Eur J Clin Pharmacol (1984) 26: 55–59

European Journal of Clinical Pharmacology

Disposition of Clotiazepam: Influence of Age, Sex, Oral Contraceptives, Cimetidine, Isoniazid and Ethanol*

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Summary. Factors influencing the disposition of clotiazepam in man were evaluated in a series of pharmacokinetic studies in healthy volunteers given a single 5 mg dose. Old age caused an increased volume of distribution of clotiazepam in women, and its clearance tended to be reduced in elderly men. Use of oral contraceptives, cimetidine, isoniazid or a single dose of ethanol had no significant effect on the kinetics of clotiazepam. Although clotiazepam is biotransformed by microsomal oxidation, its clearance appears to be relatively uninfluenced by factors known to alter the clearance of other oxidized benzodiazepines.

Key words: clotiazepam, drug interaction; cimetidine, isoniazid, ethanol, pharmacokinetic, oral contraceptives, age

Clotiazepam is a thienodiazepine derivative used in clinical practice as an antianxiety agent. Its major metabolic pathway in humans involves the simultaneous oxidative biotransformations of N-demethylation and hydroxylation, yielding pharmacologically active metabolic products [1]. The present study is an evaluation of the pharmacokinetic profile of single oral doses of clotiazepam in healthy human volunteers, and the effect of age and sex on the disposition kinetics of the drug. The influence of oral contraceptive steroids, cimetidine, isoniazid, and ethanol coadministration on the kinetics of single doses of clotiazepam was also examined.

* The work forms part of the doctoral thesis of H. Grehl, University of Bonn, Faculty of Medicine, 1984

Materials and Methods

Study of Age and Sex

Eleven healthy male and 18 healthy female volunteers participated after giving their informed consent (Table 1). Their ages ranged from 22 to 82 years. All the subjects were healthy, active, ambulant adults, with no history of medical disease and who were not taking any other medication.

All subjects received a single oral dose of 5 mg clotiazepam (Trecalmo, Tropon Arzneimittel) with 100–200 ml of tap water after an overnight fast. They remained fasting for 3 h after the dose. Venous blood samples were collected in additive free tubes prior to the dose and after 5, 15, 30 and 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15, 24, 30, and 36 h. Blood samples were allowed to clot, and the serum separated and frozen until assayed.

Oral Contraceptive Interaction Study

Six healthy female volunteers (Table 2), who had been users of low-dose estrogen oral contraceptive steroids (containing no more than 50 μg ethinyl estradiol or its equivalent) for at least 3 months prior to the study, participated after giving their informed consent. They received a single oral dose of clotiazepam and blood was sampled as described above.

Drug Interaction Study

Eleven healthy volunteers participated in a 4-way, single dose crossover study. At least one week elapsed between trials, the sequence of which was randomized. In each trial, subjects received a single 5 mg oral dose of clotiazepam and blood samples

Table 1. Clotiazepam kinetics in relation to age and sex

	Men ($n=11$)		Women ($n=18$)		All subjects ($n=29$)	
	Mean (range)	Correlation with Age	Mean (range)	Correlation with Age	Mean (range)	Correlation with Age
Subject characteristics						
Age [years]	43 (25–82)		46 (22–80)		45 (22–82)	
Weight [kg]	77 (65–87)	0.17 (NS)	61 (43–85)	0.52 ($p<0.05$)	67 (43–87)	0.28 (NS)
Kinetic variables of clotiazepam						
Volume of distribution [l/kg]	2.01 (0.88–3.19)	0.18 (NS)	2.75 (1.10–5.34)	0.57 ($p<0.02$)	2.47 (0.88–5.34)	0.47 ($p<0.02$)
Elimination half-life [h]	8.0 (2.5–12.1)	0.36 (NS)	8.1 (3.5–12.1)	0.56 ($p<0.02$)	8.1 (2.5–12.1)	0.46 ($p<0.01$)
Total clearance [ml/min/kg]	3.01 (2.07–4.49)	−0.31 (NS)	3.91 (2.22–7.02)	0.26 (NS)	3.59 (2.07–7.02)	0.14 (NS)

Table 2. Effect of low-dose estrogen oral contraceptives (o.c.) on clotiazepam kinetics

	Mean (range) for		Student's t
	Controls	o.c. Users	
Subject characteristics			
Number	8	6	
Age [years]	24 (23–27)	23 (20–27)	0.95 (NS)
Weight [kg]	55 (43–66)	65 (53–77)	2.48 ($p<0.05$)
Kinetic variables of clotiazepam			
Volume of distribution [l/kg]	2.08 (1.10–2.75)	3.44 (2.26–4.61)	2.47 ($p<0.05$)
Elimination half-life [h]	7.0 (3.5–9.4)	15.9 (5.8–46.2)	1.65 (NS)
Total clearance [ml/min/kg]	3.59 (2.22–6.40)	3.61 (1.15–5.84)	0.05 (NS)

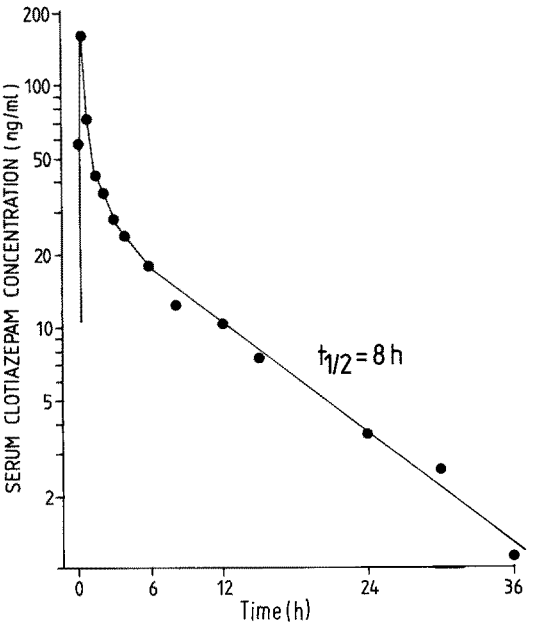

Fig. 1. Serum clotiazepam concentrations in a representative colunteer

were collected as described above. The four modes of administration were:

a) Control, without coadministration of drug.
b) During concurrent administration of cimetidine 1.0 g daily in four divided doses, beginning three days prior to the clotiazepam and continuing for the duration of the study.
c) During concurrent administration of isoniazid 90 mg (of base as the glucuronide salt) twice daily beginning 3 days prior to the clotiazepam and continuing for the duration of the study.
d) Concurrently with a single 60 ml dose of commercial vodka (80 proof).

Analysis of Samples and Pharmacokinetic Methods

Clotiazepam in the serum samples was determined by electron-capture gas-liquid chromatography [1]. Clotiazepam metabolites were not quantitated, since a previous study had shown that they were formed and disappeared in parallel with the parent compound [1].

The apparent elimination half-life of clotiazepam was determined from the slope (beta) of the terminal log-linear portion of the serum concentration curve (Fig. 1). The area under the curve up to the final detectable serum concentration was calculated by the trapezoidal method. To this was added the residual area extrapolated to infinity, determined as the final detectable concentration divided by beta, yielding the total area under the serum concentration curve (AUC). The total clearance of clotiazepam was calculated as dose/AUC, assuming complete systemic availability. The volume of distribution (V_d) was calculated as clearance/beta.

The influence of age and sex on the kinetic variables of clotiazepam were evaluated by linear regression analysis and Student's t-test. Changes in clotiazepam kinetics attributable to oral contraceptives were evaluated by comparison of kinetic variables in the oral contraceptive group with those in a group of

Table 3. Clotiazepam kinetics in the drug interaction study

	Mean (range)				F (2-way ANOVA)
	Control	w/Cimetidine	w/Isoniazid	w/Ethanol	
Volume of distribution [l/kg]	1.94 (0.88– 2.84)	1.59 (0.71– 2.72)	2.49 (1.48– 5.05)	1.75 (0.56– 2.53)	3.52 ($p<0.05$)
Elimination half-life [h]	7.2 (2.5 –12.0)	7.0 (2.0 –11.0)	8.7 (4.0 –18.2)	7.3 (2.4 –12.9)	0.47 (NS)
Total clearance [ml/min/kg]	3.13 (2.13– 4.93)	2.98 (1.90– 5.10)	3.66 (1.92– 7.20)	2.95 (1.80– 3.97)	1.43 (NS)

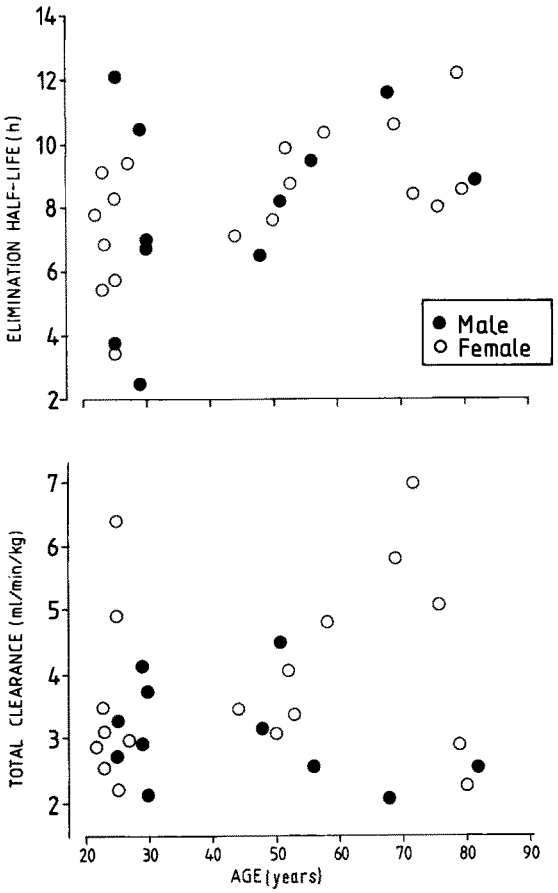

Fig. 2. Relation of age to clotiazepam elimination half-life (above) and total clearance (below). See Table 1 for statistical analysis

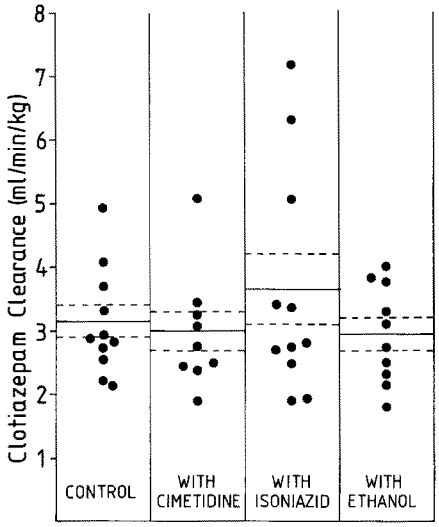

Fig. 3. Clotiazepam clearance in the control state and during coadministration of cimetidine, isoniazid and ethanol. Individual and mean (±SEM) values are shown. See Table 3 for statistical analysis

age-matched control women not receiving oral contraceptives. The influence of cimetidine, isoniazid, and ethanol on clotiazepam disposition in the four-way crossover study was assessed by analysis of variance.

Results

Influence of Age and Sex

Clotiazepam V_d was greater, although not significantly so, in women than in men, and increased with age in women (Table 1). Although age did not significantly influence clearance in either group, the latter tended to decline with age in the male subjects (Table 1; Fig. 2). The elimination half-life increased with age in all subjects (Table 1; Fig. 2).

Influence of Oral Contraceptives

Oral contraceptive recipients and controls were well matched for age (Table 2). The contraceptive group was significantly heavier than controls and also had a significantly larger V_d for clotiazepam. The change in clotiazepam distribution in the contraceptive group resulted in a non-significant prolongation of the elimination half-life. This was mainly attributable to one female with an unusually long half-life of 46 h. Mean values of total metabolic clearance in the control and contraceptive groups were almost identical.

Drug Interactions

Analysis of variance indicated that clotiazepam V_d varied significantly in the treatment groups (Table 3). However, the elimination half-life and total clear-

ance of clotiazepam were not significantly influenced by coadministration of cimetidine, isoniazid or ethanol (Table 3; Fig. 3).

Discussion

The influence of age and sex on the pharmacokinetics of clotiazepam is consistent with that observed for other lipophilic benzodiazepines, such as diazepam and desmethyldiazepam [2–5]. The weight-corrected V_d of clotiazepam was greater in women than in men, probably due to the greater fraction of adipose tissue relative to total body weight associated with female gender. Furthermore, V_d increased with age in women, which may be explained both by the age-related increase in total body weight (probably consisting mainly of adipose tissue) in the female study population, together with the well-documented change in body composition with age regardless of total body weight [6]. Although age-related changes in clotiazepam clearance did not attain statistical significance, clearance tended to decline with age in men, whereas clearance if anything increased with age in women. Again, this is consistent with previous studies of oxidized drugs in other study populations in demonstrating an age-related decrement in drug oxidizing capacity which is far more striking in men than in women [2]. Although the elimination half-life of clotiazepam increased with age in the female population, this was due to the increased V_d rather than to a change in clearance.

The estrogen component of oral contraceptive steroids leads to impaired capacity to biotransform a number of drugs metabolized by hepatic microsomal oxidation [7–10]. Although clotiazepam is similarly biotransformed by hepatic oxidation, its total clearance did not differ significantly between a series of oral contraceptive users and age-matched women not taking oral contraceptives. The weight-corrected V_d of clotiazepam was greater in contraceptive users than in controls, leading to prolongation of its half-life in the contraceptive group, but this was probably due to the higher total body weight and greater relative amount of adipose tissue in the women taking contraceptive steroids.

The H_2-receptor antagonist cimetidine has the additional pharmacological property of impairing hepatic microsomal oxidizing capacity. Studies from our laboratory and elsewhere have consistently indicated that coadministration of cimetidine impairs the metabolic clearance of oxidized benzodiazepines, including chlordiazepoxide, diazepam, desmethyldiazepam, alprazolam, and triazolam [11–15]. The antituberculous agent isoniazid also impairs microsomal oxidative enzymes, and in previous studies it has been shown to diminish the metabolic clearance of diazepam [16] and triazolam [17]. In the present study, however, neither cimetidine nor isoniazid had any measurable influence on the metabolic clearance of clotiazepam. Finally, the disposition of clotiazepam was not altered by coadministration of a typical "social cocktail". The influence of coadministration of ethanol on the pharmacokinetics of benzodiazepines has been very variable, depending on the specific study design and circumstances of administration [18–20].

Thus, the pharmacokinetic properties of the thienodiazepine derivative clotiazepam are altered only to a small degree in old age, and are not significantly changed by a number of factors known to influence hepatic drug oxidizing capacity. Further studies are needed to establish the mechanism of the apparent resistance of the oxidative metabolism of clotiazepam to the inhibiting effects of estrogens, cimetidine and isoniazid.

Acknowledgements. We are grateful for the assistance of Ms A. Locniskar, A. M. Zumbo, R. Matlis, E. Moritz and M. Linden, and Dr. R. M. Arendt.

The study was supported in part by Grant 10/6-3 from the Deutsche Forschungsgemeinschaft, by Grant MH-34223 from the United States Public Health Service, and by the Arbeitskreis Alkohol, Bonn, FRG.

References

1. Arendt R, Ochs HR, Greenblatt DJ (1982) Electron-capture GLC analysis of the thienodiazepine clotiazepam: Preliminary pharmacokinetic studies. Arzneimittelforsch 32: 453–455
2. Greenblatt DJ, Sellers EM, Shader RI (1982) Drug disposition in old age. N Engl J Med 306: 1081–1088
3. Greenblatt DJ, Allen MD, Harmatz JS, Shader RI (1980) Diazepam disposition determinants. Clin Pharmacol Ther 27: 301–312
4. Shader RI, Greenblatt DJ, Ciraulo DA, Divoll M, Harmatz JS, Georgotas A (1981) Effect of age and sex on disposition of desmethyldiazepam formed from its precursor clorazepate. Psychopharmacology 75: 193–197
5. Ochs HR, Greenblatt DJ, Divoll M, Abernethy DR, Feyerabend H, Dengler HJ (1981) Diazepam kinetics in relation to age and sex. Pharmacology 23: 24–30
6. Greenblatt DJ, Divoll M, Abernethy DR, Harmatz JS, Shader RI (1982) Antipyrine kinetics in the elderly: prediction of age-related changes in benzodiazepine oxidizing capacity. J Pharmacol Exp Ther 220: 120–126
7. Abernethy DR, Greenblatt DJ (1981) Impairment of antipyrine metabolism by low-dose oral contraceptive steroids. Clin Pharmacol Ther 29: 106–110
8. Abernethy DR, Greenblatt DJ, Divoll M, Arendt R, Ochs HR, Shader RI (1982) Impairment of diazepam metabolism by

low-dose estrogen oral contraceptive steroids. N Engl J Med 306: 791–792
9. Patwardhan RV, Desmond PV, Johnson RF, Schenker S (1980) Impaired elimination of caffeine by oral contraceptive steroids. J Lab Clin Med 95: 603–608
10. Homeida M, Halliwell M, Branch RA (1978) Effects of an oral contraceptive on hepatic size and antipyrine metabolism in premenopausal women. Clin Pharmacol Ther 24: 228–232
11. Desmond PV, Patwardhan RV, Schenker S, Speeg KV (1980) Cimetidine impairs elimination of chlordiazepoxide (Librium) in man. Ann Int Med 93: 266–268
12. Klotz U, Reimann I (1980) Influence of cimetidine on the pharmacokinetics of desmethyldiazepam and oxazepam. Eur J Clin Pharmacol 18: 517–520
13. Abernethy DR, Greenblatt DJ, Divoll M, Ameer B, Shader RI (1983) Differential effect of cimetidine on drug oxidation (antipyrine and diazepam) versus conjugation (acetaminophen and lorazepam): prevention of acetaminophen toxicity by cimetidine. J Pharmacol Exp Ther 224: 508–513
14. Abernethy DR, Greenblatt DJ, Divoll M, Moschitto LJ, Harmatz JS, Shader RI (1983) Interaction of cimetidine with the triazolo benzodiazepines alprazolam and triazolam. Psychopharmacol 80: 275–278)
15. Divoll M, Greenblatt DJ, Abernethy DR, Shader RI (1982) Cimetidine impairs clearance of antipyrine and desmethyldiazepam in the elderly. J Am Geriatr Soc 30: 684–689
16. Ochs HR, Greenblatt DJ, Roberts G-M, Dengler HJ (1981) Diazepam interaction with antituberculosis drugs. Clin Pharmacol Ther 29: 671–678
17. Ochs HR, Greenblatt DJ, Knüchel M (1983) Differential effect of isoniazid on triazolam oxidation and oxazepam conjugation. Br J Clin Pharmacol 16: 743–746
18. Sellers EM, Busto U (1982) Benzodiazepines and ethanol. J Clin Psychopharmacol 2: 249–262
19. Ochs HR, Greenblatt DJ, Arendt RM, Hübbel W, Shader RI (1983) Pharmacokinetic noninteraction of triazolam and ethanol. J Clin Psychopharmacol (in press)
20. Divoll M, Greenblatt DJ (1981) Alcohol does not enhance diazepam absorption. Pharmacology 22: 263–268

Received: June 6, 1983
accepted in revised form: July 1, 1983

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