

## THE EFFECT OF CIMETIDINE ON TOLBUTAMIDE KINETICS

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Although possible on theoretical grounds, no interaction between cimetidine and tolbutamide could be demonstrated in ten healthy volunteers. The plasma tolbutamide concentrations over 12 h following 0.5 g orally were essentially the same before and after 1 and 7 days cimetidine (400 mg twice daily).

**Keywords** cimetidine tolbutamide interaction pharmacokinetics

### Introduction

Cimetidine inhibits hepatic microsomal enzyme activity decreasing the rate of metabolism of several drugs such as warfarin, diazepam, chlorthalidone and propranolol (Heagerty *et al.*, 1981). The interaction is thought to be a specific inhibitory effect on the cytochrome P 450 system, and although pharmacologically interesting with such drugs as diazepam it is only clinically significant when patients are taking drugs with a narrow therapeutic index. Tolbutamide is such a drug and is an effective oral hypoglycaemic agent. It is initially oxidised by the hepatic microsomal hydroxylation system to hydroxytolbutamide which is then converted in part to carboxytolbutamide (Jackson & Bressler, 1981). A clinically important interaction between cimetidine and tolbutamide could occur and the present study attempted to investigate this possibility.

### Methods

Ten healthy non-smoking, non-pregnant or lactating volunteers took part. Seven were females and the mean age was  $26.1 \pm 3.7$  years (range 22 to 33). Routine physical examination, haematological and biochemical investigations were normal in all volunteers except for one who had an unexplained bilirubin value of  $23 \mu\text{mol/l}$  (normal range 3 to 17). The nature of the study which had ethical committee permission was fully explained to each volunteer who signed a consent form.

The volunteers attended the laboratory at 08.00 h on each of the 3 study days, having fasted overnight. At 08.00 h on the first study day volunteers were given

tolbutamide 0.5 g orally with 50 g of glucose. They then had nothing orally for a further 6 h except water. Venous blood samples were taken for assay of plasma tolbutamide concentration and blood glucose via an indwelling cannula kept patent with heparinised saline at 0, 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10 and 12 h after administration of the drug.

The volunteers then took cimetidine 400 mg on waking and at 22.00 h on the next day and returned at 08.00 h on the following day for study day 2 which was a repeat of day 1.

After a further 7 days treatment with cimetidine 400 mg twice daily the volunteers returned for study day 3 which was as on days 1 and 2. If symptoms of hypoglycaemia developed volunteers took glucose orally. The blood samples taken at time 0 on each day were assayed for blood cimetidine concentration using a high pressure liquid chromatography method with ultraviolet detection specific for cimetidine (Heagerty *et al.*, 1981). These samples were inadvertently thawed and lost in the first three subjects.

Total plasma tolbutamide was measured using a modification of the h.p.l.c. method of Hill & Crechiolo (1978).

### Pharmacokinetic analysis

Examination of semi-logarithmic plots of plasma concentration vs time for the individual subjects indicated that a one-compartment model with a single exponential function described tolbutamide removal from plasma. Areas under the plasma tolbutamide concentration time curves were calculated using a trapezoidal method. The half-life for each volunteer

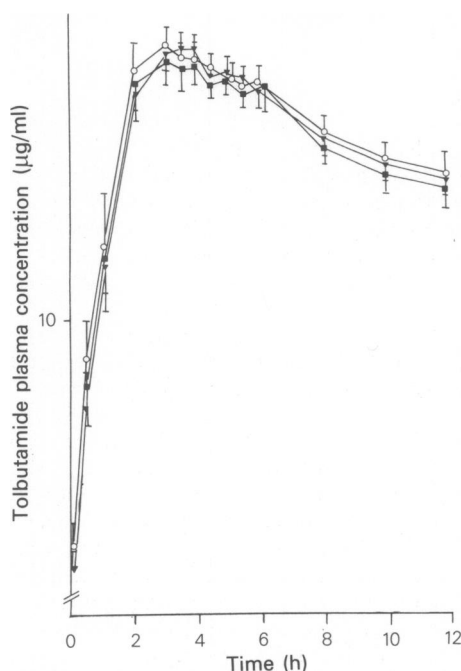
on each study day was calculated by fitting a regression line to the linear section of the plasma concentration time curve after the peak.

### Statistical analysis

The areas under the plasma tolbutamide concentration-time curves, peak concentrations, times to peak and half-lives were compared using a two-way analysis of variance data programme at the 5% significance level.

### Results

All ten volunteers successfully completed the study. Neither acute nor chronic dosage of cimetidine produced any significant change in plasma tolbutamide concentration (Figure 1), or in tolbutamide pharma-



**Figure 1** Log linear plot of mean ( $\pm$  s.e. mean) plasma tolbutamide concentration-time curve. ● study day 1, ○ study day 2, ▼ study day 3.

cokinetics (Table 1). The mean blood glucose concentrations over 12 h did not differ between any of the study days, remaining within normal limits (3.6–6.7 mmol/l).

There was no difference observed in the number of side effects reported on each study day or in the amount of glucose ingested to combat the side effects. Most of the volunteers (70%) felt unwell approximately 2.5 h after ingestion of tolbutamide. Symptoms included sweating, dizziness, nausea and resolved either spontaneously about 4 h later or after oral ingestion of a small amount of glucose.

Blood cimetidine concentrations showed good compliance in all but one subject on one occasion, but exclusion of her data did not alter the results of the analysis.

### Discussion

The data from this study suggest that cimetidine does not affect tolbutamide kinetics, since it had no significant effect on the plasma tolbutamide concentrations or on the incidence of symptoms of hypoglycaemia over the 3 study days. These results are initially surprising since tolbutamide has a relatively slow rate of intrinsic clearance and thus a decrease in enzyme activity with cimetidine should produce a greater area under the curve and a longer half-life (Wilkinson & Shand, 1975). However, smoking does not influence tolbutamide elimination (Jackson & Bressler, 1981) and cimetidine is known to affect different hepatic oxidative microsomal enzyme systems to different degrees in rats (Pelkonen & Puurunen, 1980). An alternative explanation is that cimetidine has only a small effect on tolbutamide kinetics which was not detected in this relatively coarse experimental study. Nevertheless the study has established that cimetidine has no clinically important effects on tolbutamide pharmacokinetics.

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**Table 1** Mean  $\pm$  1s.d pharmacokinetic data for tolbutamide in 10 subjects

Study day	$AUC_{12}$ ( $\mu\text{g ml}^{-1} \text{h}$ )	Peak concentration ( $\mu\text{g/ml}$ )	Time to peak concentration (h)	$t_{1/2,z}$ (h)
1	$377.9 \pm 63.5$	$51.0 \pm 8.4$	$3.0 \pm 0.7$	$7.0 \pm 2.0$
2	$409.2 \pm 97.1$	$56.1 \pm 12.5$	$2.7 \pm 1.0$	$8.0 \pm 2.6$
3	$391.7 \pm 75.6$	$54.6 \pm 12.0$	$2.8 \pm 0.8$	$7.2 \pm 1.8$

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