Br. J. clin. Pharmac. (1987), **23**, 317–321

The effect of cimetidine on the single dose pharmacokinetics of oral clobazam and *N*-desmethylclobazam

T. PULLAR, D. EDWARDS, J. R. M. HAIGH, S. PEAKER & M. P. FEELY
Clinical Pharmacology Unit, University of Leeds, General Infirmary, Leeds LS1 3EX

1 The effect of cimetidine on the single dose pharmacokinetics of orally administered clobazam and *N*-desmethylclobazam (NDMC) was studied in volunteers.
2 Cimetidine inhibited the elimination of both clobazam and NDMC and inhibited the rate of formation of NDMC from clobazam.
3 The increase in the AUC for NDMC generated from clobazam was relatively greater than that for clobazam itself. This suggests that NDMC elimination is inhibited to a relatively greater extent than clobazam elimination.
4 The increase in AUC for NDMC generated from clobazam was also relatively greater than that for NDMC administered orally. This would suggest that cimetidine either increases the bioavailability of clobazam or reduces that of NDMC.
5 The increase in the AUC for NDMC and for clobazam in some individuals was of a magnitude which is likely to be clinically significant.

Keywords cimetidine clobazam *N*-desmethylclobazam pharmacokinetics

Introduction

Cimetidine is well known as a competitive inhibitor of the hepatic P-450 mixed function oxidase system (Greene, 1984). It has been shown to inhibit metabolism of the 1,4-benzodiazepines diazepam, desmethyldiazepam, chlordiazepoxide and midazolam (Klotz & Reimann, 1980a,b; Desmond *et al.*, 1980; Klotz *et al.*, 1985). However, it does not interfere with the metabolism of oxazepam or lorazepam which are biotransformed via the glucuronidation pathway (Patwardhan *et al.*, 1980). In the case of midazolam the interaction with cimetidine has been shown to be of clinical significance (Salomen *et al.*, 1986). In addition, absorption of the benzodiazepines diazepam and lorazepam is also facilitated by co-administration of cimetidine (McGowan & Dundee, 1982) probably as a result of its pharmacological role in reducing gastric acidity.

Clobazam, a 1,5-benzodiazepine, is commonly used as adjunctive therapy in the treatment of refractory epilepsy. Metabolism of clobazam is similar to that of diazepam; both undergo *N*-demethylation and ring hydroxylation with subsequent glucuronidation (Volz *et al.*, 1979). *N*-desmethylclobazam (NDMC) is an active metabolite (Jawad *et al.*, 1984) and its potential as an oral anticonvulsant drug is currently being evaluated (Haigh *et al.*, 1987).

Methods

Local ethics committee approval was obtained for the study and all volunteers gave their informed consent. Ten non-smoking healthy volunteers (9M, 1F; age 20–40 years) were studied. As cimetidine may affect both benzo-

Correspondence: Dr T. Pullar, University Department of Medicine, Martin Wing, The General Infirmary, Leeds LS1 3EX

diazepine absorption and elimination oral dosing was used in order to give an overall view of the result of any interactions. Following an overnight fast six volunteers were given clobazam 30 mg orally and six were given NDMC 30 mg orally (two volunteers were given both drugs separated by a 5 week wash-out period) at 09.00 h. One volunteer (who had already been studied using clobazam) given NDMC had to withdraw because of cimetidine-induced diarrhoea. Venous blood samples were taken pre-dose, then 0.5, 1, 1.5, 2, 3.5, 4.5, 8, 12, 18, 24, 32 and 48 h post-dose and thereafter at 09.00 h each day for a total of 14 days. On day 15, the volunteers were commenced on oral cimetidine 400 mg twice daily which they continued until day 36. On day 22 the benzodiazepine was again administered and the sampling procedure repeated.

Venous blood samples were collected in lithium heparin tubes, centrifuged at 900 *g* for 20 min and the plasma decanted and stored at −20° C until required for analysis. Concentrations of clobazam and NDMC were assayed by reversed phase high performance liquid chromatography using modifications of the method described by Ratnaraj *et al.* (1984).

For clobazam (10–100 ng ml^{-1}) the column used was 5 μm Nova Pak C18 (Waters Assoc., Milford, USA); the calibration curve was linear over this clobazam concentration range (r = 0.999) and the inter-assay reproducibility was 4.8% (CV) at 10 ng ml^{-1}, the lower limit of accurate detection. For NDMC, the column was 10 μm Resolve C18 Radial Pak (Waters Assoc. Milford, USA) and the mobile phase contained 0.05% ammonia. Calibration was linear over the NDMC concentration range 25–3000 ng ml^{-1} (r = 0.999) and the inter-assay reproducibility was 2.7% (CV) at 100 ng ml^{-1}. In both modifications, ether was used as the extraction solvent and diazepam was used as the internal standard.

The following pharmacokinetic parameters were calculated from the plasma concentration-time curves for each compound and expressed as mean ± s.e. mean: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), plasma elimination half-life ($t_{½}$: from the terminal portion of the $\log_{10}$ plasma concentration time curves), area under the curve from time 0 to infinity (AUC: calculated by the trapezoid rule) and the rate of formation of NDMC from clobazam (k_m) was calculated from the $\log_{10}$ plasma concentration-time plot by feathering the curve. As no intravenous preparations of either drug are available we were unable to calculate values for either the bioavailability or the clearance of clobazam or NDMC. Values before and during cimetidine administration were compared using a paired t-test.

Results

Following clobazam administration

Pharmacokinetic parameters for clobazam and NDMC derived from clobazam both before and during cimetidine administration are shown in Tables 1 and 2. During cimetidine administration all volunteers displayed an increase in the AUC for clobazam ranging from 30% to 143% (mean 65%; P = 0.0024). The $t_{½}$ for clobazam also increased in five out of six volunteers (mean 38% range −2% to +79%) and this just failed to reach statistical significance (P = 0.051). AUC for NDMC derived from clobazam also increased in all volunteers with a mean increase of 83.5% ranging from 19% to 145% (P = 0.0002). C_{max} and $t_{½}$ for NDMC also showed an increase in all volunteers (mean 27%; range 11% to 48%; P = 0.0257 and mean 100%; range 66% to 185%; P = 0.0036 respectively). The rate of formation of NDMC from clobazam during cimetidine administration was reduced in all volunteers (P = 0.018). Figure 1 shows the plasma concentration time curves before and during cimetidine administration for subject 1.

Following NDMC administration

Pharmacokinetic values following a 30 mg oral dose of NDMC before and during cimetidine administration are shown in Table 3. Cimetidine prolonged the $t_{½}$ (mean 26%; range 19% to 39%) in all volunteers (P = 0.0002). The AUC was increased in four out of five volunteers giving a mean increase of 40% ranging from −1% to +90%; this increase failed to reach statistical significance (P = 0.0692). The plasma concentration-time curve for subject 1 is shown in Figure 1.

Discussion

In this study the mean $t_{½}$ for clobazam was 31 (± 5) h. This is similar to the $t_{½}$ found by Tedeschi *et al.* (1981) but is somewhat shorter than that found by Greenblatt *et al.* (1981) and by Rupp *et al.* (1979). The $t_{½}$ was calculated similarly in all these studies and it is likely that the differences are merely a result of the small numbers of patients in each study. It is of interest that Greenblatt *et al.* (1981) found a much longer $t_{½}$ in their female subjects as the one female in our group (subject No. 3) had a short $t_{½}$. The

Table 1 Pharmacokinetic parameters for clobazam in six healthy volunteers following a single oral dose of 30 mg clobazam given before and during cimetidine administration.

Subject	t_{max} (h)		C_{max} (ng ml^{-1})		$t_{1/2}$ (h)		$AUC\ o-\infty$ (μg ml^{-1} h)	
	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine
1	0.5	0.5	724	875	23	32	12.1	18.3
2	1.5	1.5	373	419	41	70	12.8	23.2
3	2.0	2.0	519	690	24	43	9.2	22.3
4	1.5	0.5	743	785	13	15	9.9	13.4
5	3.5	1.0	642	918	44	55	20.8	31.2
6	1.0	0.5	730	650	44	43	21.0	27.2
Mean	1.7	1.0	622	723	31	43	14.2	22.6
(± s.e. mean)	(± 0.42)	(± 0.25)	(± 60)	(± 74)	(± 5)	(± 7)	(± 2.15)	(± 2.57)
Paired *t*-test	$P = 0.16$		$P = 0.1$		$P = 0.051$		$P = 0.0024$	

Table 2 Pharmacokinetic parameters for NDMC in six healthy volunteers following a single oral dose of 30 mg clobazam given before and during cimetidine administration.

Subject	t_{max} (h)		C_{max} (ng ml^{-1})		$t_{1/2}$ (h)		$AUC\ o-\infty$ (μg ml^{-1} h)		k_m	
	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine	Control	Cimetidine
1	32.0	48.0	133	151	55	100	18.0	34.6	0.045	0.029
2	72.0	96.0	79	88	86	187	16.5	37.0	0.035	0.023
3	24.0	48.0	111	152	61	108	15.3	37.6	0.064	0.022
4	32.0	48.0	152	186	20	57	14.8	26.2	0.078	0.051
5	72.0	72.0	173	221	70	116	35.2	50.4	0.033	0.024
6	48.0	123.0	212	314	131	231	74.6	89.1	0.028	0.019
Mean	47.0	72.5	143	185	70	133	29.1	45.8	0.047	0.028
(± s.e. mean)	(± 8.5)	(± 13.0)	(± 19)	(± 31)	(± 15)	(± 26)	(± 9.63)	(± 9.22)	(± 0.0035)	(± 0.0044)
Paired *t*-test	$P = 0.057$		$P = 0.0257$		$P = 0.0036$		$P = 0.0002$		$P = 0.018$	

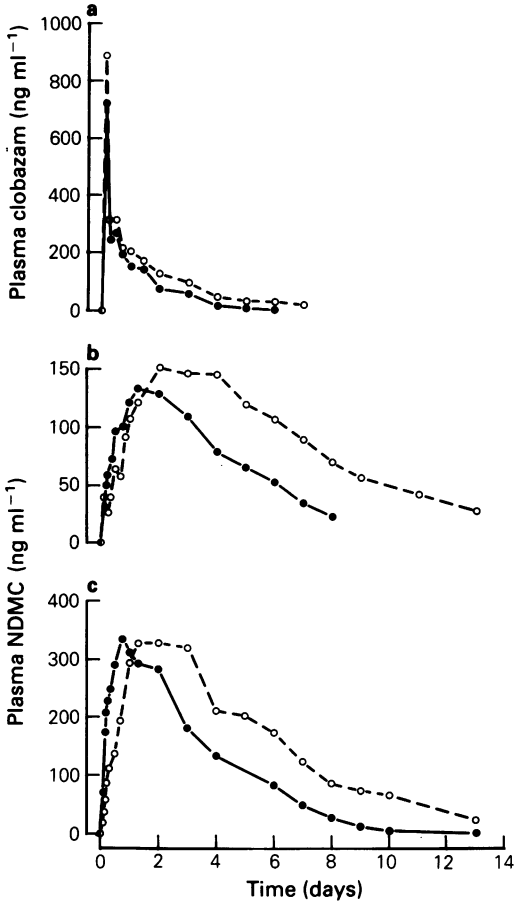

Figure 1 Plasma concentration time curves in volunteer No. 1 before (●) and during (○) cimetidine administration, (a) clobazam, (b) NDMC derived from clobazam and (c) NDMC following an oral dose of NDMC.

AUC for clobazam in our study was similar to that found by Jawad *et al.* (1984) and, assuming a linear relationship with dose, that found by Tedeschi *et al.* (1981). Our data on NDMC is also consistent with previous work which states that it has a $t_{½}$ roughly twice that of clobazam (Rupp *et al.*, 1979).

Concurrent administration of cimetidine produced a reduction in the rate of elimination of NDMC and also of clobazam. This reduction in the rate of elimination of both the parent drug and its *N*-desmethyl metabolite is similar to the situation seen with diazepam (Klotz & Reimann, 1980a,b). Some of the inhibition of clobazam elimination is due to a reduction in the rate of formation of NDMC. However, despite this the AUC for NDMC generated from clobazam is

Table 3 Pharmacokinetic parameters for NDMC in five healthy volunteers following a single oral dose of 30 mg NDMC given before and during cimetidine administration.

	t_{max} (h)		C_{max} (ng ml^{-1})		$t_{½}$ (h)		$AUC\,o-\infty$ (μg ml^{-1} h)	
Subject	*Control*	*Cimetidine*	*Control*	*Cimetidine*	*Control*	*Cimetidine*	*Control*	*Cimetidine*
1	18.0	32.0	334	330	52	65	32.0	52.1
7	12.0	32.0	311	291	41	51	29.6	31.6
8	4.5	24.0	242	300	33	46	17.3	32.9
9	32.0	32.0	225	207	47	56	26.1	26.0
10	24.0	24.0	231	268	50	64	24.0	34.3
Mean	18.1	28.8	269	279	45	56	25.8	35.4
(± s.e. mean)	(± 4.7)	(± 2.0)	(± 22)	(± 21)	(± 3)	(± 4)	(± 2.5)	(± 4.4)
Paired *t*-test	$P = 0.0759$		$P = 0.54$		$P = 0.0002$		$P = 0.0692$	

greater during cimetidine administration. This could in part be explained by a relatively greater inhibition of NDMC elimination as compared to clobazam elimination. The increase in the AUC for NDMC derived from clobazam is, however, proportionately greater than that for NDMC administered directly. This suggests that either the bioavailability of clobazam is increased or that of oral NDMC decreased by concomitant cimetidine administration; the increase in AUC in relation to $t_{\frac{1}{2}}$ would suggest that the former explanation is more likely.

The inhibition of demethylation by cimetidine is similar to the situation with chlordiazepoxide (Desmond *et al.*, 1980), but in a study of diazepam the authors stated that no significant differences in the time course and plasma concentrations of desmethyldiazepam generated from diazepam could be demonstrated (Klotz & Reimann, 1980a).

Ideally the relevance of the effect of cimetidine on the single dose pharmacokinetics of clobazam and NDMC in normal volunteers should be further investigated in patients receiving clobazam or NDMC chronically. Unfortunately such a study is impractical in epileptics (the only patient group to be given NDMC to date) as the 1,5-benzodiazepines are used as adjunctive therapy and the co-administration of cimetidine would interfere with other anticonvulsants such as phenytoin and carbamazepine. Although it is difficult to comment upon steady state levels from single dose studies, in a previous study (Haigh *et al.*, 1987) two of five patients whose dose of NDMC was increased from 30 mg daily to 30 mg/60 mg on alternate days experienced sedation. This dose increase is of a similar magnitude to the increase in AUC produced by cimetidine. Thus it seems that the observed changes are likely to be of clinical significance. Studies relating single dose kinetics to steady state levels in volunteers are currently being performed.

We should like to thank Hoechst for supplies of NDMC, Dr R. Calvert for his advice on the interpretation of the data, Mrs M. E. Smith for typing the manuscript and the volunteers for agreeing to participate.

References

Desmond, P. V., Patwardhan, R., Schenker, S. & Speeg, K. V. (1980). Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. *Ann. int. Med.*, **93**, 266–268.

Greenblatt, D. J., Divoll, M., Puri, S. K., Ho, I., Zinny, M. A. & Shader, R. I. (1981). Clobazam kinetics in the elderly. *Br. J. clin. Pharmac.*, **12**, 631–636.

Greene, W. (1984). Drug interactions involving cimetidine—mechanisms, documentation, implications. *Rev. Drug Metab. Drug Interact.*, **5**, 25–51.

Haigh, J. R. M., Pullar, T., Gent, J. P., Dailley, C. & Feely, M. (1987). *N*-desmethylclobazam: a possible alternative to clobazam in the treatment of refractory epilepsy? *Br. J. clin. Pharmac.*, **23**, 213–218.

Jawad, S., Richens, A. & Oxley, J. (1984). Single dose pharmacokinetics study of clobazam in normal volunteers and epileptic patients. *Br. J. clin. Pharmac.*, **18**, 873–877.

Klotz, U. & Reimann, I. (1980a). Delayed clearance of diazepam due to cimetidine. *New Engl. J. Med.*, **302**, 1012–1014.

Klotz, U. & Reimann, I. (1980b). Influence of cimetidine on the pharmacokinetics of desmethyldiazepam and oxazepam. *Br. J. clin. Pharmac.*, **18**, 517–520.

Klotz, U., Arvela, P. & Rosenkranz, B. (1985). Effect of single doses of cimetidine and ranitidine on the steady-state plasma levels of midazolam. *Clin. Pharmac. Ther.*, **38**, 652–655.

McGowan, W. A. W. & Dundee, J. W. (1982). The effect of intravenous cimetidine on the absorption of orally administered diazepam and lorazepam. *Br. J. clin. Pharmac.*, **14**, 207–211.

Patwardhan, R. U., Yarborough, G. W., Desmond, P. V., Johnson, R. F., Schenker, S. & Speeg, K. V. (1980). Cimetidine spares the glucuronidation of lorazepam and oxazepam. *Gastroenterology*, **79**, 912–916.

Ratnaraj, N., Goldberg, V. & Lascelles, P. T. (1984). Determination of clobazam and desmethylclobazam in serum using high-performance liquid chromatography. *Analyst*, **109**, 813–815.

Rupp, W., Badian, M., Christ, O., Hajdu, P., Kulkarni, R. D., Taeuber, K., Uihlen, M., Bender, R. & Vanderbeke, O. (1979). Pharmacokinetics of single and multiple doses of clobazam in humans. *Br. J. clin. Pharmac.*, **7**, 51S–57S.

Salomen, M., Aantaa, E., Aaltomen, L. & Kanto, J. (1986), Importance of the interaction of midazolam and cimetidine. *Acta Pharmac. Tox.*, **58**, 91–95.

Tedeschi, G., Riva, R. & Baruzzi, A. (1981). Clobazam plasma concentrations: pharmacokinetic studies in healthy volunteers and data in epileptic patients. *Br. J. clin. Pharmac.*, **11**, 619–622.

Volz, M., Christ, O., Kellner, H. M., Kuch, H., Fehlhaker, H. W., Gantz, D., Hajdu, P. & Cavagna, F. (1979). Kinetics and metabolism of clobazam in animals and man. *Br. J. clin. Pharmac.*, **7**, 41S–50S.

(Received 11 August 1986, accepted 5 November 1986)