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Pharmacokinetics of *N*-desmethylclobazam in healthy volunteers and patients with epilepsy

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1 The single dose pharmacokinetics of *N*-desmethylclobazam (NDMC) and clobazam were studied in eight healthy male volunteers.

2 Steady-state pharmacokinetic data are described from four healthy male volunteers and eight epileptic patients taking NDMC.

3 A single 30 mg dose of NDMC produced a greater C_{max} ($P < 0.001$) and AUC 0–∞ ($P < 0.005$) and a shorter t_{max} ($P < 0.05$) and $t_{½}$ ($P < 0.01$) for NDMC than did 30 mg clobazam.

4 Mean steady-state NDMC concentrations were greater in male patients than in female patients and also in male patients compared with male volunteers. The differences between patients and volunteers might be explained by concomitant antiepileptic medication.

Keywords *N*-desmethylclobazam clobazam pharmacokinetics antiepileptic drug interactions

Introduction

Oral *N*-desmethylclobazam (NDMC), the active metabolite of clobazam, may have a role in the management of patients with refractory epilepsy (Haigh *et al.*, 1987). Animal studies have suggested that administration of NDMC may be associated with less anticonvulsant tolerance than administration of clobazam, despite comparable plasma concentrations of NDMC in both instances (Haigh *et al.*, 1987). In a similar study of chemically-induced seizures in dogs, the major active metabolite of diazepam (*N*-desmethyldiazepam) has been shown to produce less anticonvulsant tolerance than its parent compound (Frey *et al.*, 1984). *N*-desmethyldiazepam has also been shown to produce less psychomotor impairment than diazepam (Aranko *et al.*, 1984). Thus there are reasons to suggest that NDMC might offer some advantages over clobazam in the management of epilepsy. Furthermore, some knowledge of the pharmacokinetics of NDMC might increase our understanding of the disposition of clobazam.

In this paper we describe the single dose pharmacokinetics of NDMC in eight healthy male volunteers and compare, in the same individuals, the pharmacokinetic parameters of NDMC derived from clobazam. We also report and compare the steady-state pharmacokinetics of NDMC in four of these volunteers and in eight patients with epilepsy.

Methods

Local ethics committee approval was obtained for all studies. Supplies of NDMC and clobazam were obtained from Hoechst.

Study 1

Following an overnight fast eight healthy male

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volunteers (age 23–40 years) were given, in random order and separated by at least 3 weeks, clobazam 30 mg or NDMC 30 mg orally. The capsules were given with 150 ml of water and volunteers were allowed nothing else by mouth for 2 h. Venous blood samples were taken pre-dose, then 0.5, 1.0, 1.5, 2.0, 3.5, 4.5, 8.0, 12.0, 18.0, 24.0, 32.0 and 48.0 h post-dose and daily thereafter until day 14. Blood (10 ml) was collected in lithium heparin tubes, centrifuged at 900 *g* for 20 min and the plasma stored at −20° C until analysis was performed. Concentrations of clobazam and NDMC were assayed using modifications of the method described by Ratnaraj *et al.* (1984). These modifications have been described previously (Pullar *et al.*, 1987). The following pharmacokinetic parameters were calculated for the volunteers from the plasma concentration-time curves for each compound: time to maximum plasma concentration (t_{max}), maximum plasma concentration (C_{max}), plasma elimination half-life ($t_{½}$; from the terminal portion of the $\log_{10}$ plasma concentration-time curves) and the area under the curve from 0 to infinity (AUC 0–∞; calculated by the trapezoid rule).

Study 2

Four of the healthy male volunteers described in study 1 (age 24–40 years) were given oral NDMC 30 mg daily for 14 days. On day 14 venous blood was taken immediately before the final dose, then 1, 2, 4, 6, 12 and 24 h post-dose and daily thereafter for a total of 14 days. Eight epileptic patients (5F, 3M; age 19–55 years) who had been taking NDMC 30 mg daily for at least 3 weeks had venous blood samples taken pre-dose and 1, 2, 4, 6, 8, 12 and 24 h post-dose. Twenty-four hour urine collections were also made from these patients. In addition to NDMC, two patients were taking carbamazepine (CBZ) alone, two CBZ plus phenytoin (PHT), two CBZ plus primidone (PRM), one PHT plus PRM, and one PHT plus CBZ plus phenobarbitone (PB). The clinical results of treatment in these patients have already been described (Haigh *et al.*, 1987).

Plasma NDMC concentrations were assayed as in study 1. Urine NDMC concentrations were assayed by the same method. Peak (C_{ss}, max), trough (C_{ss}, min) and mean ($\bar{C}_{ss}$) steady-state concentrations and the area under the 24 h plasma concentration-time curve (AUC 0–24 h) were calculated from the plasma concentration-time curve. For the volunteers the elimination half-life ($t_{½}$) was also calculated from the terminal portion of the plasma concentration-time curve. The relevant parameters were recalculated after plasma concentrations of NDMC had been adjusted for body weight by dividing the plasma concentration by the dose expressed as mg kg^{-1} body weight. The resultant value calculated from $\bar{C}_{ss}$ represents the reciprocal of the plasma clearance, assuming a fractional bioavailability of unity.

Results from both studies are expressed as mean ± s.e. mean and the statistical analysis was carried out using Student's *t*-test (paired or unpaired as appropriate).

Results

Study 1

Figure 1 shows the plasma concentration-time curves for clobazam, NDMC derived from clobazam, and NDMC in the eight healthy male

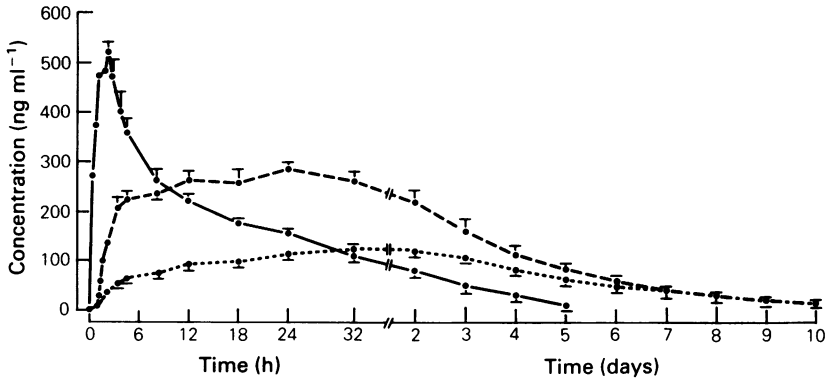

Figure 1 Plasma concentrations of clobazam (●——●), and NDMC (●·····●) following clobazam 30 mg, and NDMC (●--●) following NDMC 30 mg administration in normal volunteers (mean ± s.e. mean).

volunteers receiving single doses of each compound. Pharmacokinetic parameters for clobazam and NDMC in these volunteers are shown in Table 1. C_{max} and AUC 0–∞ for NDMC were significantly greater and t_{max} and $t_{½}$ significantly less following NDMC administration than following administration of clobazam.

Seven volunteers complained of drowsiness and mental impairment and all eight appeared impaired 1–3 h after clobazam administration, whereas no symptoms or signs of impairment were apparent following NDMC.

Study 2

Figure 2 shows the steady-state 24 h plasma concentration-time curves in the four healthy male volunteers and in all eight patients (the three male and the five female). The pharmacokinetic parameters at steady-state are shown in Table 2. No patient excreted more than 8% of the ingested NDMC dose unchanged in their urine. $\bar{C}_{ss}$; C_{ss}, max; C_{ss}, min and AUC 0–24 h were all significantly greater in the patients than in the volunteers. When adjustments were made for body weight the differences between all patients and volunteers just failed to reach statistical significance ($0.05 < P < 0.1$ for all parameters). However, when a comparison was made between only male patients and the (male) volunteers the male patients all had greater steady-state concentrations ($\bar{C}_{ss}$ median 2470, range 2330–2850 ng ml^{-1}) than did the volunteers ($\bar{C}_{ss}$, median 1215, range 1100–1650 ng ml^{-1}). All female patients had lower $\bar{C}_{ss}$ (median 1900, range 1210–2300 ng ml^{-1}) than the male patients. Although, because of small numbers, formal statistical analysis is not possible the probability of such permutations occurring by chance are 1 in 35 and 1 in 56 respectively.

Table 1 Pharmacokinetic parameters (mean ± s.e. mean) in eight healthy male volunteers given clobazam 30 mg and NDMC 30 mg on separate occasions

	C_{max} (ng ml^{-1})	t_{max} (h)	$t_{½}$ (h)	AUC (0–∞) (μg ml^{-1} h)
(a) Clobazam	584 ± 49	1.5 ± 0.3	30 ± 6.3	13.0 ± 1.7
(b) NDMC derived from clobazam	126 ± 10	41.0 ± 6.4	64 ± 4.3	17.5 ± 2.3
(c) NDMC	289 ± 19	20.0 ± 2.8	46 ± 5.5	27.6 ± 4.1
Paired *t*-test (b *vs* c)	$P < 0.001$	$P < 0.05$	$P < 0.01$	$P < 0.005$

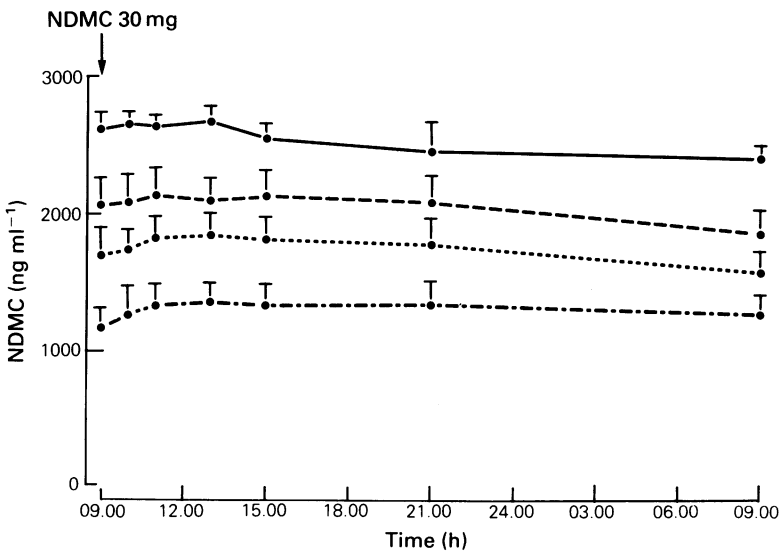

Figure 2 Twenty-four hour plasma concentration profiles for NDMC in normal volunteers (●——●), all epileptic patients (●--●), male epileptic patients (●——●) and female epileptic patients (●---●) taking 30 mg NDMC daily (mean ± s.e. mean).

Table 2 Steady-state pharmacokinetic parameters (mean ± s.e. mean) for healthy volunteers and patients taking NDMC 30 mg daily

	$\bar{C}_{ss}$ (ng ml^{-1})	C_{ss}, max (ng ml^{-1})	C_{ss}, min (ng ml^{-1})	AUC (0–24 h) (μg ml^{-1} h)	$t_{1/2}$ (h)
Volunteers $n = 4$	1270 ± 125	1412 ± 138	1080 ± 129	30.6 ± 3.2	42.25 ± 3.2
Patients $n = 8$	2040 ± 171	2269 ± 195	1847 ± 176	48.8 ± 4.4	
t-test	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P = 0.01$	

Additional drug therapy in the three male patients consisted of CBZ + PHT, CBZ + PHT + PB and CBZ + PRM. In three of the four volunteers the $t_{1/2}$ following chronic dosing was very similar to the $t_{1/2}$ following a single dose of NDMC (46 and 48 h, 50 and 49 h, 33 and 33 h) and in one case the $t_{1/2}$ was shorter after multiple dosing (40 h and 49 h).

None of the volunteers complained of cognitive impairment during chronic dosing with NDMC.

Discussion

Previous studies following single doses of clobazam in young healthy volunteers have reported pharmacokinetic values which are broadly similar to those described here (Tedeschi *et al.*, 1981; Greenblatt *et al.*, 1983; Jawad *et al.*, 1984). The last of these papers, however, described a shorter t_{max} (6–36 h) for NDMC derived from clobazam.

One previous study reporting plasma NDMC concentrations in only three volunteers following a single oral dose of NDMC 40 mg found a similar $t_{1/2}$ to that which we describe (Rupp *et al.*, 1979). The only other report of plasma levels following NDMC administration is our own investigation of the effect of cimetidine on clobazam and NDMC pharmacokinetics (Pullar *et al.*, 1987). In that study we reported data from six volunteers following a single dose of clobazam 30 mg and five volunteers following a single dose of NDMC 30 mg. Four members of the clobazam group and four of the NDMC group are included in the present study (although in our previous study paired data on clobazam and NDMC were available from only one volunteer common to both groups). Pharmacokinetic parameters for clobazam and NDMC from those volunteers in the previous investigation who were not included in the current study were consistent with those reported here.

In the single dose study we calculated a longer $t_{1/2}$ for NDMC following clobazam administration (64 ± 4.3 h) than following NDMC (42.2 ± 3.2 h). The most likely explanation for this is that even when clobazam is undetectable in the plasma a significant tissue reservoir of clobazam is present and available for metabolism to NDMC, resulting in a falsely long estimation of the NDMC $t_{1/2}$. In this study all our volunteers were male; unpublished data which we have accumulated from nine female volunteers taking single dose clobazam 30 mg or NDMC 30 mg on separate occasions with measurement of plasma concentrations 1, 2, 24 and 48 h post-dose show similar drug levels. This period, however, represents mainly the absorption and distribution phases and gives little information on clearance of the drugs.

There are no previous reports of steady-state data for NDMC in either volunteers or patients receiving NDMC. The steady-state concentrations achieved in patients in this study are of the same order as those found in epileptic patients receiving therapeutic doses of clobazam (Callaghan & Goggin, 1984). In our patients receiving chronic dosing, steady-state concentrations were much higher in males than in females. These differences persisted even when the dose was adjusted for body weight and thus indicate a more rapid plasma clearance of NDMC in female patients. Steady-state NDMC concentrations were also higher in patients than in volunteers. Although the patients had taken NDMC for longer than the volunteers, all volunteers had received NDMC for 14 days which is far in excess of five half-lives; thus the disparity in the duration of treatment is not an explanation for the observed difference in concentration. In this paper the single dose investigation has been described as 'Study 1' and the steady-state investigation as 'Study 2', as this seemed a logical mode of presentation, but the volunteer studies were actually carried out in the opposite order. Thus we had no prior knowledge of the NDMC $t_{1/2}$s in volunteers who entered the steady-state study and the difference is not due to the selection of volunteers with short $t_{1/2}$s in order to reduce the duration of sampling.

The most likely explanation for the difference between volunteers and patients is concomitant anticonvulsant drug therapy. Previous studies of clobazam have described reduced clobazam and increased NDMC levels in patients receiving PHT and/or CBZ (Cano *et al.*, 1981; Jawad *et al.*, 1984) implying induction of clobazam metabolism. The observation in our study that steady-state NDMC concentrations following regular NDMC administration were higher in patients taking additional anticonvulsant drugs than in healthy volunteers suggests that induction of clobazam demethylation is not the only mechanism whereby NDMC levels are higher in epileptic patients taking clobazam along with CBZ and/or PHT.

Although formal psychomotor testing was not carried out in these experiments it was obvious in the single dose study of healthy male volunteers that impairment was produced by clobazam but not NDMC and that the occurrence of impairment corresponded closely to the peak clobazam concentration. Further formal studies of psychomotor performance with single and multiple doses of NDMC are currently underway.

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