig. 3. Mean cumulative amount of sulpiride excreted in urine after administration of 200 mg sulpiride syrup with and without food (averages of 4 subjects). △, Control; ●, with food.

availability of sulpiride in dogs and reported a bioavailability of 85% for the oral hydrochloride solution and 75% for the free-base suspension. Sulpiride, a benzamide, is present in the syrup in an acidic aqueous vehicle and the possibility of precipitation in gastric fluid is highly unlikely. However, the possibility of precipitation in the intestine cannot be ruled out. Inefficient absorption of sulpiride may be partly due to low solubility in the intestinal milieu, but may also be related to site-specific absorption. These factors are likely to affect the syrup more than solid dosage forms because of faster gastric emptying and intestinal transit rates of liquids.

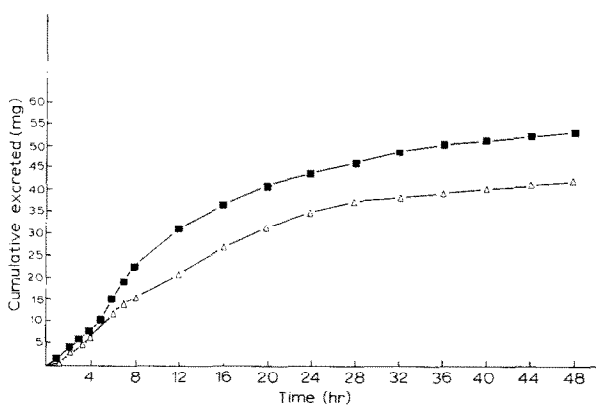

Fig. 4. Mean cumulative amount of sulpiride excreted in urine after administration of 200 mg sulpiride syrup with and without propantheline (averages of 4 subjects). △, Control; ■, after propantheline.

When a drug is taken with solid food there is a delay in stomach emptying and a longer residence period in the small intestine. The effect of a standard breakfast on the urinary excretion of sulpiride from the syrup is shown in Table 2 and Fig. 3. Food increased the bioavailability from 20 to 27% approximately. These results are of borderline significance (paired t-test, $P < 0.1$).

Propantheline bromide is an anticholinergic drug which decreases gastric emptying and intestinal transit rates. Administration of 30 mg of propantheline bromide, 0.5 h before sulpiride syrup, resulted in a significant increase in absorption (paired t-test, $P < 0.01$). The bioavailability increased from 21 to 27% as shown in Table 3 and Fig. 4. Food and anticholinergics have been found to increase the bioavailability of several drugs (Levy et al., 1972; Jaffe, 1975; Welling et al., 1982). The increased absorption due to food or an anticholinergic drug support the possibility of specific sites for sulpiride absorption. The decreased gastric motility and emptying rate cause the sulpiride solution to leave the stomach at a slower rate over a longer period of time. This allows for more contact time between sulpiride and its absorption sites and hence, increases absorption.

In conclusion, oral bioavailability of sulpiride from capsules and tablets is low, but essentially the same. Oral bioavailability from the syrup is less than that from solid dosage forms. Food and anticholinergics increase the syrup bioavailability. These results, together with reported values of the biological half-life of sulpiride, suggest that when sulpiride is administered in the liquid form, it should be given 3 times daily with meals.

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