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Absorption of Oral and Intramuscular Chlordiazepoxide*

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Summary. The absorption of oral and intramuscular (i.m.) chlordiazepoxide hydrochloride (CDX · HCl) was compared in two pharmacokinetic studies. In Study One, single 50-mg doses of CDX · HCl were administered orally and by i.m. injection to 14 healthy volunteers using a crossover design. Whole-blood concentrations of chlordiazepoxide (CDX) and its first active metabolite, desmethylchlordiazepoxide (DMCDX), were determined in multiple samples drawn after the dose. Mean pharmacokinetic variables for CDX following oral and i.m. administration, respectively, were: highest measured blood concentration, 1.65 vs 0.87 μg/ml ($p < 0.001$); time of highest concentration, 2.3 vs 7.6 h after dosing ($p < 0.001$); apparent absorption half-life, 0.71 vs 3.39 h ($p < 0.001$). Biphasic absorption after i.m. injection, consistent with precipitation at the injection site, was observed in 9 of 14 subjects. Based upon comparison with previous intravenous data, the completeness of absorption was 100% for oral vs 86% for i.m. CDX · HCl ($p < 0.1$). In Study Two, 28 male chronic alcoholics with clinical manifestations of the acute alcohol withdrawal syndrome were randomly assigned to one of four treatment conditions: 50 or 100 mg doses of CDX · HCl, by mouth or by i.m. injection. Concentrations of CDX and DMCDX, determined in plasma samples drawn every 20 min for 5 h following the dose, were significantly higher after oral administration of a given dose than at corresponding points in time after i.m. injection after the same dose. Thus absorption of oral CDX is reasonably rapid and complete, whereas the absorption rate of i.m. CDX is slow.

Key words: Chlordiazepoxide, benzodiazepines, pharmacokinetics, bioavailability, intramuscular injection, alcohol withdrawal.

Chlordiazepoxide hydrochloride (Librium) is commonly administered by intramuscular injection in clinical situations requiring sedative effects of rapid onset [8]. Previous studies, however, suggest that the rate of absorption of chlordiazepoxide following intramuscular injection is slow [1, 4, 12]. Oral administration, on the other hand, gives relatively rapid and apparently complete absorption [1, 10, 12, 19]. The present study compared the rate of absorption and absolute systemic availability of oral and intramuscular chlordiazepoxide administered to a series of healthy male and female volunteers. Data is also presented on the rate of chlordiazepoxide absorption following these two routes of administration in a series of patients receiving the drug for treatment of acute alcohol withdrawal.

Materials and Methods

Study One

Fourteen healthy volunteers (6 male and 8 female), aged 21 to 38 years, participated after giving informed consent. All were free of identifiable medical or psychiatric disease, and were taking no psychotropic medications on a regular basis. No other drugs were ingested during the study.

Each subject received single 50-mg oral and intramuscular (i.m.) doses of chlordiazepoxide hydrochloride[1] (CDX · HCl) in random sequence with

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[1] Librium®, Roche Laboratories, Nutley, N.J.

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at least one week elapsing between trials. Oral CDX · HCl was administered as two 25-mg capsules with 100 ml of water following an overnight fast. CDX · HCl was prepared for i.m. injection by addition of 2 ml of Special Intramuscular Diluent (the customary solvent) to 100 mg of sterile powder. One ml of this solution (50 mg of CDX · HCl) was administered as a single deltoid intramuscular injection, using a 2.5-cm gauge-20 hypodermic needle.

Venous blood samples were drawn into heparinized tubes from an indwelling Butterfly cannula, or by venipuncture, prior to drug administration, and at 0.5, 1.0, 1.5, 2.0, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 h after administration. Whole blood samples were immediately frozen until the time of assay. Concentrations of chlordiazepoxide (CDX) and its first pharmacologically active metabolite, desmethylchlordiazepoxide (DMCDX), were determined by a spectrophotofluorometric method [13, 18, 20], having sensitivity limits of approximately 0.1 μg/ml for CDX and 0.05 μg/ml for DMCDX.

Blood concentrations of CDX for individual subjects, as well as "composite" data points formed by the across-subject mean concentrations at corresponding points in time, were analyzed by iterative weighted nonlinear least-squares regression analysis [22]. The iterative process was allowed to proceed until convergence criteria were met, or a total of 50 iterative steps was completed. Following oral administration of CDX · HCl, each set of data was fitted to the following two functions:

$$C = -(A + B)e^{-k_a t} + Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

$$C = A(e^{-\beta t} - e^{-k_a t}). \quad (2)$$

In both of these equations, C is the blood CDX concentration at time t after dosage. A and B are hybrid intercept coefficients, and α and β are hybrid exponents representing the "distribution" and "elimination" phases of the blood concentration curve [3, 5, 7, 23]. k_a is the hybrid exponent representing the apparent first-order absorption rate constant. It was used to calculate the apparent first-order absorption half-life ($t_{½a}$) as follows:

$$t_{½a} = (1n\,2)/k_a = 0.693/k_a. \quad (3)$$

For each set of data the choice between Equations (1) or (2) as functions of "best fit" was determined by comparison of the sum of squares of weighted residual errors, and by assessment of the randomness of "scatter" of actual data points about the fitted function [2]. Since CDX concentrations generally fell below the limits of reliable quantitation after 48 h, only those data points obtained up to 48 h after dosage were used for analysis.

Following i.m. injection of CDX · HCl, data points were again fitted to the above two functions. In some cases, however, neither function provided an adequate fit, and it was necessary to provide for two rates of absorption, termed the "rapid" and "slow" rates. The following function was applicable:

$$C = -Ae^{-k_1 t} - Be^{-k_2 t} + (A + B)e^{-\beta t}. \quad (4)$$

The quantities C, t, A, B, and β have the same meaning as in Equations (1) and (2). k_1 and k_2 are apparent first-order rate constants representing the "rapid" and "slow" phases of drug absorption. This approach has been used previously to describe absorption of i.m. chlordiazepoxide [1], phenytoin [14], and quinidine [7]; it is consistent with precipitation of the drug at the injection site, followed by slow redissolution.

Thirteen of the fourteen subjects had participated in a previous study of intravenously-administered CDX · HCl [9]. In these subjects absolute systemic availability of oral and i.m. chlordiazepoxide was estimated by comparison of the area under the 48-hour CDX blood concentration curve following the two extravascular modes of administration to that observed in the same subject following intravenous injection of the same dose. Also assessed was the area under the 72-hour blood concentration curve for DMCDX following oral and i.m. administration in comparison with intravenous injection.

Study Two

Twenty-eight male subjects participated after giving informed consent. All were chronic alcoholics who presented at emergency treatment facilities with signs and symptoms consistent with acute alcohol withdrawal. In all subjects administration of chlordiazepoxide as a sedative agent was clinically indicated. The following patient characteristics were recorded: age, body weight, total serum bilirubin, serum albumin, serum creatinine, alkaline phosphatase, and serum glutamic oxaloacetic transaminase (SGOT).

Subjects were randomly assigned to one of the following four treatment groups:

a) 100 mg of CDX · HCl by mouth with water;
b) 100 mg of CDX · HCl by deltoid i.m. injection;
c) 50 mg of CDX · HCl by mouth with water;
d) 50 mg of CDX · HCl by i.m. injection.

Comparability of the treatment groups with respect to the above characteristics was assessed by one-way analysis of variance [21].

Venous blood samples were drawn into heparinized tubes from an indwelling Butterfly cannula, or by venipuncture, prior to drug administration, and every 20 min thereafter until a total of 5 h

Table 1. Pharmacokinetics of chlordiazepoxide absorption in study one

Subject	Maximum blood concentration (μg/ml)		Time of maximum concentration (h after dose)		First-order absorption half-life		
	oral	i.m.	oral	i.m.	oral (hours)	i.m.	
						First phase (min)	Second (dominant) phase (h)
JMK	1.39	0.96	2.5	12	0.48	–	0.64[a]
GLN	2.07	1.23	1.0	2.5	0.33	0.2[b]	1.18
DJL	1.70	0.66	1.5	8	0.54	~0[b]	3.90
SN	1.92	1.10	6	8	0.35	–	2.05
LDF	1.93	1.00	1.0	12	0.42	7.3	4.31
AP	1.41	0.82	2.5	6	0.70	–	1.99
RIS	1.58	0.66	1.5	6	1.12	13.1	4.59
RAD	1.15	0.77	6	8	3.12	–	0.80
KMJ	1.16	0.48	1.5	2.5	0.92	11.2	9.63
LM	1.80	0.52	1.0	8	0.32	8.5	5.06
DJG	1.88	1.05	1.0	8	0.94	9.6	2.62
RRG	1.64	1.13	1.0	6	0.86	30.9	6.21
AJS	1.90	1.18	1.5	8	0.58	~0[b]	2.47
JSH	1.64	0.56	4	12	0.69	–	2.05
Mean (±SE)	1.65 (±0.08)	0.87 (±0.07)	2.3 (±0.5)	7.6 (±0.8)	0.71 (±0.19)	9.0 (±3.2)	3.39 (±0.66)
	$t = 11.30$, $p < 0.001$		$t = 6.47$, $p < 0.001$		$t = 3.65$, $p < 0.005$		
Composite	1.46	0.78	1.5	6	0.64	0[b]	2.34

[a] Lag time = 0.85 h prior to the start of absorption
[b] Iterative analysis yielded a very large rate constant for the first phase of absorption, corresponding to a very small or essentially zero half-life value

had elapsed since drug administration. At that point the study terminated, and subsequent treatment was administered by the attending physician according to clinical needs.

Plasma was separated and frozen until the time of assay. Plasma concentrations of CDX and DMCDX were determined by spectrophotofluorometric assay [13, 18, 20].

Differences between oral and i.m. administration between subject groups receiving the same dose were assessed by calculating across-subject mean plasma concentrations of CDX and DMCDX at corresponding points in time. Differences in plasma levels were tested using Student's unpaired two-tailed *t*-test [21].

Results

Study One

All subjects complained of moderate to severe local pain associated with the intramuscular injection. The injection caused elevations in serum creatinine phosphokinase concentrations in the individuals in whom this was measured [11].

Highest measured CDX concentrations following oral administration averaged 1.65 μg/ml, and were attained an average of 2.3 h after dosage (Table 1). The blood concentration curves in all subjects were adequately described by functions having the form of Equation (1) or (2) (Fig. 1). The mean apparent first-order absorption half-life was 0.71 h (Table 1). After i.m. injection, however, highest measured levels averaged only 0.87 μg/ml and were reached at an average of 7.6 h after dosing. Both of these values were significantly lower and later, respectively, than those observed in the same subjects following oral administration of the same dose. Two phases of absorption were observed in nine of the fourteen subjects (Fig. 1); the initial rapid phase in these individuals proceeded with a mean apparent half-life of 9.0 min (Table 1). In the other five subjects, a single phase of absorption was evident, although in one subject (JMK) a lag time of 0.85 h elapsed prior to the start of absorption (Table 1). The mean absorption half-life for all 14 subjects following i.m. injection (using the second or dominant phase for the 9 "biphasic" individuals) averaged 3.39 h, which was significantly longer than that observed following oral administration of the same dose (Table 1). Thus i.m.

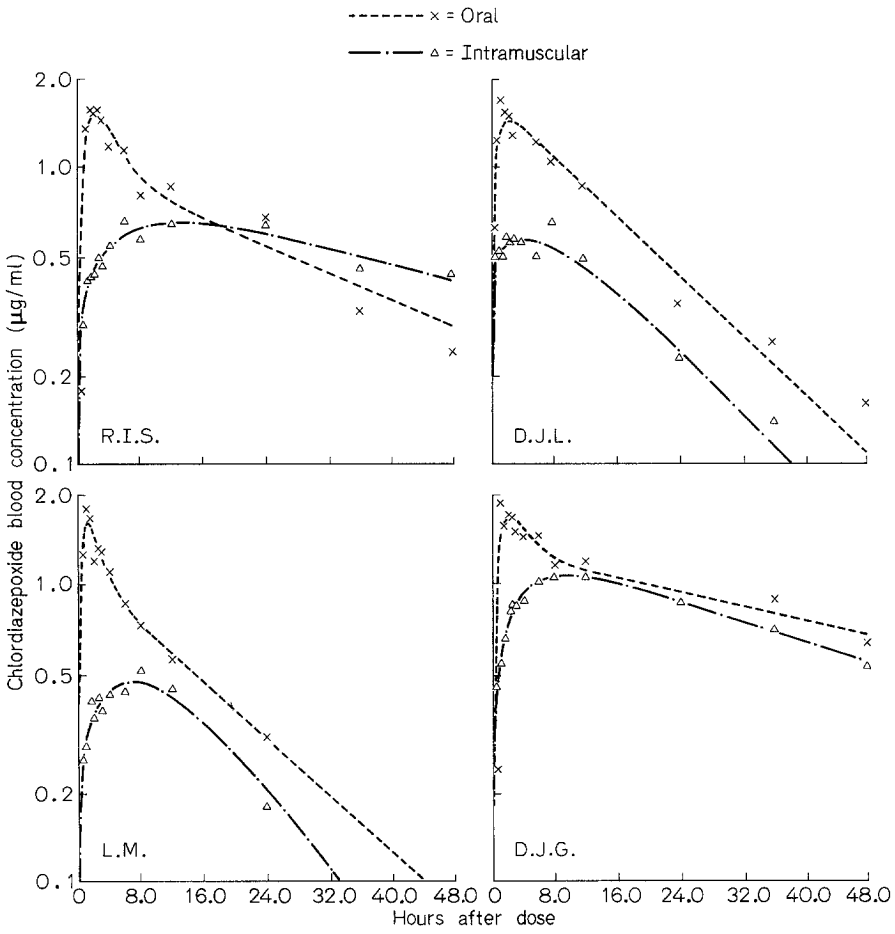
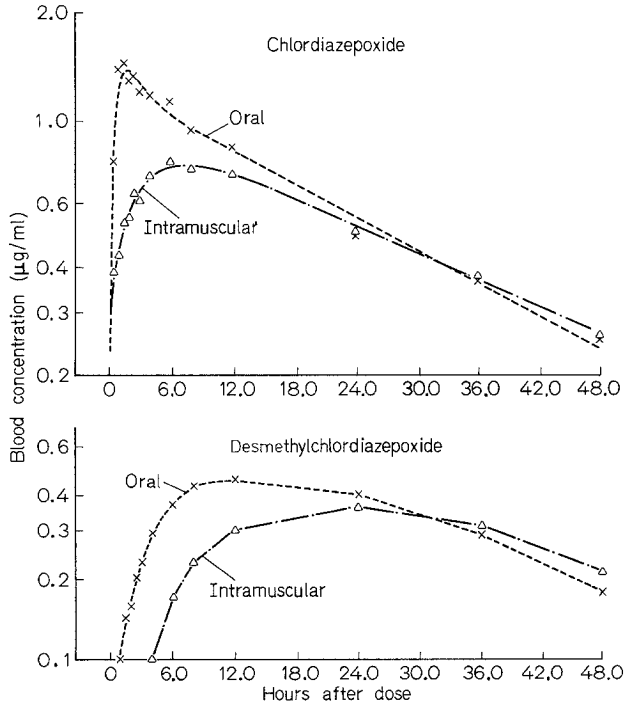


Fig. 1. Blood concentrations of chlordiazepoxide, together with calculated pharmacokinetic functions of best fit, in 4 subjects following oral and intramuscular administration of 50 mg of chlordiazepoxide hydrochloride



CDX · HCl is absorbed more slowly than after oral administration (Fig. 1 and 2). In most subjects, absorption proceeds as a biphasic process, consistent with precipitation at the injection site.

The absolute systemic availability of oral CDX · HCl relative to intravenous administration averaged 102.4%, which was not significantly different from 100%. Following i.m. CDX · HCl, systemic availability averaged 86.1% of the corresponding intravenous value; the difference between this value and 100% availability approached but did not reach statistical significance ($t = 1.79$, $p < 0.1$) (Fig. 3), as did the difference between oral and i.m. CDX · HCl (paired $t = 1.99$, $p < 0.1$). Following oral CDX · HCl, the area under the 72-hour blood concentration curve for DMCDX averaged 115.7% of the intravenous value. After i.m. injection, the area under the

Fig. 2. Mean blood concentrations of chlordiazepoxide and desmethylchlordiazepoxide following oral and intramuscular administration of 50 mg of chlordiazepoxide hydrochloride. Each point is the mean value for all 14 subjects at the corresponding time. Also shown are the calculated pharmacokinetic functions of best fit for oral and intramuscular chlordiazepoxide

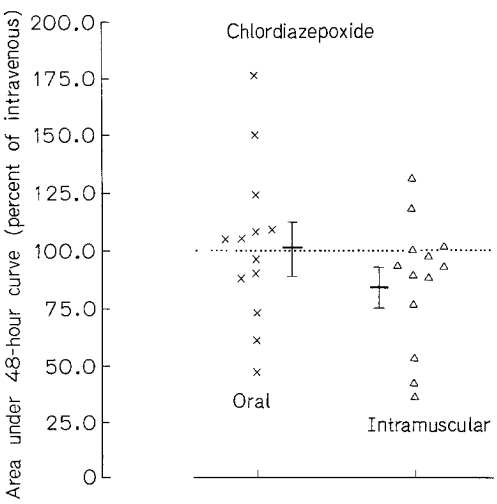


Fig. 3. Area under the 48-hour blood concentration curve for chlordiazepoxide following oral and intramuscular administration of 50 mg of chlordiazepoxide hydrochloride. Each value is expressed as a percentage of the corresponding intravenous value in the same subject. Also shown are mean (±SE) values for all 13 subjects in each group

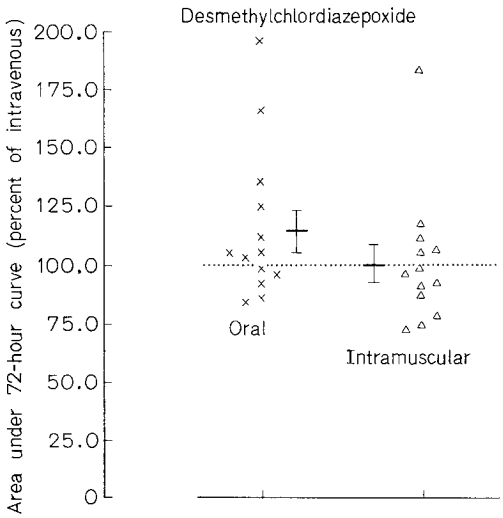


Fig. 4. Area under the 72-hour blood concentration curve for desmethylchlordiazepoxide following oral and intramuscular administration of 50 mg of chlordiazepoxide hydrochloride. Each value is expressed as a percentage of the corresponding intravenous value in the same subject. Also shown are mean (±SE) values for all 13 subjects in each group

Table 2. Characteristics of patients in study two

Characteristics	Mean (±SE) for Each Treatment Group				Value of F from One-Way ANOVA[a]
	100 mg p.o.	100 mg i.m.	50 mg p.o.	50 mg i.m.	
Number of patients	6	7	7	8	–
Age (years)	37.3 (±4.2)	42.9 (±3.2)	44.4 (±6.2)	38.5 (±3.1)	0.62
Weight (kg)	72.9 (±5.7)	63.0 (±3.5)	56.9 (±3.0)	70.5 (±4.0)	2.50
Serum concentrations:					
Albumin (g/100 ml)	3.6 (±0.2)	3.6 (±0.3)	4.0 (±0.2)	4.2 (±0.3)	1.07
Total bilirubin (mg/100 ml)	1.08 (±0.22)	1.06 (±0.28)	0.96 (±0.16)	1.13 (±0.12)	0.14
Creatinine (mg/100 ml)	0.88 (±0.04)	0.90 (±0.11)	0.94 (±0.02)	0.88 (±0.04)	0.24
Alkaline phosphatase (IU/ml)	40.0 (±6.6)	33.6 (±1.4)	34.6 (±5.2)	33.1 (±2.9)	0.52
SGOT (IU/ml)	48.0 (±13.6)	98.6 (±41.5)	27.1 (±4.4)	37.6 (±6.7)	2.14

[a] For all values, $p > 0.1$

72-hour DMCDX curve averaged 100.7% of the intravenous value. Neither of these values was significantly different from 100%, nor from each other (Fig. 4). Thus absorption of both oral and i.m. CDX was essentially complete on the average.

Study Two

One-way analysis of variance indicated that the four treatment groups were comparable with respect to the variables under study (Table 2). In all 4 groups, mean values of total bilirubin, alkaline phosphatase, and SGOT were near or above the usual upper limits of normal, consistent with mild alcoholic hepatitis (Table 2).

During the 5-hour interval following the 100-mg dose of CDX · HCl, mean plasma concentrations of CDX after oral dosage were significantly higher at all corresponding points in time than the levels measured after i.m. injection of the same dose ($p < 0.05$) (Fig. 5). Mean levels of DMCDX also were significantly higher at all corresponding points in time following oral administration than after i.m. injection. The results were similar following the 50-mg dose (Fig. 6). Plasma concentrations of CDX were significantly higher at all corresponding times after oral dosage than after i.m. injection. Differences in plasma levels of DMCDX at corresponding points in time also were higher following oral administration, but the differences were of borderline significance due to the large individual variation. Thus i.m. injection of CDX · HCl during acute alcohol withdrawal

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