Noninteraction of Temazepam and Cimetidine

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Received October 6, 1982, from the *Division of Clinical Pharmacology, Departments of Psychiatry and Medicine, Tufts-New England Medical Center, Boston, MA 02111.* Accepted for publication February 11, 1983.

Abstract □ The possible kinetic interaction of the hypnotic temazepam and the H_2-receptor antagonist cimetidine was evaluated. Nine healthy male and female volunteers received a 30-mg oral dose of temazepam on two occasions in random sequence, separated by at least 1 week. On one occasion, temazepam was given in the otherwise drug-free state; on the other, temazepam was given with concurrent administration of cimetidine, 300 mg every 6 h. Mean pharmacokinetic parameters for temazepam in control *versus* cimetidine trials were: peak plasma concentration, 560 *versus* 498 ng/mL; time of peak concentration, 2.0 *versus* 2.1 h after the dose; volume of distribution, 1.30 *versus* 1.39 L/kg; elimination half-life, 9.9 *versus* 11.4 h; total clearance, 1.59 *versus* 1.60 mL/min/kg; free fraction of temazepam in plasma, 4.1 *versus* 3.8% unbound. Cimetidine has been shown to reduce the metabolic clearance of the benzodiazepines that are biotransformed by oxidative mechanisms. Temazepam, transformed by conjugation, appears unaffected by the coadministration of cimetidine.

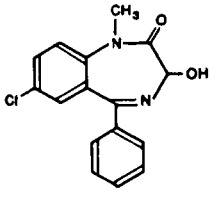
Keyphrases □ Temazepam—noninteraction with cimetidine, pharmacokinetics □ Cimetidine—noninteraction with temazepam, pharmacokinetics □ Pharmacokinetics—noninteraction of temazepam and cimetine

Temazepam (I) is a 3-hydroxybenzodiazepine derivative utilized in clinical practice as an hypnotic (1). Previous studies have suggested that the widely prescribed antiulcer agent cimetidine (2, 3) may have the additional capacity to impair hepatic microsomal oxidizing capacity and thereby impair the metabolic clearance of certain benzodiazepine derivatives when the two are administered together. Cimetidine coadministration reduces the metabolic clearance of the oxidatively biotransformed benzodiazepines chlordiazepoxide, diazepam, desmethyldiazepam, alprazolam, and triazolam (4–9). However, cimetidine has very little influence on the clearance of benzodiazepines transformed by glucuronide conjugation, including oxazepam and lorazepam (8–10). Since temazepam is also metabolized by glucoronide conjugation (11), the present study was undertaken to test the hypothesis that cimetidine coadministration would similarly have little effect on the metabolic clearance of temazepam.

EXPERIMENTAL

Subjects and Procedure—Nine healthy male and female volunteers, aged 21–67 years, participated after giving written informed consent. All were healthy, active, ambulatory adults with no evidence of medical disease and were taking no other medications.

All subjects received a 30-mg oral dose of temazepam[1] on two occasions in random sequence separated by at least 1 week. On one occasion, temazepam was given in the control state without coadministration of other drugs. For the other trial, temazepam was administered during concurrent treatment with cimetidine[2], 300 mg taken every 6 h beginning 12 h prior to temazepam dosage and continuing for the entire 48-h duration of the temazepam kinetic study.



TEMAZEPAM

After an overnight fast, a single 30-mg oral dose of temazepam was administered with 100–200 mL of tap water. Subjects were tested for an additional 3 h after the dose. Venous blood samples were drawn into heparinized tubes prior to temazepam administration and at the following postdosage times: 5, 10, 15, 30, and 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32, and 48 h. Blood samples were centrifuged and the plasma separated and frozen until the time of assay.

Analysis of Samples—Plasma concentrations of temazepam were determined by electron-capture GC using a previously described method (12) with minor modifications. The analytical instrument[3] was a gas chromatograph equipped with a 15-mCi electron-capture detector, an automatic sampler, and an electronic data processor–integrator. The column was coiled glass, 183 cm in length by 2-mm i.d., packed with 1% OV-17 on 80/100 Chromosorb WHP. The column temperature was 270°C, and the injection port and detection temperatures were 310°C. The carrier gas was argon–methane (95:5) at 30 mL/min. After addition of 3-hydroxyprazepam as the internal standard, calibration standards and unknown plasma samples were extracted once with benzene–dichloromethane (80:20). After mixing and centrifugation, the organic extract was separated, evaporated to dryness, reconstituted, and injected into the chromatograph using the automatic sampler. Sensitivity, replicability, and linearity were as described previously (12). All samples

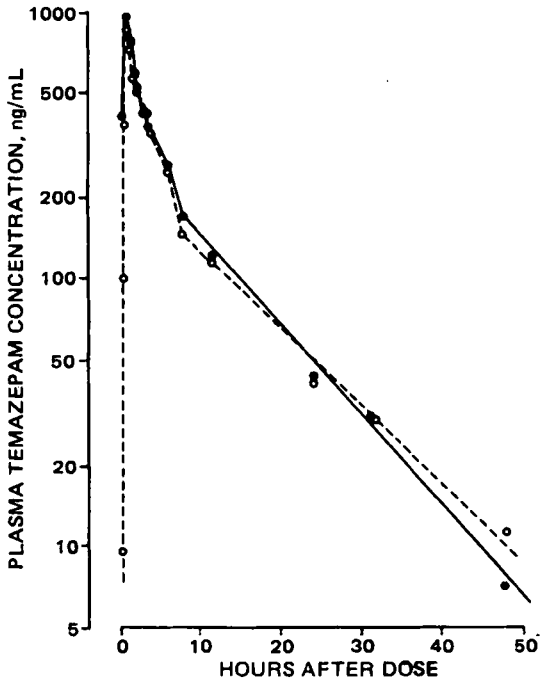


Figure 1—*Plasma temazepam concentrations in a representative volunteer after administration of 30 mg of temazepam in the control state and during concurrent treatment with cimetidine. Key: (●) control; (○) with cimetidine.*

[1] Restoril (C-IV) capsules; Sandoz Pharmaceuticals, East Hanover, N.J.

[2] Tagamet; Smith Kline and French, Philadelphia, Pa.

[3] Model 5830A or 5840A; Hewlett-Packard.

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Table I—Effect of Cimetidine on Temazepam Kinetics

	Mean (with Range) Values		Value of Student's *t* test
	Control	With Cimetidine	
Peak plasma concentration, ng/mL	560 (326–1002)	498 (367–849)	1.46 (NS)[a]
Time to peak concentration, h, postdose	2.1 (1.0–4.0)	2.0 (0.75–6.0)	0.14 (NS)
Volume of distribution, L/kg	1.30 (0.72–2.15)	1.39 (0.90–2.06)	0.81 (NS)
Elimination half-life, h	9.9 (5.6–17.7)	11.4 (5.5–21.4)	1.53 (NS)
Total clearance, mL/min/kg	1.59 (0.92–2.40)	1.60 (0.87–2.61)	0.11 (NS)
Free fraction, % unbound	4.1 (3.2–5.6)	3.8 (2.8–4.8)	1.99 (NS)

[a] NS = not significant.

from a given subject's two trials were extracted and analyzed on the same day using the same calibration standards.

For each subject the influence of cimetidine on temazepam plasma protein binding was determined using a 6-mL sample of plasma obtained in the nonfasting state during the control temazepam trial (without cimetidine treatment). Cimetidine (5 μg/mL) was added to one 3-mL plasma aliquot; no cimetidine was added to the other. Both aliquots were then spiked to contain 3.2 nCi/mL of [^{14}C]temazepam (specific activity: 11 μCi/mg). The extent of temazepam protein binding in each sample was determined in duplicate by equilibrium dialysis for 18 h at 37°C (13, 14). Compliance with the prescribed cimetidine regimen during the temazepam–cimetidine trial was verified by measurement of plasma cimetidine concentrations by HPLC (15) in samples drawn prior to temazepam dosage and at 12, 24, 32, and 48 h after the dose.

Kinetic Analysis—The apparent elimination half-life of temazepam was determined using the slope of the terminal log-linear plot of the plasma concentration curve (Fig. 1). The area under the curve from time zero until the final detectable concentration was determined using the trapezoidal method. To this was added the residual area extrapolated to infinity, calculated as the final concentration divided by the terminal rate constant (β). The sum of these two areas represents the total area under the plasma concentration curve (AUC). The total clearance of temazepam was calculated as dose/AUC, assuming that the entire 30-mg dose was available to the systemic circulation. Likewise, the apparent volume of distribution was calculated as clearance/β. Differences between control and cimetidine treatment conditions were analyzed by the Student's paired *t* test.

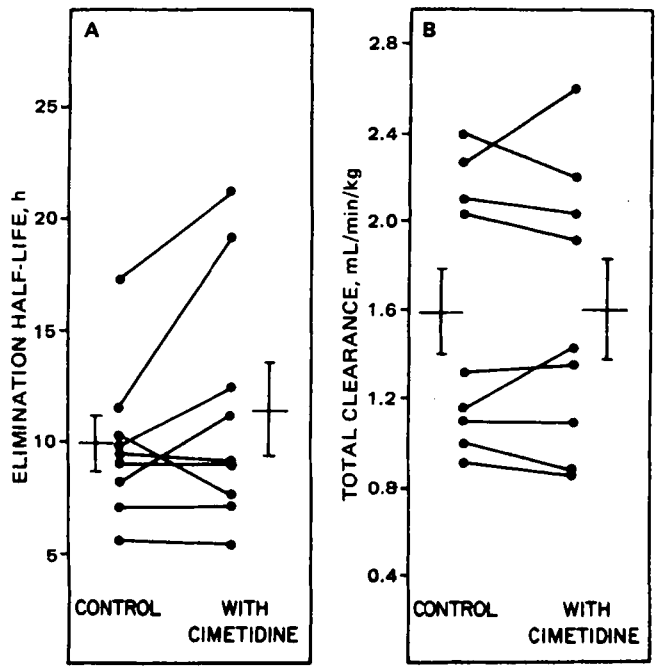

Figure 2—*Temazepam elimination half-life (A) and total metabolic clearance of temazepam (B) in the control state and during coadministration with cimetidine. Individual and mean (±SE) values are shown.*

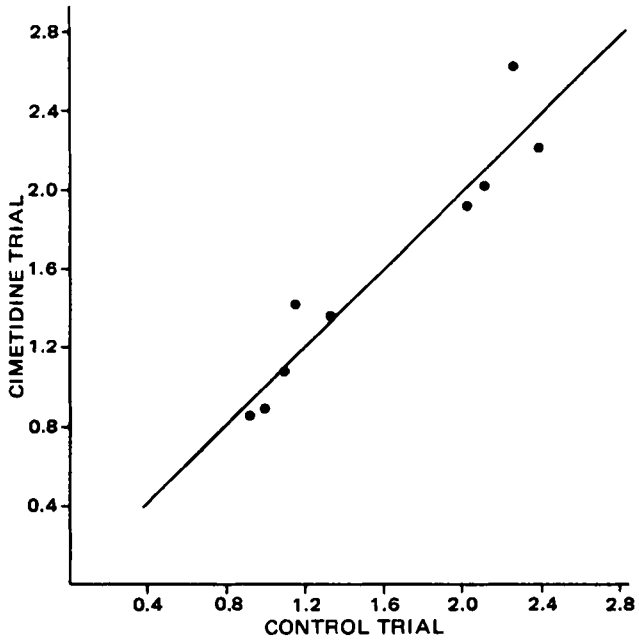

Figure 3—*Values of temazepam clearance (●) in mL/min/kg for the nine individuals during the control trial (x axis) and during coadministration with cimetidine (y axis). Solid line was determined by least-squares regression analysis. Note the high correlation and the regression line slope, which is not significantly different from unity. Slope = 0.98; r = 0.96.*

RESULTS

Compliance with the prescribed cimetidine regimen was acceptable in all subjects. Mean (±*SE*) plasma cimetidine concentrations were: prior to temazepam dosage, 1.43 (±0.32) μg/mL; 12 h postdose, 1.23 (±0.39) μg/mL; 24 h, 2.05 (±0.44) μg/mL; 32 h, 1.06 (±0.23) μg/mL; 48 h, 1.76 (±0.45) μg/mL.

Absorption of temazepam was not significantly influenced by cimetidine. The peak plasma concentration in control and cimetidine treatment conditions averaged 560 and 498 ng/mL, respectively, and the times of peak concentration averaged 2.0 and 2.1 h after the dose. Neither of these differences approached significance (Table I).

Temazepam volume of distribution, elimination half-life, and total clearance were similar between control and cimetidine treatment conditions (Table I, Figs. 1 and 2). Mean half-life values were 9.9 and 11.4 h, respectively, in the two conditions, with an overall range of 6–21 h. None of the differences approached statistical significance. Furthermore, for any given individual, temazepam clearance was highly reproducible between the two trials (Fig. 3). Temazepam free fraction in plasma averaged 4.1 and 3.8% in the two conditions; again the difference did not approach significance.

DISCUSSION

Cimetidine, an H_2-receptor antagonist that is extensively used in the treatment of peptic ulcer disease (2, 3), also has the secondary pharmacological property of impairing hepatic microsomal oxidizing capacity. Previous studies have indicated that benzodiazepines biotransformed by oxidative mechanisms, including diazepam, chlordiazepoxide, desmethyldiazepam, alprazolam, and triazolam, have reduced metabolic clearance during coadministration of cimetidine as opposed to the drug-free control state (4–9). This interaction appears not to occur for benzodiazepines biotransformed by conjugation as opposed to oxidation, including oxazepam and lorazepam (8–10). Temazepam is a 3-hydroxybenzodiazepine biotransformed by conjugation at the 3-position to glucuronic acid, yielding a water-soluble glucuronide metabolite that is excreted in the urine (11). The present study indicated that coadministration of temazepam with cimetidine had no influence on the pattern of temazepam absorption, distribution, or clearance. Consistent with

previous reports (16), absorption of temazepam from the hard gelatin capsule utilized in the United States occurs relatively slowly, with peak plasma concentrations an average of 2.0–2.1 h after dosage. Temazepam elimination half-lives ranged from 6 to 21 h, and total metabolic clearances ranged from 0.9 to 2.6 mL/min/kg. None of these kinetic variables were significantly influenced by cimetidine coadministration, nor was the extent of temazepam binding to plasma protein altered by cimetidine. Furthermore, for any given individual, the kinetic profile for temazepam was highly consistent between the two treatment trials.

The clinical implications of an interaction or noninteraction with cimetidine for any particular benzodiazepine cannot at present be determined. The present study nonetheless suggests that, consistent with its biotransformation pathway mainly involving glucuronide conjugation, the pharmacokinetic profile of temazepam is not influenced by concurrent treatment with cimetidine.

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Dissolution Rates of Corticoid Solutions Dispersed on Silicas

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Abstract □ Two nonporous and three porous amorphous silicas were used as dispersion media to convert corticoid solutions into free-flowing powders. The corticoids (prednisone, prednisolone, and hydrocortisone) were dissolved in *N,N*-dimethylacetamide–polyethylene glycol 400 (7:3 v/v) and their 10% (w/v) solutions were mixed with the silicas (1:3 v/w). Dissolution rates of the corticoids from such powdered solutions were more rapid than their micronized powders in various aqueous media.

Keyphrases □ Dissolution rate—corticoid solutions dispersed on silicas, prednisone, prednisolone, hydrocortisone, free-flowing powders □ Corticoids—solutions dispersed on silicas, dissolution rates, prednisone, prednisolone, hydrocortisone, free-flowing powders □ Powders, free-flowing—corticoid solutions dispersed on silicas, dissolution rates, prednisone, prednisolone, hydrocortisone

The USP (1) requires that ≥60% of the prednisone or prednisolone from their respective tablets must dissolve within 20 min in deaerated water. These water-insoluble neutral drug molecules could exhibit poor dissolution rates from improperly prepared capsule or tablet dosage forms. Oral absorption efficiency of the corticoids from such solid dosage forms could be impaired.

Concentrated solutions of three corticoids (prednisone, prednisolone, and hydrocortisone) had been prepared in *N,N*-dimethylacetamide, a high-boiling, water-miscible liquid (2). These earlier studies had shown that the addition of 30% (v/v) polyethylene glycol 400 to the *N,N*-dimethylacetamide would prevent the softening effect of the latter on hard gelatin capsules. As a consequence, this mixture of solvents was used to prepare 10% (w/v) solutions of the three corticoids.

Simple admixture of the corticoid solutions with amorphous, porous, or nonporous silicas converted them to free-flowing powders. The corticoids in such powdered solutions are thus in a molecular state of subdivision. Dissolution rates of such water-insoluble, neutral compounds should be instantaneous if localized dilution with simulated GI media does not cause their precipitation.

The purpose of this study was to convert solutions of corticoids to free-flowing powders by dispersing them on various silicas. Dissolution rates in simulated GI media are compared with those of micronized powders. A comparison of the dissolution rate with ball-milled or solvent-deposited prednisone–silica dispersions is also presented (3).

Table I—UV Wavelengths Used in the Development of Calibration Curves for the Three Drugs in Various Solvents

Solvent	Wavelength of Light, nm I	II	III
Simulated gastric fluid (without pepsin)	248	243	247
Simulated intestinal fluid (without pancreatin)	248	243	247
Ethanol	248	243	247

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