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Effects of Cimetidine, Ranitidine and Omeprazole on Tolbutamide Pharmacokinetics

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Abstract

This randomized, four-way crossover study in 16 healthy subjects compared the effects of cimetidine 800 mg, ranitidine 300 mg and omeprazole 40 mg against placebo given daily after breakfast for seven days on the pharmacokinetics of a single oral dose of tolbutamide (500 mg) given on day 4.

Plasma tolbutamide and urinary hydroxytolbutamide and carboxytolbutamide concentrations were determined by HPLC. Ranitidine had no significant effects on tolbutamide metabolism. Cimetidine produced a 20% increase in AUC ($P < 0.001$) and a 14% increase in $t_{\frac{1}{2}}$ ($P < 0.01$), while omeprazole produced a 10% increase in AUC ($P < 0.01$). The effect of these agents on urinary concentrations of the tolbutamide metabolites was small.

These results do not indicate that interactions of major clinical significance occur in healthy subjects.

Tolbutamide, an oral sulphonylurea hypoglycaemic agent used in the management of non-insulin-dependent diabetes, is metabolized by hepatic microsomal oxidation to hydroxytolbutamide (Thomas & Ikeda 1966) and subsequently to carboxytolbutamide (McDaniel et al 1969). These metabolites in urine account for 90% of an administered dose of tolbutamide (Thomas & Ikeda 1966).

Two studies have compared the effects of daily cimetidine (1·2 g) and ranitidine (300 mg) on the pharmacokinetics of a single dose of tolbutamide (1 g) (Cate et al 1986; Adebayo & Coker 1988). The first of these studies was a randomized double-blind crossover design involving 12 healthy subjects in which 300 mg cimetidine given four times per day for four days significantly increased the area under the plasma concentration-time curve (AUC) of tolbutamide, given on day 3, by 20% and its elimination half-life ($t_{\frac{1}{2}}$) by 17%, whereas ranitidine 150 mg twice a day had no effect on these parameters (Cate et al 1986). The second study was an open randomized crossover design in eight subjects which showed no significant effects of either H_2-receptor antagonist on $t_{\frac{1}{2}}$, apparent volume of distribution or apparent clearance of tolbutamide (Adebayo & Coker 1988). Three other studies have investigated the effects of cimetidine on tolbutamide pharmacokinetics (Dey et al 1983; Stockley et al 1986; Back et al 1988), two of which found no significant effects when a cimetidine dose of 400 mg twice a day was used (Dey et al 1983; Stockley et al 1986). The third study showed an increase in $t_{\frac{1}{2}}$ and decrease in clearance at higher doses of cimetidine up to 400 mg four times per day (Back et al 1988).

Omeprazole is the first of a new class of anti-secretory agents which is becoming more widely used. Omeprazole is extensively metabolized by the liver and a reduction in the apparent clearance of several concomitantly administered drugs has been reported, the most striking change being that with diazepam (Gugler & Jensen 1985). However, there have as yet been relatively few reports on the possible effects of omeprazole on drug metabolism.

In view of the conflicting results for the effects of cimetidine on tolbutamide metabolism, and the absence of data for the possible effects of omeprazole, the present study undertook to compare the effect of cimetidine 800 mg mane, ranitidine 300 mg mane and omeprazole 40 mg mane on the pharmacokinetics of a single 500 mg oral dose of tolbutamide.

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Materials and Methods

Design

The study comprised a balanced partially blinded, randomized, four-way crossover design. Each subject received either placebo (matching ranitidine), cimetidine 800 mg, ranitidine 300 mg (given as ranitidine hydrochloride) or omeprazole 40 mg daily after breakfast for seven days. A single dose of tolbutamide 500 mg was administered 1 h after the other study medication on day 4. Dosing periods were separated by a minimum of seven days wash-out.

Ethics

The study protocol was approved by an independent Ethics Committee. The study was performed in accordance with the guidelines of the Declaration of Helsinki for biomedical research involving human subjects (Hong Kong amendment 1989). Each subject gave written informed consent after a full explanation of the study had been provided.

Subjects

Sixteen healthy male subjects (mean age 25, range 19–31 years) were recruited. Before entering the study, each subject had a full medical examination, and routine biochemical, haematological and microbiological investigations. No

clinically relevant abnormalities were found. Subjects who had a medical history of diabetes, severe or multiple allergies, or any other significant medical history were excluded.

Clinical procedures

The subjects fasted from 2000 h of day 3 until they attended the Clinical Unit at 0700 h on day 4. A standardized breakfast (cereal, toast and a drink) was given on arrival and a light standardized lunch approximately 4 h after dosing with tolbutamide. A standardized evening meal was provided approximately 10 h post-dosing. Only non-caffeinated foods and drinks were permitted from 12 h before attending the Clinical Unit on day 4 and for the whole of that day.

An additional drink of orange squash with added sugar and two biscuits was given to maintain adequate blood glucose concentrations at approximately 1·5–2 h following tolbutamide dosing. Subjects were not allowed to drink alcohol for 24 h before and for the duration of the four study phases. Full medical cover was provided for the duration of the study.

On day 4, blood samples were taken pre-dose and at 0·5, 1, 1·5, 2, 3, 4, 6, 8 and 12 h post-dose via an indwelling cannula sited in a forearm ante-cubital vein. At 24, 36, 48 and 72 h post-dose, blood samples were taken by direct venepuncture of an ante-cubital vein. Blood samples were placed in plastic tubes containing lithium heparin-coated granules and centrifuged at 1000 *g* for 10 min. Plasma was then separated using a disposable glass pipette, placed in labelled tubes, and stored at −18°C.

Urine collections were made during the 24-h period before tolbutamide administration and during the periods 0–4, 4–8, 8–12, 12–24, 24–48 and 48–72 h post-dose. The weights of the samples were noted and a 10-mL portion taken and stored at −20°C.

As a safety precaution, blood glucose measurements were made using Ames Glucostix and electronically (Glucometer II) at 1, 2 and 3 h post-dosing with tolbutamide. Symptoms of hypoglycaemia accompanying blood glucose concentrations < 3·0 mM were treated by a glucose-containing drink.

Analytical method

Plasma tolbutamide and urine metabolite concentrations were determined using a specific, validated reversed-phase high-performance liquid chromatographic (HPLC) assay with UV-absorbance detection. The analytical column (15 cm × 4·6 mm) containing 3 μm ODS2 was used with an HP1050 series automated LC system, a Spectroflow 773 absorbance detector set at a wavelength of 200 nm, and an HP3396A reporting integrator. The mobile phase comprised acetonitrile (40% v/v for plasma and 20% v/v for urine assays) in 0·05% v/v phosphoric acid. The retention times were 5·3 min for tolbutamide in plasma, and 2·8 and 3·9 min for hydroxytolbutamide and carboxytolbutamide, respectively, in urine.

To 100 μL plasma was added 250 μL acetonitrile. After vortex mixing for 10 s the mixture was centrifuged for 5 min. The resulting clear supernatant was pipetted into glass vials for HPLC analysis. Urine samples were thoroughly mixed after thawing and 200 μL portions were placed directly into glass autosampler vials.

Six tolbutamide calibration standards (concentration range 2·5–51·8 $\mu g\,mL^{-1}$) were used in triplicate to form a calibration curve for each analytical batch. Six quality control samples comprising duplicates of high, intermediate and low plasma tolbutamide concentrations were also included with each batch of samples analysed. Six urine standards (concentration range 10–500 $\mu g\,mL^{-1}$) and quality control samples containing both metabolites were also used. Accuracy and precision was < 15% for all three species.

Pharmacokinetics

The plasma tolbutamide concentration-time data were analysed using a peeling algorithm (Siphar, Simed, Creteil, France) and were adequately described by a single-compartment model following extra-vascular dose administration.

The elimination rate constant (k) was obtained directly from the fitting procedure and $t_{\frac{1}{2}}$ was calculated from ln 2/k.

AUC was calculated using the linear trapezoid approximation from time zero up to the last time point, t, and extrapolated from the last experimentally determined concentration C_t to infinity using the approximation C_t/k. The extrapolated area contributed less than 10% of the total AUC.

The apparent total clearance (CL/F) was calculated as dose/AUC, where the dose was the administered oral dose of tolbutamide (500 mg). The apparent volume of distribution (Vd/F) was obtained from dose/AUC.k.

The maximum plasma tolbutamide concentration (C_{max}) and the time taken to achieve that concentration post-dosing (t_{max}) were both determined directly from the data.

The proportion of the administered dose of tolbutamide excreted as either hydroxy- or carboxytolbutamide was calculated as $fm = \Sigma Ae_m/dose \cdot 100$, where ΣAe_m is the cumulative amount of a particular metabolite excreted into the urine.

Statistics

The linear calibration curves, used in the analytical method, were produced by the method of weighted least squares.

All other statistical analyses were undertaken using SPSS-PC+ statistical software. Assessment of homogeneity within individual data sets was undertaken using Levene's test.

Normality of distribution was assessed for all pharmacokinetic parameters (other than t_{max}) using the test of Kolmogorov-Smirnov. A multiple analysis of variance with contrasts was undertaken to assess differences between treatments. Factors entering the analysis were subject, treatment and period. Statistical assessment of changes in t_{max} was undertaken using two-way non-parametric analysis of variance (for subjects and treatments).

Results

All 16 subjects completed the study. Despite several blood sugar concentrations < 3·0 mM, there were few physical symptoms reported associated with hypoglycaemia. One subject felt dizzy, sweaty and light-headed with a blood glucose concentration of 1·8 mM. This rapidly resolved after a glucose drink. Another subject suffered a vaso-vagal faint

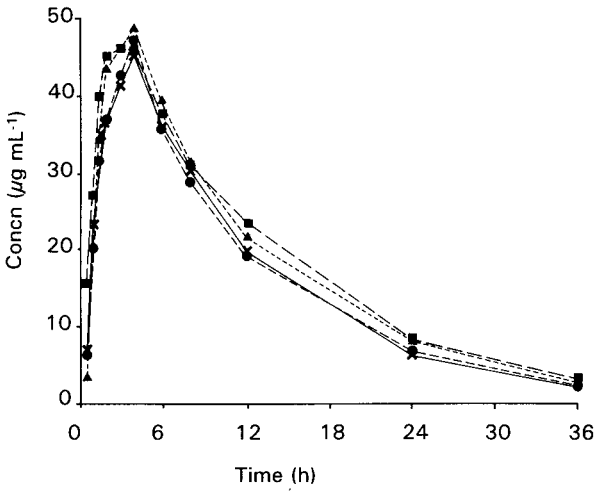

FIG. 1. Average plasma tolbutamide concentration-time profiles following oral administration of 500 mg tolbutamide in the absence (×) and presence of chronically administered ranitidine (●) or cimetidine (■) or omeprazole (▲) in 16 healthy young male volunteers.

resulting from blood sampling (blood sugar normal) and subsequently had nausea and vomiting following glucagon injection. One other subject had an episode of diarrhoea during dosing with omeprazole.

Mean plasma tolbutamide concentration-time curves during co-administration of placebo, cimetidine, ranitidine and omeprazole are shown in Fig. 1. The mean (± s.d.) pharmacokinetic results for plasma tolbutamide are summarized in Table 1.

C_{max} was found to be non-normally distributed with or without logarithmic transformation. C_{max} and t_{max} were therefore both analysed using a non-parametric two-way analysis of variance (Friedman). All other parameters were normally distributed and homogeneous. A significant period effect was found for CL/F, AUC, Vd/F and $t_{\frac{1}{2}}$ which was attributable to the third treatment period. The basis of the period effect could not be established, particularly as all of the samples for each subject were analysed within the same analytical batch.

Chronic ranitidine administration did not affect the pharmacokinetics of tolbutamide. Multiple dosing with cimetidine or omeprazole inhibited the metabolism of tolbutamide but to differing degrees. Cimetidine produced a 20% increase in AUC ($P < 0.001$) as compared with a 10% increase produced by omeprazole ($P < 0.01$). Significant changes of similar relative magnitude were also seen for apparent clearance. Cimetidine also produced a 14% increase in $t_{\frac{1}{2}}$ ($P < 0.01$) and a 5·8% decrease ($P < 0.05$) in the apparent volume of distribution (Table 1).

The effect of the antisecretory agents on the urinary concentrations of metabolites of tolbutamide was small (Table 2). The only observed significant change ($P < 0.05$) in metabolite-related parameters was in the amount of carboxytolbutamide excreted. However, pairwise comparisons could not establish the source of this statistical significance despite a 19% increase in the amount of carboxytolbutamide excreted during 72 h of concomitant cimetidine dosing.

Discussion

In agreement with two previous studies (Cate et al 1986; Adebayo & Coker et al 1988), the present investigation found no effect of ranitidine on the pharmacokinetics of tolbutamide. A modest increase in AUC and $t_{\frac{1}{2}}$, with accompanying changes in CL/F and Vd/F, were noted during co-administration of cimetidine, while a small increase in AUC was noted during omeprazole therapy.

Although normal clinical practice is to administer single daily doses of H_2-receptor antagonists at night, the dose was given in the morning so that blood sampling could be carried out during the daytime. This design feature is unlikely to have affected the study outcome. Similarly, some subjects exhibit a second peak in their plasma concentration-time profiles after ingestion of an H_2-receptor antagonist, but this variability may be eliminated when medication is taken with food without reducing the total amount of drug absorbed (Bodemar et al 1979).

Tolbutamide is metabolized in man by the cytochrome P4502C9 (Relling et al 1990). This isozyme has also been found to govern the primary metabolic pathway of (*S*)-warfarin, leading to the formation of 7-hydroxywarfarin (Rettie et al 1992). In previous investigations the interaction between cimetidine and warfarin (Toon et al 1987; Niopas et al 1991), and omeprazole and warfarin (Sufin et al 1989) have been shown to be stereoselective with metabolic

Table 1. Mean (± s.d.) pharmacokinetic parameter values of tolbutamide.

	Placebo	Ranitidine	Cimetidine	Omeprazole
C_{max} (μg mL^{-1})	51·4 (7·72)	53·7 (9·72)	54·9 (7·78)	53·4 (6·87)
AUC (μg mL^{-1} h)	606·4 (117·5)	596·3 (149·6)	728·9*** (198·0)	665·5** (106·8)
$t_{\frac{1}{2}}$ (h)	7·19 (1·16)	6·94 (1·55)	8·19** (2·46)	7·55 (1·19)
CL/F (L h^{-1})	0·85 (0·14)	0·88 (0·20)	0·73*** (0·18)	0·77** (0·12)
Vd/F (L)	8·65 (1·11)	8·41 (1·01)	8·15* (0·81)	8·23 (0·77)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with placebo treatment.

Table 2. Mean (± s.d.) total urinary excretion of metabolites of tolbutamide over 72 h.

	Placebo	Ranitidine	Cimetidine	Omeprazole
Hydroxytolbutamide (mg)	74·2 (15·6)	87·3 (30·0)	72·8 (20·5)	79·7 (35·0)
(% dose)	14·0 (2·9)	16·5 (5·7)	13·8 (3·9)	15·1 (6·6)
Carboxytolbutamide (mg)	383·6 (47·7)	422·2 (63·0)	357·4 (85·5)	421·3 (46·9)
(% dose)	69·0 (8·6)	76·0 (11·3)	64·4 (15·4)	75·9 (8·5)
Carboxytolbutamide/ hydroxytolbutamide ratio	4·93 (1·35)	4·61 (1·61)	4·67 (1·25)	5·03 (1·14)

The % dose was corrected for molecular weight.

inhibition by the two antisecretory agents affecting the less pharmacologically active (*R*)-enantiomer. The lack of effect of cimetidine and omeprazole on the metabolism of (*S*)-warfarin indicates that these compounds are weak inhibitors of P4502C9, an observation which is supported by the present investigation.

There are now six studies which report the possible effects of cimetidine on tolbutamide pharmacokinetics, three of which suggest an interaction. These three studies generally involved higher daily doses of cimetidine, suggesting a dose-dependent effect, but other differences in study designs may have contributed to the variation in results, particularly the relative timings of cimetidine and tolbutamide administration.

This is the first reported study to investigate the possible interaction between omeprazole and tolbutamide. Although a statistically significant interaction was observed, it was less pronounced than that seen with cimetidine. Other drug–drug interactions have been reported for omeprazole but more studies are required to establish the full range of interactions for omeprazole and other proton pump inhibitors.

The present study used a single dose of tolbutamide in healthy subjects. Whilst the findings of the present investigation do not indicate interactions of major clinical significance, the interaction profile with any of the three drugs may be different in diabetic patients receiving chronic tolbutamide therapy, and it is only in this latter setting that the clinical relevance of the interactions observed in the present study can be properly established.

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