

Single dose pharmacokinetic study of clobazam in normal volunteers and epileptic patients

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1 The pharmacokinetics of clobazam were studied in six healthy volunteers and six age and sex matched enzyme-induced epileptic patients.

2 In the epileptic patients the area under the plasma concentration-time curve for clobazam was significantly smaller and the area under the plasma concentration-time curve for *N*-desmethylclobazam was significantly greater than in the healthy volunteers.

3 Plasma *N*-desmethylclobazam concentrations were found to be much higher than those of clobazam in the epileptic patients, raising the possibility that the antiepileptic properties of clobazam are to be attributed more to its metabolite than the parent drug.

Keywords clobazam desmethylclobazam epilepsy enzyme induction
1,5 benzodiazepines

Introduction

Clobazam is a 1,5 benzodiazepine which is well absorbed following oral administration, and peak plasma concentrations are reached after 1-4 h (Rupp *et al.*, 1979). Its metabolism has been studied in man, rat, dog and monkey (Volz *et al.*, 1979). Up to fourteen metabolites have been identified, the most important being the pharmacologically active *N*-desmethylclobazam. The elimination half-life of the parent compound has been estimated to be 18 h (Rupp *et al.*, 1979).

Clinical trials have proved the efficacy of clobazam as an adjuvant treatment in refractory epilepsy on a short term basis (Allen *et al.*, 1983). As this drug is often administered to patients receiving microsomal enzyme inducing antiepileptic drugs such as phenytoin, phenobarbitone, primidone and carbamazepine, we have compared the pharmacokinetics of a single dose of clobazam in normal volunteers and enzyme-induced epileptic patients.

Methods

Six healthy normal volunteers, and six age and sex matched residents at the Chalfont Centre for Epilepsy, Chalfont St Peter, Buckinghamshire, were included in the study (Tables 1 and 2). The six epileptic patients were receiving chronic phenytoin and/or carbamazepine therapy and the doses of these drugs (Table 2) had been stable for at least 3 months. None was receiving any other benzodiazepine drug. The nature of the study was explained to all the subjects and approval was given by the Ethics Committee of the Welsh National School of Medicine. Three 10 mg capsules of clobazam (Frisium, Hoechst) were administered orally with 100 ml of water on empty stomach after an overnight fast. The subjects were given a standard breakfast 1 h after drug administration. The patients received their routine drug therapy at the usual time. Blood samples were collected through i.v. cannulae (Venflon) at the following times: 15, 30, 45 min, 1, 2, 3, 4, 6, 12, 24,

Table 1 Pharmacokinetic data on clobazam and *N*-desmethylclobazam in normal volunteers

| Subject | Age (years) | Sex | $AUC_{0-\infty}$ ($\mu\text{g l}^{-1} \text{h}$) clobazam | $AUC_{0-192 \text{ h}}$ ($\mu\text{g l}^{-1} \text{h}$) <i>N</i> -desmethylclobazam | Antipyrine CL ($\text{l h}^{-1} \text{kg}^{-1}$) |
|------------|-------------|-----|--|--|--|
| 01 | 21 | F | 11596 | 14736 | 0.033 |
| 02 | 18 | M | 15894 | 15777 | 0.040 |
| 03 | 20 | M | 12064 | 13886 | 0.038 |
| 04 | 20 | M | 13906 | 22265 | 0.046 |
| 05 | 24 | M | 15947 | 22160 | 0.032 |
| 06 | 20 | M | 15947 | 38537 | 0.032 |
| Mean | 20.8 | | 13741 | 21227 | 0.037 |
| \pm s.d. | ± 2 | | ± 1867 | ± 9244 | ± 0.007 |

36, 48, 72, 96, 144 and 192 h following clobazam administration. Plasma was separated and stored at -18°C for subsequent measurement of clobazam, *N*-desmethylclobazam, phenytoin and carbamazepine concentrations.

Plasma concentrations of clobazam and *N*-desmethylclobazam were measured by h.p.l.c. utilizing nitrazepam as an internal standard. In outline the method was as follows: to 100 μl of plasma, 200 $\mu\text{g/l}$ nitrazepam was added, and the three benzodiazepines were extracted using ether. To the dried residue, 100 μl of the mobile phase was added and 25–75 μl was injected into the chromatogram under the following conditions: mobile phase 70:30 mixture of $\text{K}_2\text{H}_2\text{PO}_4$ (pH 6.8): acetonitrile; column:

C8 cartridge; wavelength: 254 nm; run time: 10 min. The lower limit of the sensitivity of the assay was 25 $\mu\text{g/l}$ for clobazam and *N*-desmethylclobazam. The assay was checked regularly by quality control samples prepared in our laboratories. Antipyrine clearance was used as a measure of enzyme induction (Davies *et al.*, 1973). Antipyrine (600 mg) in normal saline was given intravenously to the subjects and saliva samples were collected at 1, 2, 3, 4, 5, 6, 8 and 24 h. The assay method used was the gas chromatographic technique described by Fraser *et al.* (1976).

Plasma phenytoin and carbamazepine concentrations were measured using enzyme immunoassay (EMIT, Syva) in samples taken at

Table 2 Pharmacokinetic data as clobazam and *N*-desmethylclobazam in epileptic patients

| Patient | Age (years) | Sex | $AUC_{0-\infty}$ ($\mu\text{g l}^{-1} \text{h}$) | $AUC_{0-192 \text{ h}}$ ($\mu\text{g l}^{-1} \text{h}$) | Treatment (mg/day) | Mean plasma concentrations of antiepileptic drugs (mg/l) | Antipyrine CL ($\text{l h}^{-1} \text{kg}^{-1}$) |
|------------|-------------|-----|--|---|--------------------|--|--|
| 01 | 22 | F | 4899 | 43230 | CBZ 600 | 6.5 | 0.078 |
| 02 | 18 | M | 5979 | 99236 | CBZ 600 DPH 200 | 8.6 18.0 | 0.089 |
| 03 | 23 | M | 5864 | 35361 | CBZ 600 | 6.6 | 0.088 |
| 04 | 24 | M | 7828 | 33396 | DPH 300 | 12.0 | 0.072 |
| 05 | 31 | M | 5904 | 123590 | CBZ 600 DPH 100 | 9.4 18.0 | 0.081 |
| 06 | 20 | M | 5071 | 28978 | CBZ 400 | 6.8 | 0.082 |
| Mean | 23 | | 5924 | 61465 | | | 0.082 |
| \pm s.d. | ± 4.4 | | ± 1040 | ± 39965 | | | ± 0.006 |
| P^* | NS | | 0.001 | 0.05 | | | 0.001 |

*Significance of difference compared with normal volunteers. CBZ carbamazepine, DPH phenytoin.

the following times after clobazam administration -2, 4, 6, 12, 24, 72, 96, 144, 192 h. Antipyrine clearance was calculated by dividing dose by AUC. The results were analysed statistically using unpaired Student's *t*-tests: Conversion: from mass to molar units: carbamazepine 1 mg/l = 4.2 μ mol/l, phenytoin 1 mg/l = 4.0 μ mol/l, clobazam 1 mg/l = 3.3 μ mol/l, *N*-desmethyloclobazam 1 mg/l = 3.5 μ mol/l.

Results

Figures 1 and 2 show plasma concentrations of clobazam and *N*-desmethyloclobazam vs time in normal volunteers and epileptic patients respectively. Plasma concentrations of clobazam increased rapidly, reaching a peak concentration in 1-3 h, and declining in a biexponential fashion in both groups. *N*-desmethyloclobazam

concentrations, however, reached much higher levels in the epileptic patients than in the normal volunteers. Peak concentrations were also achieved significantly earlier in the patients (3-6 h) compared with the normal volunteers (6-36 h).

In epileptic patients, the mean $AUC_{0-\infty}$ for clobazam was smaller ($P < 0.05$) than in the volunteers and the $AUC_{0-192\text{ h}}$ for *N*-desmethyloclobazam was significantly larger.

Discussion

This study has shown that the $AUC_{0-\infty}$ for the parent drug following single oral doses of clobazam in enzyme-induced epileptic patients is less than in normal volunteers, presumably due to increased desmethylation in the liver resulting from enzyme induction by phenytoin and carbamazepine. The pharmacokinetic parameters in normal volunteers were similar to

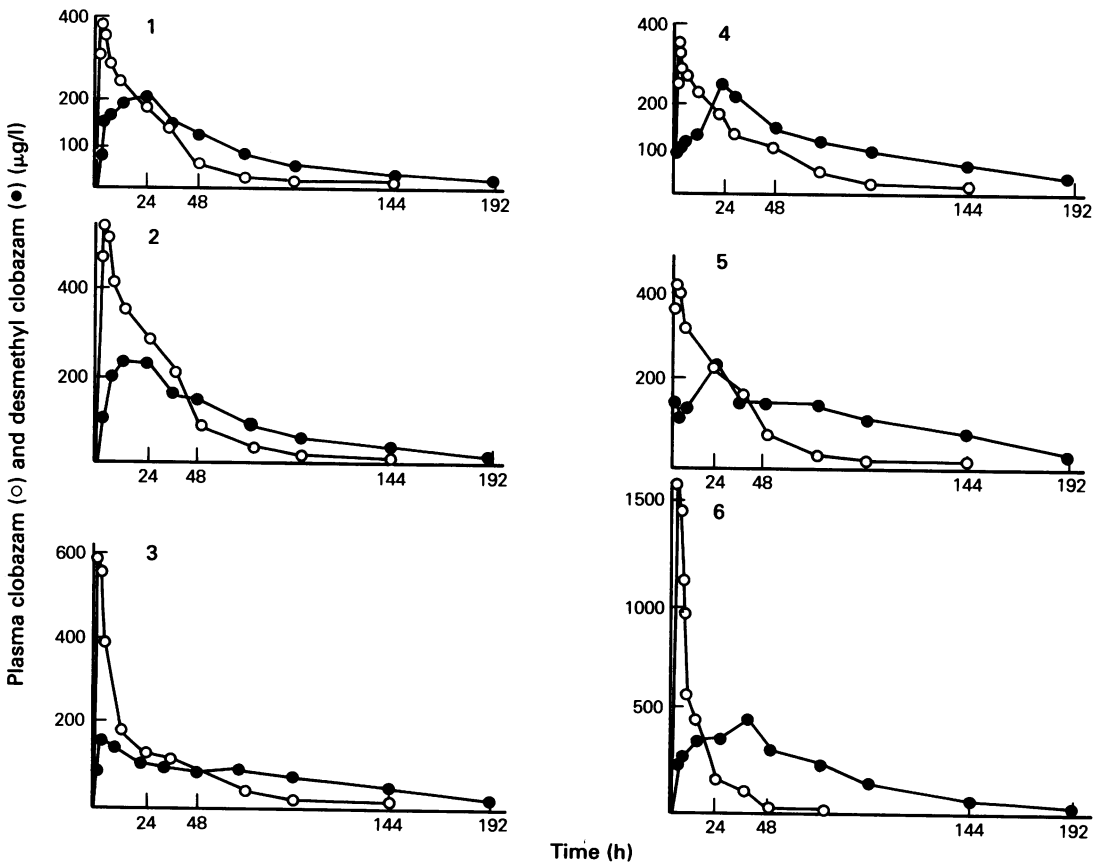


Figure 1 Plasma clobazam (○) and *N*-desmethyloclobazam (●) concentrations vs time in six normal volunteers.

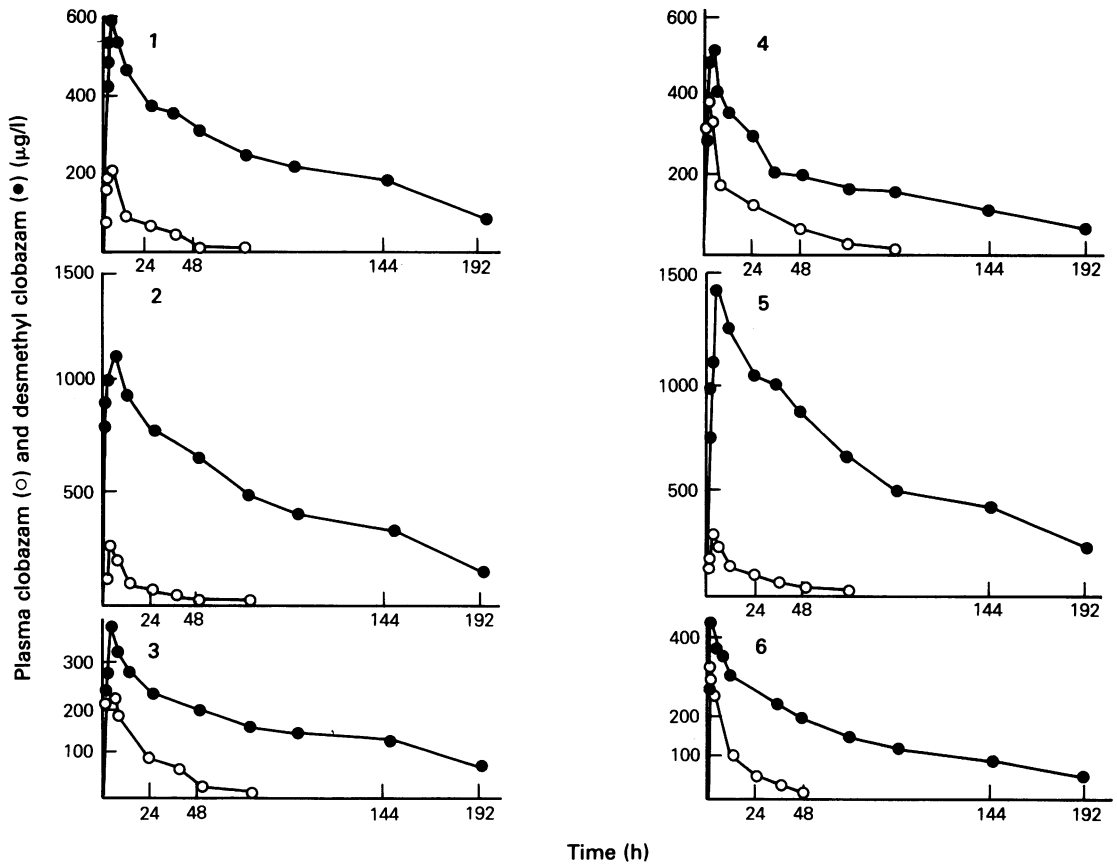


Figure 2 Plasma clobazam (○) and *N*-desmethylclobazam (●) concentrations vs time in six enzyme-induced epileptic patients.

values reported previously (Rupp *et al.*, 1979; Tedeschi *et al.*, 1981; Divoll *et al.*, 1982).

That induction of clobazam metabolism is the likely explanation for the above finding is supported by two observations: first, the elimination half-life of antipyrine in the epileptic patients was significantly reduced compared with the normal volunteers (Davies *et al.*, 1973). Second, in the epileptic patients, mean $AUC_{0-192\text{ h}}$ for *N*-desmethylclobazam was significantly larger and peak plasma concentrations were reached earlier than in normal volunteers (Figures 1 and 2).

The induction of benzodiazepine metabolism has previously been studied in animal and human experiments. Marucci *et al.* (1970) demonstrated an increase in the rate of diazepam metabolism in rats, mice and guinea pigs treated with phenobarbitone. Ohnhaus *et al.* (1979) showed that the metabolism of diazepam in man was increased following the induction of liver microsomal enzymes by antipyrine. Dhillon & Richens (1981) found that the elimination

half-life of an i.v. dose of diazepam is significantly shorter and the plasma clearance significantly higher in enzyme-induced epileptic patients than in normal volunteers. Serum *N*-desmethyldiazepam concentrations were higher and the time to peak serum concentration was earlier in the former group. The half-life of clonazepam, following carbamazepine administration, is significantly reduced in normal men (Lai *et al.*, 1978). Our results suggest that *N*-desmethylation of clobazam is similarly affected.

Clobazam is recommended as an adjuvant treatment in refractory epilepsy (Allen *et al.*, 1981) and with chronic administration, we have found the steady state plasma concentration of *N*-desmethylclobazam far exceeds that of clobazam (unpublished data). Since *N*-desmethylclobazam is an active metabolite with a potency of one-fifth that of clobazam (Fielding & Hoffman, 1979), it is likely that the antiepileptic effect of clobazam on chronic administration to epileptic patients can be attributed more to *N*-desmethylclobazam.

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