

# A Study of the Potential Effect of Sertraline on the Pharmacokinetics and Protein Binding of Tolbutamide

Larry M. Tremaine,<sup>1</sup> Keith D. Wilner<sup>1</sup> and Sheldon H. Preskorn<sup>2</sup>

<sup>1</sup> Pfizer Central Research, Groton, Connecticut, USA

<sup>2</sup> Department of Psychiatry, University of Kansas School of Medicine, Wichita and Psychiatric Research Institute, St Francis Regional Medical Center, Wichita, Kansas, USA

## Summary

The effect of the selective serotonin reuptake inhibitor (SSRI) sertraline 200 mg/day on the metabolism of intravenously administered tolbutamide was examined in a randomised nonblinded parallel-group study in 25 healthy male volunteers. There was a small but statistically significant decrease (16%) in the clearance of tolbutamide in patients receiving the maximum recommended dosage of sertraline. The terminal elimination rate constant was also significantly reduced, corresponding to the increase in the terminal elimination half-life (from 6.9 to 8.6 hours). The decrease in clearance was not associated with any significant changes in plasma protein binding or in the apparent volume of distribution of tolbutamide. This suggests that the change in tolbutamide clearance may be due to a slight inhibition of the cytochrome P450 (CYP) isoenzyme CYP2C9/10 when sertraline was administered in its maximum recommended dosage. However, the small changes in the volume of distribution and plasma binding of tolbutamide after sertraline treatment indicate that there is a minimal interaction between sertraline and tolbutamide.

Tolbutamide is a sulphonylurea antihyperglycaemic drug used in the treatment of non-insulin-dependent diabetes mellitus. Metabolised by a single hepatic cytochrome P450 (CYP) isoenzyme designated CYP2C9/10, which mediates the hydroxylation of the parent drug,<sup>[1]</sup> tolbutamide can serve as a model drug to examine the effects of concomitantly prescribed drugs on CYP2C9/10 function. Medications that inhibit the CYP2C9/10 isoenzyme, such as phenylbutazone, nifedipine, verapamil and cimetidine, can therefore potentiate the pharmacological effects of tolbutamide and other drugs also metabolised by this isoenzyme, such as warfarin and phenytoin.<sup>[2]</sup>

Some monoamine oxidase inhibitors such as

phenelzine are known to inhibit CYP2C9/10, and coadministration of these agents with tolbutamide can result in severe adverse effects, including excessive hypoglycaemia.<sup>[3]</sup>

Hypoglycaemia has also been reported after the ingestion of certain selective serotonin reuptake inhibitors (SSRIs) by patients taking insulin or oral antihyperglycaemic agents.<sup>[4]</sup> For example, fluoxetine may affect glycaemic control in patients receiving insulin or oral antihyperglycaemic agents, requiring dosage adjustment of the antihyperglycaemic agent,<sup>[5]</sup> and paroxetine potentially increases adverse effects when co-administered with oral antihyperglycaemic agents.<sup>[5]</sup> Thus, it is clear that other SSRIs have

**Table I.** Dosage schedule for 30-day study. All participants were male, aged 18 to 40 (mean 26) years, and within 10% of ideal bodyweight for age and height

Day	Drug administered	Dose of drug per day (mg)
1	Tolbutamide	1000 (IV)
2-8	No drug	No drug
9-29	Sertraline or placebo	50-200
9-11	Sertraline or placebo	50
12-14	Sertraline or placebo	100
15-17	Sertraline or placebo	150
18-29	Sertraline or placebo	200
30	Sertraline or placebo + tolbutamide	200, 1000 (IV)

demonstrated pharmacodynamic drug interactions with oral antihyperglycaemic agents, although it is unknown whether a pharmacokinetic effect is exerted by these drugs.<sup>[5]</sup>

This study was designed to examine the pharmacokinetic effect of sertraline on CYP2C9/10, using tolbutamide as the model drug in healthy volunteers.

## 1. Materials and Methods

### 1.1 Study Participants

Individuals considered for inclusion in this randomised nonblinded parallel-group study were men aged 18 to 40 years who had no evidence of clinical disease and were within 10% of the ideal bodyweight for age and height. Smokers and individuals with a condition that might affect drug absorption, known drug or alcohol dependence, known drug allergies, or organic disease of any type were ineligible for enrolment. Individuals who had participated in any other investigational study within the 4 weeks prior to this trial were also excluded. Individuals who met these criteria were asked to abstain from taking any drugs for at least 2 weeks before the study. Written informed consent was obtained from all study participants.

### 1.2 Study Design and Medications

Individuals were assigned according to computer-generated random permutations to either the sertraline or placebo treatment group. The assigned medication was given orally once daily in the morning with breakfast for 22 days from day 9 of the study. Sertraline was started at a dosage of

50 mg/day and increased to the maximum recommended dosage, 200 mg/day, in 50mg increments every 3 days. The 200 mg/day dosage was then maintained for the remainder of the study (table I).

Each individual received a single 5-minute intravenous infusion of tolbutamide 1000mg on 2 occasions. The first infusion was given at the start of the study (day 1), before administration of either sertraline or placebo. There was a washout period of at least 1 week after the first infusion before administration of sertraline or placebo (day 9). The second infusion was given at least 3 hours after the last dose of sertraline or placebo on day 30 (table I).

### 1.3 Laboratory Evaluations

To monitor the pharmacokinetics of tolbutamide in the presence and absence of sertraline or placebo, 8ml of blood from each individual was collected in a heparinised tube at the following times: baseline, i.e. before administration of tolbutamide ( $t = 0$ ), and 0.08, 0.16, 0.25, 0.5, 1, 2, 6, 8, 12, 18, 24, and 32 hours after the initiation of each infusion. Plasma tolbutamide concentrations were measured by high-performance liquid chromatography according to the method of Nation et al.<sup>[6]</sup>

For testing purposes, 10ml of blood was obtained for the measurement of tolbutamide protein binding just before each infusion of tolbutamide. The plasma protein binding of tolbutamide was determined by equilibrium dialysis, at a fortified concentration of 50 mg/L, with [<sup>3</sup>H]tolbutamide.<sup>[7]</sup>

To ensure compliance with the sertraline dosage regimen, blood was collected into a heparinised tube and used to measure plasma sertraline concentrations before the start of sertraline or placebo

administration and at the end of the 22 days of drug administration (day 30). All plasma samples were separated from the whole blood in a refrigerated centrifuge and stored at  $-20^{\circ}\text{C}$  until analysis. These samples were then assayed for sertraline by gas chromatography-electron capture.<sup>[8]</sup> This technique had a lower limit of detection of  $1.0\ \mu\text{g/L}$ , with an upper limit of quantification of  $60\ \mu\text{g/L}$ . Samples with drug concentrations above  $60\ \mu\text{g/L}$  were diluted prior to re-assay.

#### 1.4 Pharmacokinetic Parameters and Statistical Analysis

The clearance of tolbutamide and the percentage of unbound tolbutamide in plasma were computed for each tolbutamide infusion. The apparent volume of distribution ( $V_d$ ) of tolbutamide, the terminal elimination rate constant ( $k_{el}$ ), and the terminal elimination half-life ( $t_{1/2\beta}$ ) were also computed for each dose. The  $k_{el}$  was calculated by the least squares regression of the data points over the linear portion of the log plasma concentration versus time curve. The mean  $t_{1/2\beta}$  was calculated from the mean  $k_{el}$  (i.e.  $\ln 2/\text{mean } k_{el}$ ). The difference between the baseline value (day 1) and the final infusion (day 30) was computed, and 2-sample t-tests between the 2 groups (sertraline + tolbutamide vs placebo + tolbutamide) were performed.

The area under the plasma concentration-time curve (AUC) for tolbutamide from time 0 to the last time point ('t') that tolbutamide could be measured in the plasma ( $AUC_t$ ) was estimated by linear trapezoidal approximation. The AUC from time 't' to infinity ( $AUC_{t-\infty}$ ) was estimated as  $C_t/k_{el}$ , where  $C_t$  represents the tolbutamide concentration at time 't'. The total AUC (i.e.  $AUC_{\infty}$ ) was estimated from the sum of these two AUC values. The volume of distribution at steady-state ( $V_{d_{ss}}$ ) was calculated as clearance (CL)  $\times$  MRT, where MRT was the mean residence time [ $(AUMC/AUC) - \tau/2$ ],  $\tau$  is the infusion duration (5 minutes), and AUMC represents the area under the first moment curve from time 0 to infinity. Clearance of tolbutamide was calculated as  $\text{dose}/AUC_{\infty}$ .

## 2. Results

A total of 25 men (mean age 26 years; weight 61 to 88kg) were admitted to the study and randomised to receive either placebo ( $n = 13$ ) or sertraline ( $n = 12$ ).

One individual assigned to receive placebo was withdrawn from the study after the first dose of tolbutamide, because of laboratory abnormalities unrelated to the treatment. One sertraline-treated individual did not reach the anticipated plasma concentration of tolbutamide within the expected time range after the first infusion (0.17 to 0.25 hour; this person's plasma concentration was  $10\ \text{mg/L}$  at 0.25 hour, compared with the group mean  $\pm$  SD of  $135 \pm 14\ \text{mg/L}$ ), although the expected tolbutamide concentration was reached after the second infusion. It was concluded that the initial infusion rate of the drug had been too low, and data related to this individual were therefore excluded from statistical analyses.

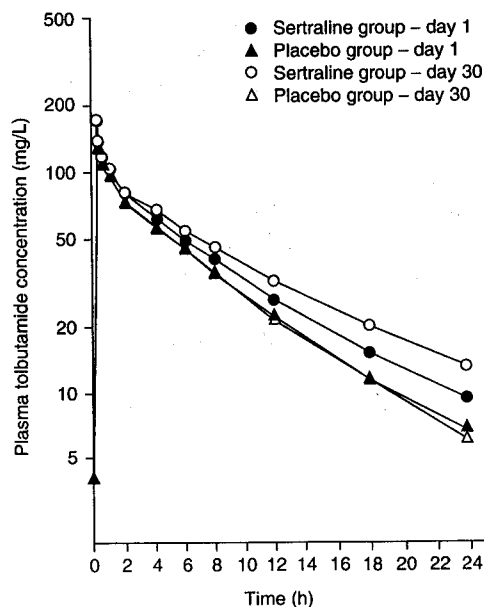


Fig. 1. Mean plasma tolbutamide concentrations after intravenous infusion of tolbutamide 1000mg before and after 22 days of treatment with sertraline or placebo.

**Table II.** Mean values ( $\pm$  SD) for pharmacokinetic parameters and plasma protein binding of tolbutamide at baseline (day 1) and after 22 days of treatment with sertraline or placebo (day 30)

Parameter	Sertraline group (n = 11)		Placebo group (n = 12)		p value <sup>a</sup>
	day 1	day 30	day 1	day 30	
Vd <sub>ss</sub> (L)	10.2 $\pm$ 1.0	10.8 $\pm$ 1.5	10.5 $\pm$ 1.4	10.7 $\pm$ 1.2	0.191
k <sub>el</sub> (h <sup>-1</sup> )	0.100 $\pm$ 0.020	0.081 $\pm$ 0.018	0.113 $\pm$ 0.018	0.112 $\pm$ 0.016	0.020
CL (ml/min)	17.7 $\pm$ 3.8	14.9 $\pm$ 3.3	21.0 $\pm$ 5.4	21.0 $\pm$ 4.0	0.006
Plasma binding (% unbound)	2.4 $\pm$ 0.2	2.5 $\pm$ 0.3	2.4 $\pm$ 0.3	2.5 $\pm$ 0.3	0.348
t <sub>1/2<math>\beta</math></sub> (h) <sup>b</sup>	6.9	8.6	6.2	6.2	

a Two-sample t-test was carried out on the changes from day 1 between the 2 groups.

b Harmonic mean only, therefore no SD.

Abbreviations: CL = total body clearance from the plasma; k<sub>el</sub> = terminal elimination rate constant; t<sub>1/2 $\beta$</sub>  = terminal elimination half-life; Vd<sub>ss</sub> = apparent volume of distribution at steady-state.

Plasma tolbutamide concentrations during the 24-hour period after each infusion are shown in figure 1. Pharmacokinetic and tolbutamide protein binding data are shown in table II.

There was a reduction in tolbutamide clearance from a mean of 17.7 ml/min at baseline to 14.9 ml/min on day 30 in patients receiving sertraline. This decrease of 16% was small but statistically significant. Sertraline administration was also associated with a statistically significant 19% decrease in the k<sub>el</sub> for tolbutamide, which corresponded to a 1.7-hour increase in t<sub>1/2 $\beta$</sub> . Vd<sub>ss</sub> and plasma protein binding did not change significantly, despite administration of sertraline at the maximum recommended dosage. No changes in pharmacokinetic parameters or protein binding were apparent in the placebo group.

Trough plasma sertraline concentrations (24 hours after the last day of treatment) ranged from 40 to 130  $\mu$ g/L in sertraline-treated individuals, which is consistent with the plasma drug concentration range expected at steady-state on sertraline 200 mg/day.<sup>[9]</sup> It was concluded that individuals had complied with the prescribed regimen.

No clinical symptoms of hypoglycaemia were noted in either the sertraline or the placebo groups.

### 3. Discussion

This study was designed to test whether sertraline could affect drugs that are metabolised by the CYP2C9/10 isoenzyme. Tolbutamide was selected

as a model drug. Although most depressed patients are effectively treated with sertraline 50 mg/day,<sup>[10]</sup> this study employed the highest recommended dosage (200 mg/day) in order to assess the effect of the maximal sertraline dosage on tolbutamide pharmacokinetics. Sertraline was administered for a sufficient period to ensure that steady-state plasma concentrations were attained. Sertraline has dose-linear pharmacokinetics over the recommended dosage range of 50 to 200 mg/day; thus, higher doses of sertraline would be expected to produce the greater effects on the CYP2C9/10 isoenzyme and consequently on tolbutamide pharmacokinetics unless the enzyme was completely inhibited. At 200 mg/day, sertraline produced a small but statistically significant decrease in the clearance of tolbutamide (16%). There was also a parallel decrease in the tolbutamide k<sub>el</sub> corresponding to an increase in t<sub>1/2 $\beta$</sub>  from 6.9 to 8.6 hours. The observed changes in tolbutamide pharmacokinetics did not result in the development of any hypoglycaemic episodes in participating volunteers.

Tolbutamide clearance in man is predominantly by biotransformation of hydroxy-tolbutamide<sup>[12]</sup> and mediated by the hepatic CYP2C9/10 isoenzyme.<sup>[1]</sup> Several sulphonamides, including sulfaphenazole and phenylbutazone potently and selectively inhibit CYP2C9/10 *in vitro*.<sup>[2,13]</sup> Other studies have examined the pharmacokinetics of tolbutamide in humans with the co-administration of sulfaphenazole, phenylbutazone, oxyphenbutazone

and sulfinpyrazone,<sup>[14-17]</sup> with similar baseline CL and half-life values for tolbutamide as observed in this study. When administered at therapeutic doses, these drugs caused up to an 80% decrease in tolbutamide clearance and increases in half-life from 180% to 430%. Therefore, potent inhibitors of CYP2C9/10 can cause marked effects on tolbutamide clearance and half-life.

The use of tolbutamide as a model substrate for the CYP2C9/10 isoenzyme in this study may permit these results to be extrapolated to other drugs also metabolised by this enzyme. In fact, sertraline 200 mg/day has also been shown to have no effect on phenytoin, another CYP2C9/10 substrate.<sup>[18]</sup> Thus, sertraline, on the basis of its minimal effect on tolbutamide and phenytoin, may be unlikely to cause a significant pharmacokinetic drug interaction with an agent metabolised by CYP2C9/10.

Sertraline at its maximum recommended dosage also did not alter the protein binding or the  $V_{d,ss}$  of tolbutamide. Even though sertraline, in common with other SSRIs, is highly protein bound, displacement of bound drugs is rarely the sole causative factor in clinically significant pharmacokinetic interactions. Sertraline has no significant effect on the protein binding of diazepam<sup>[4]</sup> and warfarin<sup>[11,19]</sup> (both highly protein-bound drugs), although there are minor variations in the protein binding of these agents in the presence of sertraline.

There are several reasons to be cautious when using fluoxetine or paroxetine with tolbutamide. Although fluoxetine is the only other SSRI studied with regard to its effect on tolbutamide and did not produce any change in tolbutamide pharmacokinetics, the fluoxetine study did not accurately reproduce actual steady-state clinical conditions.<sup>[20]</sup> Both fluoxetine and paroxetine have been associated with hypoglycaemia in patients receiving oral antihyperglycaemic agents in addition to insulin.<sup>[4]</sup> In this study, no significant episodes of hypoglycaemia were observed, despite the steady-state sertraline plasma concentrations being attained.

When tolbutamide is contraindicated, patients with non-insulin-dependent diabetes may be treated with other oral antihyperglycaemic agents, e.g.

glibenclamide (glyburide). In a study undertaken in healthy volunteers, sertraline 200 mg/day was not associated with any significant changes in glibenclamide pharmacokinetics or glucose levels.<sup>[21]</sup>

More studies are needed to confirm the frequency and nature of adverse drug interactions associated with the use of SSRIs. The interactions may be pharmacodynamic (such as episodes of hypoglycaemia) or pharmacokinetic (such as isoenzyme CYP2C9/10 interactions associated with increased plasma drug concentrations). Studies investigating the effects of paroxetine, fluvoxamine or citalopram on the pharmacokinetics or pharmacodynamics of tolbutamide are also lacking.

#### 4. Conclusions

Sertraline, at a dosage 4 times higher than the usually effective dose for the treatment of depression, decreased the CL, and increased the  $t_{1/2\beta}$ , of tolbutamide; however, the  $V_d$  and protein binding were unaffected. These results indicate that sertraline has a small effect on the hepatic isoenzyme CYP2C9/10 and thus would not be expected to produce significant pharmacokinetic interactions with other drugs dependent on this enzyme for their clearance. However, clinicians should carefully monitor therapy when sertraline is added to a regimen involving drugs metabolised by CYP2C9/10, to ensure that there are no effects associated with increased drug concentrations.

#### References

1. Veronese ME, Mackenzie PI, Doecke CJ, et al. Tolbutamide and phenytoin hydroxylations by cDNA-expressed human liver cytochrome P4502C9. *Biochem Biophys Res Commun* 1991; 175 (3): 1112-8
2. Miners JO, Smith KJ, Robson RA, et al. Tolbutamide hydroxylation by human liver microsomes. Kinetic characterization and relationship to other cytochrome P-450-dependent xenobiotic oxidations. *Biochem Pharmacol* 1988; 37: 1137-44
3. Davis JM, Glassman AH. Antidepressant drugs. In: Kaplan HI, Sadock BJ, editors. *Comprehensive textbook of psychiatry*. 5th ed. Baltimore: Williams & Wilkins, 1989: 1627-55
4. Feighner JP, Boyer WF. *Selective serotonin re-uptake inhibitors*. New York: John Wiley, 1991: 81-7
5. Goodnick PJ, Henry JH, Buki VM. Treatment of depression in patients with diabetes mellitus. *J Clin Psychiatry* 1995; 56: 128-36

6. Nation RL, Peng GW, Chiou WL, et al. Simple, rapid and micro high-pressure liquid chromatographic method for the simultaneous determination of tolbutamide and carboxytolbutamide in plasma. *J Chromatogr* 1978; 146: 121-31
7. Tremaine LM, Welch WM, Ronfeld RA. Metabolism and disposition of the 5-hydroxytryptamine uptake blocker sertraline in the rat and dog. *Drug Metab Dispos* 1989; 17: 542-50
8. Tremaine LM, Joerg EA. Automated gas chromatographic-electron-capture assay for the selective serotonin uptake blocker sertraline. *J Chromatogr* 1989; 496: 423-9
9. Ronfeld RA, Tremaine LM, Wilner KD. Pharmacokinetics of sertraline and its *N*-demethyl metabolite in elderly and young male and female volunteers. *Clin Pharmacokinet* 1997; 32 Suppl. 1: 22-30
10. Preskorn SH, Lane RM. Sertraline 50mg daily: the optimal dose in the treatment of depression. *Int Clin Psychopharmacol* 1995; 10: 129-41
11. Apseloff G, Wilner KD, Gerber N, et al. Effect of sertraline on protein binding of warfarin. *Clin Pharmacokinet* 1997; 32 Suppl. 1: 37-42
12. Back DJ, Orme ML. Genetic factors influencing the metabolism of tolbutamide. *Pharmacol Ther* 1989; 44: 147-55
13. Newton DJ, Wang RW, Lu AYH. Cytochrome P450 inhibitors. Evaluation of specificities in the *in vitro* metabolism of therapeutic agents by human liver microsomes. *Drug Metab Dispos* 1995; 23: 154-8
14. Pond SM, Birkett DJ, Wade DN. Mechanisms of inhibition of tolbutamide metabolism: phenylbutazone, oxyphenbutazone and sulphaphenazole. *Clin Pharmacol Ther* 1977; 22: 573-9
15. Miners JO, Foenander T, Wanwimolruk S, et al. The effect of sulphinyprazole on oxidative drug metabolism in man: inhibition of tolbutamide elimination. *Eur J Clin Pharmacol* 1982; 22: 321-6
16. Back DJ, Tija J, Monig H, et al. Selective inhibition of drug oxidation after simultaneous administration of two probe drugs, antipyrine and tolbutamide. *Eur J Clin Pharmacol* 1988; 34: 157-63
17. Veronese ME, Miners JO, Randles D, et al. Validation of the tolbutamide metabolic ratio for population screening with use of sulfaphenazole to produce model phenotypic poor metabolizers. *Clin Pharmacol Ther* 1990; 47: 403-11
18. Rapeport WG, Muirhead DC, Williams SA, et al. Absence of effect of sertraline on the pharmacokinetics and pharmacodynamics of phenytoin. *J Clin Psychiatry* 1996; 57 Suppl. 1: 24-8
19. Warrington SJ. Clinical implications of the pharmacology of sertraline. *Int Clin Psychopharmacol* 1991; 6 Suppl. 2: 11-21
20. Lemberger L, Bergstrom RF, Wolen RL, et al. Fluoxetine: clinical pharmacology and physiologic disposition. *J Clin Psychiatry* 1985; 46 (3 Pt 2): 14-9
21. Juan D, Molitch ME, Johnson MK, et al. Unaltered drug metabolizing enzyme systems in type II diabetes mellitus before and during glyburide therapy. *J Clin Pharmacol* 1990; 30: 943-7

Correspondence and reprints: Dr Larry M. Tremaine, Central Research, Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340, USA.

## Effect of Binding

Glen Apseloff,<sup>1</sup>

1 Department of  
2 Pfizer Central R

## Summary

The selective (SSRI) antidepressant sertraline is highly bound to plasma protein binding sites. Sertraline, like fluoxetine,<sup>[1]</sup> 95% bound to plasma protein binding sites. Sertraline,<sup>[3]</sup> High plasma protein binding, such as the SSRI, can displace other drugs from their plasma binding sites, increasing the free portions of free d