Br. J. clin. Pharmac. (1985), **19**, 51–57

Interaction of propoxyphene with diazepam, alprazolam and lorazepam

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1 Healthy volunteers received single doses of three benzodiazepines (diazepam, 10 mg i.v.; alprazolam, 1.0 mg orally; lorazepam, 2 mg i.v.) on two occasions in random sequence. One trial was a control; for the other, subjects ingested propoxyphene, 65 mg every 6 h, for the duration of the benzodiazepine study. The kinetics of each benzodiazepine were determined from multiple plasma concentrations measured following each dose.

2 For diazepam, propoxyphene produced a small and statistically insignificant prolongation of elimination half-life (43 *vs* 38 h) and reduction of total clearance (0.41 *vs* 0.47 ml min^{-1} kg^{-1}).

3 Propoxyphene significantly prolonged alprazolam half-life (18 *vs* 12 h, $P < 0.005$) and reduced total clearance (0.8 *vs* 1.3 ml min^{-1} kg^{-1}, $P < 0.005$).

4 Propoxyphene had no apparent influence on lorazepam half-life (13.4 *vs* 13.5 h) or clearance (1.5 *vs* 1.4 ml min^{-1} kg^{-1}).

5 Thus propoxyphene significantly impairs the clearance of alprazolam, biotransformed mainly by the oxidative reaction of aliphatic hydroxylation. Propoxyphene has far less effect on the oxidation of diazepam by *N*-demethylation, and has no apparent influence on lorazepam conjugation.

Keywords propoxyphene diazepam lorazepam alprazolam interaction

Introduction

Propoxyphene is extensively used in clinical practice as an analgesic agent (Miller, 1979). Previous studies have suggested that propoxyphene has the capacity to inhibit hepatic microsomal drug oxidizing capacity both in animals and humans (Abernethy *et al.*, 1982a; Peterson *et al.*, 1979; Kutt, 1971; Dam *et al.*, 1979; Hansen *et al.*, 1980). This pharmacokinetic interaction may cause impaired clearance of other coadministered drugs that are metabolized by microsomal oxidation, leading to elevated steady-state plasma concentrations and the potential for clinical toxicity (Abernethy *et al.*, 1982a). Since many individuals who use propoxyphene for the treatment of pain concurrently take benzodiazepine derivatives due to anxiety or sleep disorders, there is a need to evaluate the potential pharmacokinetic interaction of propoxyphene with benzodiazepines. The present study assessed the effect of propoxyphene treatment on the pharmacokinetics of diazepam and alprazolam, two benzodiazepines metabolized by microsomal oxidation (Greenblatt *et al.*, 1983a, 1983b). We also evaluated the influence of propoxyphene on the kinetics of lorazepam, a benzodiazepine meta-

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bolized principally by glucuronide conjugation (Greenblatt, 1981; Greenblatt *et al.*, 1983b).

Methods

Subjects and design

Fourteen healthy male and female volunteers aged 22 to 47 years participated after giving written informed consent. All were healthy, active, ambulatory adults without medical disease and receiving no medications.

Subjects participated in one or more pairs of single-dose two-way crossover trials of diazepam, alprazolam, or lorazepam. On one occasion, subjects received a single dose of the benzodiazepine in the control state, without drug coadministration. For the other trial, subjects began ingesting propoxyphene hydrochloride, 65 mg every 6 h, beginning 12 h prior to and continuing for the duration of the benzodiazepine pharmacokinetic study. The sequence of the two trials was randomized.

Diazepam study

Six of the subjects (four male and two female, aged 22 to 45 years) received a single 10-mg dose of diazepam by 30 s intravenous injection on two occasions: once in the drug-free control state, and again during coadministration of propoxyphene as described above. At least 2 weeks elapsed between trials. Venous blood samples were drawn into heparinized tubes prior to the dose, just after diazepam administration, and at the following post-dosage times: 5, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h. Thereafter samples were drawn every 24 to 48 h for a total of 7 days (Figure 1).

Blood samples were centrifuged, and the plasma separated and frozen until the time of assay. Concentrations of diazepam and its major metabolite, desmethyldiazepam, in each sample were determined by gas chromatography with electron capture detection (Greenblatt *et al.*, 1980). All samples from a given subject's pair of trials were extracted and analyzed on the same day using the same calibration standards.

Using iterative nonlinear least squares regression techniques, plasma concentrations were fitted to a linear sum of two or three exponential terms (Greenblatt *et al.*, 1979). Coefficients and exponents from the fitted function were used to determine diazepam elimination half-life, volume of distribution by the area method, and total clearance. Differences between control and propoxyphene treatment conditions were evaluated using Student's paired *t*-test with $P < 0.05$ taken as the criteria for statistical significance.

Alprazolam study

Because a parenteral formulation of alprazolam is not available for human use, the alprazolam

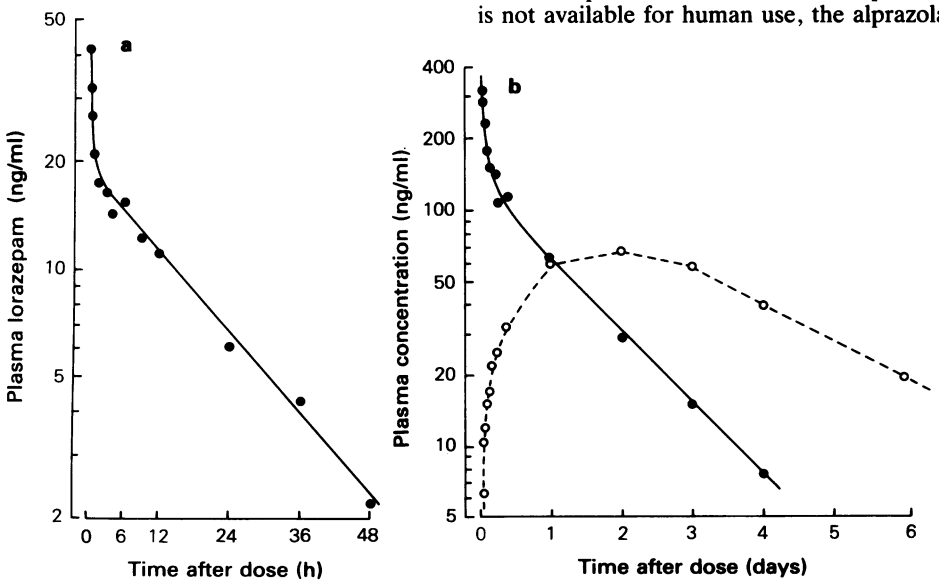

Figure 1 (a) Plasma lorazepam concentrations after a 2 mg intravenous dose of lorazepam administered to a volunteer subject in the control state. (b) Plasma diazepam (●) and desmethyldiazepam (○) concentrations after a 10 mg intravenous dose of diazepam administered to a volunteer subject in the control state.

studies were performed using the oral dosage form. Eight of the subjects (six female and two male, aged 22 to 39 years) received a single 1 mg oral dose of alprazolam following an overnight fast on two occasions: once in the drug-free control state, and again during coadministration of propoxyphene as described above. At least 1 week elapsed between trials. Subjects fasted overnight prior to and for 3 h after drug administration. Venous blood samples were drawn into heparinized tubes prior to the dose and at the following post-dosage times: 5, 10, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32, and 48 h (Figure 2).

Blood samples were centrifuged, and the plasma separated and frozen until the time of assay. Concentrations of alprazolam in all samples were determined by gas chromatography with electron capture detection (Greenblatt *et al.*, 1981, 1983c). All samples from a given subject's pair of trials were extracted and analyzed on the same day using the same calibration standards.

The elimination half-life of alprazolam was determined from the slope (λ_z) of the terminal log-linear portion of the plasma concentration curve. Area under the curve (AUC) up to the final detectable plasma concentration was determined using the trapezoidal method and extrapolated to infinity by adding the final plasma concentration divided by λ_z. Apparent oral clearance was calculated as dose/AUC (assuming complete systemic availability), and apparent volume of distribution as clearance/λ_z. Differences between control and propoxypyhene treatment conditions were statistically evaluated as described above.

Lorazepam study

Five of the subjects (four male and one female, aged 25 to 47 years) received a single 2-mg intravenous dose of lorazepam on two occasions: once in the drug-free control state, and again during coadministration of propoxyphene as described above. At least 1 week elapsed between trials. Venous blood samples were drawn into heparinized tubes prior to the dose, just after lorazepam administration, and at the following post-dosage times: 5, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32, and 48 h (Figure 1). Blood samples were centrifuged, and the plasma separated and frozen until the time of assay. Concentrations of lorazepam in all plasma samples were determined by electron-capture gas-liquid chromatography (Greenblatt, 1981; Greenblatt *et al.*, 1978). All samples from a given subject's pair of trials were extracted and analyzed on the same day using the same calibration standards.

As described above for diazepam, plasma lorazepam concentrations were analyzed by nonlinear least squares regression techniques to determine volume of distribution, elimination half-life, and total clearance. Differences between control and propoxyphene treatment conditions were statistically assessed as described above.

Results

Diazepam study

Coadministration of propoxyphene had no influence on diazepam volume of distribution.

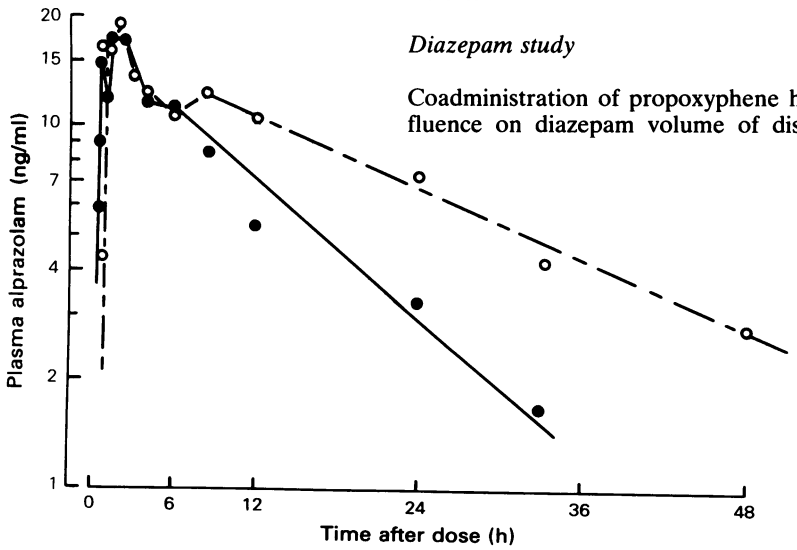

Figure 2 Plasma alprazolam concentrations in a volunteer subject after a 1.0 mg oral dose administered to a subject in the control state (•) and during propoxyphene (○) coadministration.

Table 1 Influence of propoxyphene on the kinetics of diazepam, alprazolam and lorazepam (mean ± s.e. mean values)

	Control	*With propoxyphene*	*Student's*-t
Diazepam n = 6			
Volume of distribution (l/kg)	1.36 (± 0.32)	1.41 (± 0.36)	0.95 (NS)
Elimination half-life (h)	37.6 (± 11.5)	42.8 (± 11.9)	1.08 (NS)
Total clearance (ml min^{-1} kg^{-1})	0.47 (± 0.05)	0.41 (± 0.04)	1.42 (NS)
Alprazolam (n = 8)			
Peak plasma concentration (ng/ml)	20.0 (± 2.2)	18.7 (± 2.2)	0.70 (NS)
Time of peak (h after dose)	0.64 (± 0.09)	2.22 (0.9)	1.75 (NS)
Apparent volume of distribution (l/kg)	1.23 (± 0.08)	1.24 (± 0.11)	0.10 (NS)
Elimination half-life (h)	11.6 (± 1.1)	18.3 (± 1.3)	5.00 ($P < 0.005$)
Oral clearance (ml min^{-1} kg^{-1})	1.30 (± 0.16)	0.81 (± 0.09)	5.45 ($P < 0.005$)
Lorazepam (n = 5)			
Volume of distribution (l/kg)	1.58 (± 0.06)	1.61 (± 0.10)	0.33 (NS)
Elimination half-life (h)	13.5 (± 1.6)	13.4 (± 0.07)	0.07 (NS)
Total clearance (ml min^{-1} kg^{-1})	1.36 (± 0.14)	1.50 (± 0.13)	0.86 (NS)

Diazepam elimination half-life was longer during the propoxyphene trial compared to the control trial and total metabolic clearance was less (Table 1) but the differences were not statistically significant (Figure 3). Disappearance of diazepam was always mirrored by formation of the active metabolite, desmethyldiazepam (Figure 1), but the duration of sampling was not sufficient for formal pharmacokinetic analysis of the metabolite.

Alprazolam study

Propoxyphene had no significant effect on the peak plasma alprazolam concentration. The time of peak concentration was delayed from 0.6 h after dosage in the control state to 2.2 h during propoxyphene treatment, but the difference was not significant.

Propoxyphene did not alter alprazolam apparent volume of distribution. However,

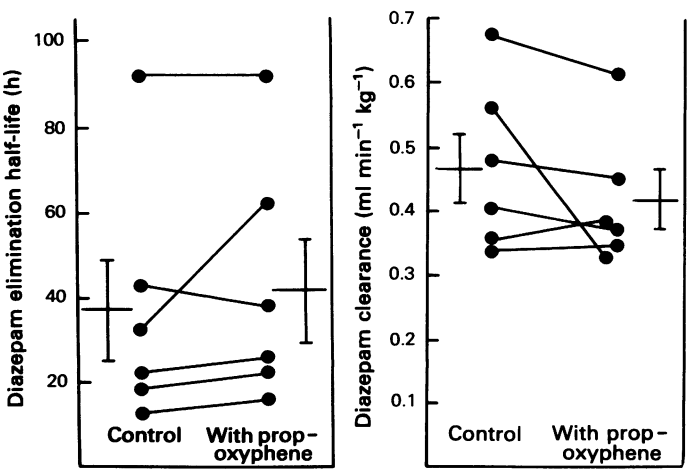

Figure 3 Diazepam elimination half-life and total clearance in the control state and during propoxyphene coadministration. Individual and mean (± s.e. mean) values are shown. See Table 1 for statistical analysis.

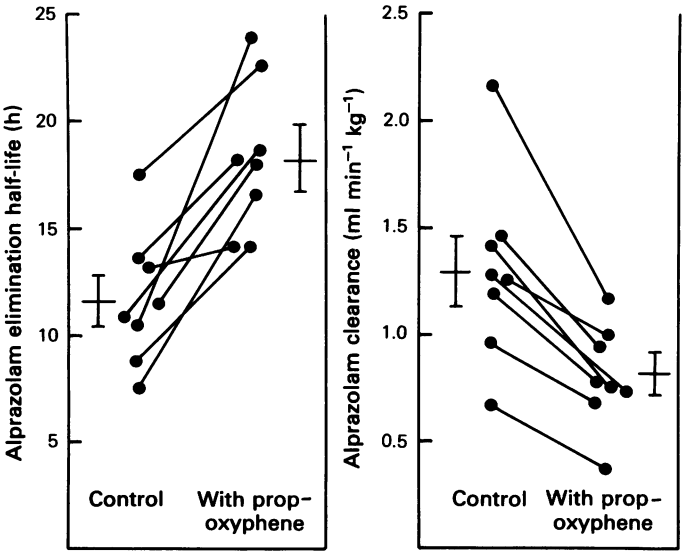

Figure 4 Alprazolam elimination half-life and total clearance in the control state and during propoxyphene coadministration. Individual and mean (± s.e. mean) values are shown. See Table 1 for statistical analysis.

propoxyphene significantly prolonged alprazolam elimination half-life from 11.6 to 18.3 h, and reduced total clearance from 1.3 to 0.8 ml min^{-1} kg^{-1} (Table 1, Figures 2 and 4).

Lorazepam study

Propoxyphene had no significant effect on any of the kinetic variables for lorazepam (Table 1). Volume of distribution, elimination half-life, and total clearance were essentially identical between trials (Figure 5).

Discussion

The present study evaluated the influence of propoxyphene coadministration on the pharmacokinetics of the oxidized benzodiazepines diazepam and alprazolam, and the conjugated benzodiazepine lorazepam. Diazepam is metabolized principally by the oxidative pathway of *N*-demethylation (Greenblatt *et al.*, 1983b), while alprazolam is metabolized by aliphatic hydroxylation (Greenblatt *et al.*, 1983a). In the case of diazepam, propoxyphene produced a

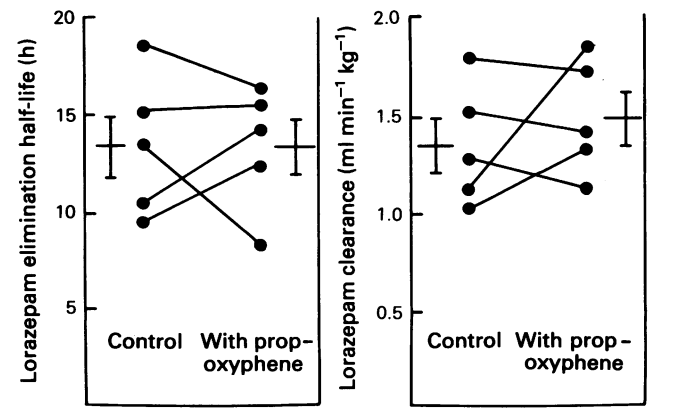

Figure 5 Lorazepam elimination half-life and total clearance in the control state and during propoxyphene coadministration. Individual and mean (± s.e. mean) values are shown. See Table 1 for statistical analysis.

small (approximately 13%) reduction of diazepam clearance following a single intravenous dose of diazepam but the difference did not reach statistical significance and could have occurred by chance. For alprazolam, on the other hand, propoxyphene caused a large and highly significant prolongation of half-life and impairment of total metabolic clearance. Thus, propoxyphene appears to have a greater capacity for impairment of alprazolam hydroxylation than of diazepam *N*-demethylation. Propoxyphene had no apparent effect on the clearance of the conjugated benzodiazepine lorazepam. This is consistent with prior studies suggesting that factors which may inhibit the capacity for microsomal drug oxidation generally have a minimal influence on the capacity for conjugation (Greenblatt *et al.*, 1982, 1983b; Abernethy *et al.*, 1982a, b; 1983a, b, c).

The clinical implications of the pharmacokinetic interaction or noninteraction of propoxyphene with benzodiazepines is not established by our study. Even without a pharmacokinetic interaction, propoxyphene and benzodiazepines share central depressant properties and therefore should be coadministered with suitable caution. A concurrent pharmacokinetic interaction, on the other hand, indicates a need for even further caution. Coadministration of propoxyphene and alprazolam, for example, would produce not only the expected pharmacodynamic interaction, but also whatever additional central depressant effect would be produced by the elevated steady-state plasma concentrations of alprazolam due to its impaired clearance.

We are grateful for the assistance of Ann Locniskar, Rita Matlis, and Christopher Willis.

This work was supported in part by Grant AM-MH-32050 and MH-34223 from the United States Public Health Service, and by a Grant-in-Aid from Wyeth Laboratories, Radnor, PA.

References

Abernethy, D. R., Greenblatt, D. J., Divoll, M., Ameer, B. & Shader, R. I. (1983a). Differential effect of cimetidine on drug oxidation (antipyrine and diazepam) versus conjugation (acetaminophen and lorazepam): Prevention of acetaminophen toxicity by cimetidine. *J. Pharmac. exp. Ther.*, **224**, 508–513.

Abernethy, D. R., Greenblatt, D. J., Divoll, M., Arendt, R., Ochs, H. R. & Shader, R. I. (1982b). Impairment of diazepam metabolism by low-dose estrogen oral contraceptive steroids. *New Engl. J. Med.*, **306**, 338–341.

Abernethy, D. R., Greenblatt, D. J., Divoll, M., Moschitto, L. J., Harmatz, J. S. & Shader, R. I. (1983c). Interaction of cimetidine with the triazolo benzodiazepines alprazolam and triazolam. *Psychopharmac.*, **80**, 178–180.

Abernethy, D. R., Greenblatt, D. J., Ochs, H. R., Weyers, D., Divoll, M., Harmatz, J. S. & Shader, R. I. (1983b). Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. *Clin. Pharmac. Ther.*, **33**, 628-632.

Abernethy, D. R., Greenblatt, D. J., Steel, K. & Shader, R. I. (1982a). Impairment of hepatic drug oxidation by propoxyphene. *Ann. Intern. Med.*, **97**, 223–224.

Dam, M., Kristensen, C. B., Hansen, B. S. & Christiansen, J. (1979). Interaction between carbamazepine and propoxyphene in man. *Acta Neurol. Scand.*, **56**, 603–607.

Greenblatt, D. J. (1981). Clinical pharmacokinetics of oxazepam and lorazepam. *Clin. Pharmacokin.*, **6**, 88–105.

Greenblatt, D. J., Divoll, M., Abernethy, D. R., Harmatz, J. S. & Shader, R. I. (1982). Antipyrine kinetics in the elderly: Prediction of age-related changes in benzodiazepine oxidizing capacity. *J. Pharmac. exp. Ther.*, **220**, 120–126.

Greenblatt, D. J., Divoll, M., Abernethy, D. R., Moschitto, L. J., Smith, R. B. & Shader, R. I. (1983a). Alprazolam kinetics in the elderly: Relation to antipyrine disposition. *Arch. gen. Psych.*, **40**, 287–290.

Greenblatt, D. J., Divoll, M., Abernethy, D. R., Ochs, H. R. & Shader, R. I. (1983b). Benzodiazepine kinetics: Implications for therapeutics and pharmacogeriatrics. *Drug Metab. Rev.*, **14**, 251–292.

Greenblatt, D. J., Divoll, M., Moschitto, L. J. & Shader, R. I. (1981). Electron-capture gas chromatographic analysis of the triazolobenzodiazepines alprazolam and triazolam. *J. Chromatogr.*, **225**, 202–207.

Greenblatt, D. J., Divoll, M. & Shader, R. I. (1983c). Automated gas chromatographic determination of plasma alprazolam concentrations. *J. clin. Psychopharmac.*, **3**, 366–368.

Greenblatt, D. J., Franke, K. & Shader, R. I. (1978). Analysis of lorazepam and its glucuronide metabolite by electron-capture gas-liquid chromatography: Use in pharmacokinetic studies of lorazepam. *J. Chromatogr.*, **146**, 311–320.

Greenblatt, D. J., Ochs, H. R. & Lloyd, B. L. (1980). Entry of diazepam and its major metabolite into cerebrospinal fluid. *Psychopharmac.*, **70**, 89–93.

Greenblatt, D. J., Shader, R. I., Franke, K., MacLaughlin, D. S., Harmatz, J. S., Allen, M. D., Werner, A. & Woo, E. (1979). Pharmacokinetics and bioavailability of intravenous, intramuscular and oral lorazepam in humans. *J. pharm. Sci.*, **68**, 57–63.

Hansen, B. S., Dam, M. & Brandt, J. (1980). Influence of dextropropoxyphene on steady state serum levels and protein binding of three antiepileptic drugs in man. *Acta Neurol. Scand.*, **61**, 357–367.

Kutt, H. (1971). Biochemical and genetic factors regulating dilantin metabolism in man. *Ann. N.Y. Acad. Sci.*, **179**, 704–722.

Miller, R. R. (1979). Propoxyphene: a review. In *Drug Therapy Reviews*, Volume 2, eds Miller, R. R. & Greenblatt, D. J., pp 218–257. New York: Elsevier.

Peterson, G. R., Hostetler, R. M., Lehman, T. & Covault, H. P. (1979). Acute inhibition of oxidative drug metabolism by propoxyphene (Darvon). *Biochem. Pharmac.*, **28**, 1783–1789.

(Received May 14, 1984, accepted September 14, 1984)