EFFECT OF ACUTE ALCOHOL INTOXICATION ON THE METABOLISM AND PLASMA KINETICS OF CHLORDIAZEPOXIDE

B. WHITING & J.R. LAWRENCE

Department of Materia Medica, University of Glasgow,
Stobhill General Hospital, Glasgow

G.G. SKELLERN

Drug Metabolism Unit, Department of Pharmaceutical Chemistry,
University of Strathclyde, Glasgow

J. MEIER

Sandoz A.G., Biopharmaceutical Department,
CH-4002 Basel, Switzerland

- 1 The metabolism and plasma kinetics of chlordiazepoxide have been determined in a group of volunteers and in a group of patients with acute alcohol intoxication.
- 2 Using the SAAM 26 non-linear least squares fitting programme, all chlordiazepoxide plasma concentration *v* time data following oral administration could be analysed in terms of a one-compartment open model with metabolic conversion of chlordiazepoxide to desmethylchlordiazepoxide.
- 3 Acutely intoxicated patients showed a prolonged elimination of chlordiazepoxide and a reduced clearance when compared with alcohol-free volunteers. The elimination of desmethylchlordiazepoxide, on the other hand, appeared to be faster in the alcoholics.
- 4 Alcohol exerts significant effects on the metabolism of chlordiazepoxide in acutely intoxicated patients.

Introduction

As a general rule, it is wise to avoid simultaneous exposure to alcohol and central nervous system depressant drugs. This is usually left to the discretion of the individual patient who should, however, have been warned about the unpredictable effects of this combination, the most dangerous one being excessive central nervous system depression. The cerebral effects of this combination are obvious, but at the metabolic level, alterations of enzyme function occur which may be related to the length and extent of exposure to alcohol. Rubin, Gang, Misra & Lieber (1970) have shown that *acute* alcohol intoxication is associated with impairment of pentobarbitone and meprobamate metabolism whereas Kater, Roggin, Tobon, Zieve & Iber (1969) showed that drug metabolism may be accelerated in *chronic* alcoholics.

In one particular instance, namely the suppression of delirium tremens which follows acute alcohol intoxication, it is traditional for a central nervous system depressant, chlordiazepoxide (CHD), to be used in relatively high dosage. It seemed pertinent, therefore, to investigate the possible effects of alcohol intoxication on the pharmacokinetics and metabolic profile of this drug.

Methods

Two groups of subjects were studied.

- (a) Five normal healthy male volunteers, aged 28–36 years (mean 31.2 years)
- and (b) Seven adult male patients, aged 38–68 years (mean 51.6 years), who had been admitted to the Psychiatric Department of Stobhill General Hospital, with a diagnosis of acute alcohol intoxication.

The volunteers were totally alcohol free at the time of the study, and had normal haematological, biochemical and liver function indices. A single oral dose of 25 mg CHD was given to each volunteer after an overnight fast and blood samples (10 ml into lithium heparin anticoagulant) were withdrawn through an indwelling 'Venflon' catheter previously inserted into an antecubital vein at the following time intervals: pre-dose (control) and 0.5, 1, 2, 4, 6, 8, 12 and 24 h after the dose. Plasma was separated by centrifugation and stored at -20°C until required for analysis of CHD and its desmethyl metabolite (DMCHD) by high pressure liquid chromatography (HPLC) (Skellern, Meier & Whiting, 1977; Skellern, Knight, Meier & Whiting, 1978).

Once it had been established that CHD would be

PLASMA (D) Chlordiazepoxide in plasma

U/M(D) urine/further metabolism

PLASMA (M) Desmethyl-chlordiazepoxide in plasma

U/M(M) urine/further metabolism

Figure 1 One compartment model for chlordiazepoxide (CHD) kinetics, showing its metabolic conversion to desmethylchlordiazepoxide (DMCHD). All rate constants are assumed to be first order. K_a is the absorption rate constant for CHD and K_m is the metabolic rate constant characterizing the conversion of CHD to DMCHD. $K_e(D)$ and $K_e(M)$ are overall elimination rate constants for CHD and DMCHD respectively.

appropriate in the management of the alcoholic patients, a 10 ml control blood sample was withdrawn, the first dose administered, and blood samples taken at the following times before the second dose: 1, 2, 3, 4, 5 and 6 h, then at 24–48 h intervals for not more than 14 days, usually immediately prior to the second morning dose. Plasma was separated and stored at -20°C until required for analysis as indicated above. An aliquot of the control sample was also reserved for routine biochemical assessment of liver function. A careful record was made of the time of administration and the amount of each dose, together with the precise times of each blood sample. The daily dose of CHD during the study period was determined by the psychiatrists under whom the patients had been admitted and ranged from initial high daily doses of 200 mg to lower doses of 30 mg given in three or four equally divided doses.

Evaluation of the data

CHD and DMCHD plasma concentration ν time data were analysed by the SAAM 26 non-linear least squares fitting programme (Berman & Weiss, 1969) on a UNIVAC 1108 digital computer. Multiple dose kinetics (alcoholic patients) were derived by use of the QO-option of the SAAM 26 programme which could accommodate up to 60 individual drug administrations. Each precise dose was entered at the previously recorded times and a fitted plasma concentration profile was obtained in each case for the duration of the study.

Figure 2 Observed and computed plasma levels of chlordiazepoxide (CHD) and desmethylchlordiazepoxide (DMCHD) in three normal volunteers following a single oral dose of CHD. (●) and (○) are concentrations of drug and metabolite measured by HPLC; the continuous lines represent the best fit of the data computed by the SAAM 26 programme, according to the model shown in Figure 1.

Results

Unless otherwise stated, all results are presented as mean $\pm$ s.d.

Kinetic analysis

After oral administration of CHD to both normal volunteers and alcoholic patients, CHD plasma concentration ν time data could be analysed in terms on a one-compartment open model (Figure 1) with metabolic conversion of CHD to DMCHD and subsequent renal elimination and/or further metabolism of both parent drug and metabolite.

Normal volunteers

Plasma concentration ν time curves for CHD and DMCHD are shown in Figure 2; the closeness of fit between computed and experimentally derived data is apparent. Corresponding pharmacokinetic parameters and rate constants appropriate to the proposed model

Figure 3 Observed and computed plasma concentrations of chlordiazepoxide (CHD ●) and desmethylchlordiazepoxide (DMCHD ○) during the first 6 days of multiple dosing of an alcoholic patient with CHD. The continuous lines represent the best fit of the data computed by the SAAM 26 programme, according to the model shown in Figure 1.

are shown in Tables 1 and 2. The mean CHD absorption half-life was 0.39 ± 0.27 h. Overall elimination half-life of the parent drug was 6.14 ± 2.12 h, and that of DMCHD was 21.90 ± 15.45 h. One volunteer appeared to have an excessively long DMCHD half-life (48.47 h) and if this value is excluded, the mean DMCHD half-life was 15.25 ± 4.86 h. Volume of distribution of CHD, based on the assumption of 100% absorption, was 18.24 ± 4.54 litres, and it was cleared at a rate of 36.42 ± 9.69 ml/min.

Patients

A typical example of the plasma profile of CHD and DMCHD following multiple dosing is shown in Figure 3, together with predicted drug and metabolite profiles according to the proposed model. Figure 4 shows CHD plasma concentrations for the first 5 h of treatment following an initial dose of 50 mg. Also included in this figure are serial plasma alcohol concentrations, measured by gas liquid chromatography, which declined linearly at a rate of $0.4 \text{ mg ml}^{-1} \text{ h}^{-1}$.

Table 1 Pharmacokinetic parameters after a single oral dose of 25 mg chlordiazepoxide: healthy volunteers.

Parameter	MM	DJS	BW	BC	JL	Mean $\pm$ s.d.
Absorption $T_{1/2}$ (h)	0.84	0.32	0.35	0.13	0.29	0.39 ± 0.27
CHD elimination $T_{1/2}$ (h)	4.33	9.33	7.27	4.66	5.10	6.14 ± 2.12
DMCHD elimination $T_{1/2}$ (h)	13.43	10.25	15.54	48.47	21.78	21.89 ± 15.44
CHD volume of distribution (l)	17.12	16.34	26.18	14.73	16.81	18.24 ± 4.54
CHD clearance (ml/min)	45.60	20.23	41.58	36.58	38.10	36.42 ± 9.69

Table 2 Computed pharmacokinetic constants for chlordiazepoxide and desmethylchlordiazepoxide

Rate constant (h^{-1})	MM	DJS	BW	BC	JL	Mean $\pm$ s.d.
K_a	0.826	2.14	1.97	5.53	2.39	2.57 ± 1.76
K_e (D)	0.0511	0.0105	0	0.0655	0	0.0254 ± 0.0307
K_m	0.109	0.0638	0.0953	0.0833	0.136	0.0975 ± 0.0272
K_e (M)	0.0516	0.0676	0.0446	0.0143	0.0318	0.0420 ± 0.0202

Figure 4 Observed plasma concentrations of chlor-diazepoxide (CHD ●) during the first 5 h of treatment of the patient shown in Figure 3. Included are serial measurements of plasma alcohol concentration (O) which decline linearly at a rate of $0.4 \text{ mg ml}^{-1} \text{ h}^{-1}$.

Patient pharmacokinetic parameters and rate constants are presented in Tables 3 and 4.

Because the results showed relatively large

intersubject variations and departure from normal distribution, the nonparametric Mann-Whitney U test (two tailed) was used to compare patients and volunteers.

No significant differences were apparent in rates of absorption, but no data were available to assess the extent of absorption.

The patients showed an overall CHD elimination half-life of $20.65 \pm 15.23 \text{ h}$, which was significantly longer than that of the volunteers ($P < 0.02$). There was also a significant difference between patient and volunteer DMCHD half-lives; patient values, $10.52 \pm 4.02 \text{ h}$ were shorter ($P < 0.05$). Volumes of distribution in the alcoholics varied from 15.08 to 69.93 l (mean $37.23 \pm 22.8 \text{ l}$), four values being in excess of the highest value found in a volunteer (26.18 l), but uncertainty about the extent of absorption precluded any further analysis of these figures. Similarly, clearance values, derived from the relationship $\text{Cl}_{\text{tot}} = V_d \cdot K_e$ were dependent on V_d , which in turn was dependent on the fraction of CHD absorbed. However, in keeping with the prolonged CHD half-lives found in alcoholic patients, associated clearance values, based on the assumption of 100% absorption, tended to be lower ($25.39 \pm 15.34 \text{ ml/min}$) than those found in volunteers ($36.42 \pm 9.69 \text{ ml/min}$). If the relatively high value found in patient 7 is excluded (55.6 ml/min), the difference becomes significant ($p = 0.01$).

On the basis of routine biochemical tests, apart from transient elevations in enzyme levels, none of the patients had any significant degree of hepatic impairment.

Table 3 Pharmacokinetic parameters after multiple doses of chlordiazepoxide: alcoholic patients

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Mean $\pm$ s.d.
Absorption $T_{1/2}$ (h)	0.240	0.150	0.289	0.231	1.090	0.619	0.748	0.481 ± 0.348
CHD elimination $T_{1/2}$ (h)	10.9	17.0	28.3	24.8	5.68	49.5	8.38	20.65 ± 15.23
DMCHD elimination $T_{1/2}$ (h)	9.92	7.44	5.33	15.10	13.12	15.30	7.41	10.52 ± 4.02
CHD volume of distribution (l)	15.08	19.45	69.93	34.13	16.34	65.36	40.32	37.23 ± 22.8
CHD clearance (ml/min)	16.0	13.2	28.5	15.9	33.2	15.3	55.6	25.39 ± 15.34

Table 4 Computed pharmacokinetic constants for chlordiazepoxide and desmethylichlordiazepoxide according to the proposed model: alcoholic patients

Rate constant (h^{-1})	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Mean $\pm$ s.d.
K_a	2.89	4.62	2.4	3.0	0.638	1.12	0.927	2.23 ± 1.43
$K_{e(D)}$	0	0	0	0	0	0	0	—
K_m	0.0634	0.0407	0.0245	0.0279	0.122	0.0140	0.0827	0.0536 ± 0.0384
$K_{e(M)}$	0.0699	0.0932	0.130	0.0459	0.0528	0.0453	0.0935	0.0758 ± 0.0315

Discussion

The data presented in this study demonstrated the suitability of the one-compartment model for describing the disposition kinetics of CHD and its metabolic conversion to DMCHD after oral administration. The lack of significant divergence between predicted and measured concentrations of drug and metabolite attested to the adequacy of the proposed model.

The major elimination pathway for CHD has been shown to be almost exclusively biotransformation to DMCHD (Koechlin, Schwartz, Krol & Oberhaensli, 1965). Almost no unchanged CHD is excreted in the urine and this places considerable emphasis on the metabolic rate constant, K_m , shown in the model. The decline of CHD levels in plasma, therefore, depends to a large extent on this constant and any change in CHD metabolism will be reflected by changes in this constant and in corresponding elimination half-lives. In the present study, CHD was eliminated from volunteers with a mean elimination half-life of 6.14 h (range 4.33–9.33 h). This was a little shorter than the mean terminal half-life of 9.4 h (range 6.6–11.4 h) found in six healthy subjects by Boxenbaum, Geitner, Jack, Dixon, Spiegel, Symington, Christian, Moore, Weissman & Kaplan (1977). The increased specificity of HPLC over the earlier differential spectrofluorimetric method (Schwartz & Postma, 1966) used by these authors, may explain this discrepancy. The elimination half-life in alcoholics, mean 20.65 h (range 5.68–49.5 h) was clearly prolonged and suggests a slower metabolic conversion of CHD and DMCHD in the acutely intoxicated patients.

The range of half-lives observed in volunteers in this study, (4.33–9.33 h) emphasizes a degree of variability which may be genetically controlled. The increase in variability in the alcoholics, with a range of 5.68–49.5 h, demonstrates the over-riding influence of external factors such as alcohol, other drugs, nutrition and possibly age and liver disease. It is also evident that the half-lives of 20–24 h, which were reported by Koechlin & D'Arconte (1963) in normal subjects were considerably overestimated as a result of lack of assay specificity. As Figures 2 and 3 show, DMCHD levels rise appreciably over a considerable length of time and would artificially prolong the measured half-life of CHD if it could not be identified separately.

The elimination of DMCHD, characterized by the rate constant K_e (M) in the model, has been shown to involve further biotransformation to the metabolite demoxepam (Kaplan, Lewis, Schwartz, Postma, Cotler, Abruzzo, Lee & Weinfeld, 1970). Thus DMCHD is an intermediate in the biotransformation of CHD to demoxepam. It is interesting that in the present study, the elimination of DMCHD, as reflected by half-lives, was faster in the alcoholics.

Acute alcohol intoxication, therefore, appears to exert a dual effect on CHD metabolism by inhibiting the first step to DMCHD and paradoxically increasing the elimination of DMCHD, possibly by inducing its conversion to demoxepam. Further studies with assessment of demoxepam levels should help to elucidate this phenomenon. Sellman, Kanto, Rajola & Pekkarinen (1975) found lower levels of the N-demethylated metabolite of diazepam in chronic alcoholics compared with levels found in control subjects. They inferred that either alcohol inhibited the N-demethylation of diazepam or that there was an alteration in the distribution of the metabolite in chronic alcoholics.

Boxenbaum *et al.* (1977) have determined that in healthy subjects, absorption following oral administration of CHD is rapid and complete, with a half-life of about 27 min. CHD was given orally in the present study to volunteers in the fasting state, and the mean absorption half-life of 23.4 min. agreed well with these workers. Moreover, the volumes of distribution of volunteers in the present study, calculated as a percentage of body weight, agreed well with those of Boxenbaum *et al.* (1977) implying a similar degree of absorption. But it is rather difficult to comment on the relatively high volumes of distribution found in the alcoholics. In the unlikely event of absorption being complete, this would imply quite marked differences in distribution, but it seems much more likely that there were considerable variations in absorption due to a number of factors, including the effects of alcohol on the gastro-intestinal tract and the non-fasting conditions under which drugs are normally administered. Sellman, Pekkarinen, Kangas & Rajola (1975) have made similar observations on diazepam in chronic alcoholics. This kind of variation would result in the relatively high distribution volumes and the marked intersubject variations which were observed in the present study.

From the clinical standpoint, the decreased elimination of CHD in patients with acute alcohol intoxication does not seem to be a disadvantage. This study produced results which suggest that alcohol exerts a significant effect on the metabolic fate of CHD in the circumstances outlined. Moreover, it appears that there may be an associated increase in the rate of removal of DMCHD. This metabolite will undoubtedly be present in relatively high concentrations because of the high doses employed in the suppression of delirium tremens. This is of interest because CHD metabolites almost certainly contribute to the overall activity of the parent drug (Boxenbaum, Geitner, Jack, Dixon & Kaplan, 1977; Randall, Scheckel & Banziger, 1965; Randall & Kappell, 1973). The lack of persisting, significant evidence of hepatic dysfunction in any of the patients again supports the contention that the disturbance in CHD metabolism was due primarily to alcohol, but it would

be difficult to quantify this effect. Alcohol levels were monitored immediately after admission in two patients in the present study, and alcohol clearance rates in both cases were approximately double the normal rate of $0.2 \text{ mg ml}^{-1} \text{ h}^{-1}$ (Forney & Harger, 1969). This is in keeping with heavy drinking (Kater, Carulli & Iber, 1969; Kater *et al.*, 1969). All patients were well known habitual drinkers with established diagnosis of alcoholism and were admitted specifically for help during the withdrawal phase.

Despite the relatively high plasma CHD concentrations observed and predicted, drowsiness was not a feature of the treatment and the patients remained alert and relatively mobile during the day. There was no doubt, however, that the anxiety and agitation associated with delirium tremens was

effectively suppressed. It appears, therefore, that delirium tremens presents a challenge to the psychopharmacological effects of relatively high doses of CHD in that it over-rides any significant sedative effect which the drug would normally exert at much lower plasma concentrations. Fortunately, the distressing symptoms of anxiety and agitation usually respond satisfactorily. The exact relationship between the suppression of delirium tremens and plasma concentrations of CHD and its metabolites remains to be determined, but by definition, alcohol will always play an important part in this relationship.

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