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DIFFERENTIAL EFFECT OF ISONIAZID ON TRIAZOLAM OXIDATION AND OXAZEPAM CONJUGATION

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Healthy volunteers received a single dose of triazolam (0.5 mg) or oxazepam (30 mg) on two occasions, once in the control state and again during coadministration of isoniazid (INH) base, 180 mg day. INH coadministration prolonged triazolam half-life (3.3 *vs* 2.5 h, $P < 0.05$) and increased total area under the curve (38.6 *vs* 26.5 ng ml^{-1} h, $P < 0.01$) consistent with a reduction of apparent oral clearance (3.9 *vs* 6.8 ml min^{-1} kg^{-1}, $0.05 < P < 0.1$). INH coadministration had no influence on the kinetics of oxazepam. INH impairs hepatic microsomal oxidation of triazolam, leading to reduced first-pass hepatic extraction as well as prolonged half-life. However INH had no influence on oxazepam conjugation.

Keywords isoniazid triazolam oxidation oxazepam conjugation

Introduction

The antituberculous agent isoniazid (INH) has the additional pharmacologic property of impairing hepatic drug metabolizing capacity (Kutt *et al.*, 1970; Miller *et al.*, 1979; Muakkassah *et al.*, 1981; Ochs *et al.*, 1981; Valsalan & Cooper, 1982; Weber & Hein, 1981). Previous studies of drug interactions with INH have involved compounds biotransformed by hepatic microsomal oxidation. The influence of INH on drug conjugating capacity is not established. The present study evaluated the influence of INH on the kinetics of triazolam (Halcion), a triazolobenzodiazepine derivative with a short elimination half-life recently released as a hypnotic agent in the United States (Eberts *et al.*, 1981; Greenblatt *et al.*, 1983; Pakes *et al.*, 1981). Also evaluated was the effect of INH on the kinetics of oxazepam (Serax), a benzodiazepine anxiolytic metabolized principally by conjugation to glucuronic acid (Greenblatt, 1981).

Methods

Triazolam study

Six healthy volunteers (four male and two female) aged 22 to 28 years, participated after giving written informed consent. They were free of medical disease and taking no other medications.

Subjects received a single 0.5 mg dose of triazolam on two occasions in random sequence with at least 1 week elapsing between trials. One trial was a control, without drug coadministration; for the other trial, subjects ingested 90 mg of INH base (as the glucuronide salt), twice daily beginning 3 days before the triazolam kinetic study and continuing for the 24 h duration of the trial. In a prior study, this dose and administration schedule of INH caused significant impairment of the clearance of diazepam, another oxidized benzodiazepine (Ochs *et al.*, 1981).

The 0.5 mg dose of triazolam was taken with 100–200 ml of tap water after an overnight fast. Subjects remained fasting until 3 h after dosage. Venous blood samples were drawn into additive-free tubes prior to triazolam administration and at the following post-dosage times: 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12 and 15 h. Blood samples were allowed to clot, and the serum separated and frozen until the time of assay. Serum concentrations of triazolam were determined by electron-capture gas-liquid chromatography (Greenblatt *et al.*, 1981).

Oxazepam study

Nine healthy volunteers (four male and five female) aged 22 to 29 years, participated after giving written informed consent. They were free of medical disease and were taking no other medications.

Subjects received a single 30 mg dose of oxazepam on two occasions in random sequence. As described above for the triazolam study, one trial was a control, while the other was during coadministration of INH.

The 30 mg oral dose of oxazepam was taken with

100–200 ml of tap water after an overnight fast. Subjects remained fasting until 3 h after dosage. Venous blood samples were drawn into additive-free tubes prior to the dose and at 5, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 30, 36 and 48 h. Blood samples were allowed to clot, and the serum separated and frozen until the time of assay. Serum oxazepam concentrations were determined by electron-capture gas-liquid chromatography (Greenblatt, 1981; Greenblatt *et al.*, 1978, 1980).

Analysis of data

For each trial, apparent elimination half-life was determined from the slope (β) of the terminal log-linear portion of the serum concentration curve. Area under the curve until the final detectable serum level was determined by the trapezoidal method; to this was added the residual area extrapolated to infinity, calculated as the final concentration divided by β, yielding the total area under the curve (AUC). Apparent oral clearance was calculated as dose/AUC. For oxazepam, apparent volume of distribution was calculated as clearance/β. No attempt was made to calculate volume of distribution for triazolam, since its relatively high value of hepatic clearance complicates interpretation of volume of distribution calculated from oral dosage data.

Results

Triazolam study

INH coadministration increased (although not significantly) the peak serum triazolam concentration, but did not alter the time of peak concentration (Table 1, Figure 1). Elimination half-life was significantly prolonged from 2.5 to 3.3 h. Total AUC was also significantly increased by INH ($P < 0.01$). This caused an average reduction in calculated apparent oral clearance of more than 40% (Table 1) although the reduction of oral clearance was of borderline statistical significance ($0.05 < P < 0.1$).

Oxazepam study

INH coadministration reduced the time of the peak serum oxazepam concentration, although the change was of borderline significance. INH had no effect on

Table 1 Effect of isoniazid (INH) on the kinetics of triazolam and oxazepam (mean ± s.e. mean value)

	Control	*with INH*	*Value of Student's-t*
Triazolam			
Peak serum concentration (ng ml)	5.9 (± 1.0)	7.1 (± 0.7)	1.32 (NS)
Time of peak concentration (h after dose)	1.04 (± 0.21)	1.21 (± 0.26)	0.75 (NS)
Elimination half-life (h)	2.54 (± 0.43)	3.32 (± 0.4)	2.90 ($P < 0.05$)
Total AUC (ng ml^{-1} h)	26.5 (± 5.4)	38.6 (± 5.5)	4.61 ($P < 0.01$)
Oral clearance (ml min^{-1} kg^{-1})	6.83 (± 2.2)	3.93 (± 1.0)	2.35 ($P < 0.1$)
Oxazepam			
Peak serum concentration (ng ml)	675 (± 58)	697 (± 84)	0.26 (NS)
Time of peak concentration (h after dose)	1.83 (± 0.30)	1.36 (± 0.15)	2.29 ($P < 0.1$)
Elimination half-life (h)	6.3 ± 0.4)	7.0 (± 0.8)	1.27 (NS)
Total AUC (ng ml^{-1} h)	5330 (± 656)	5220 (± 694)	0.16 (NS)
Volume of distribution (l kg)	0.94 (± 0.11)	1.10 (± 0.15)	0.91 (NS)
Oral clearance (ml min^{-1} kg^{-1})	1.70 (± 0.16)	1.85 (± 0.22)	0.82 (NS)

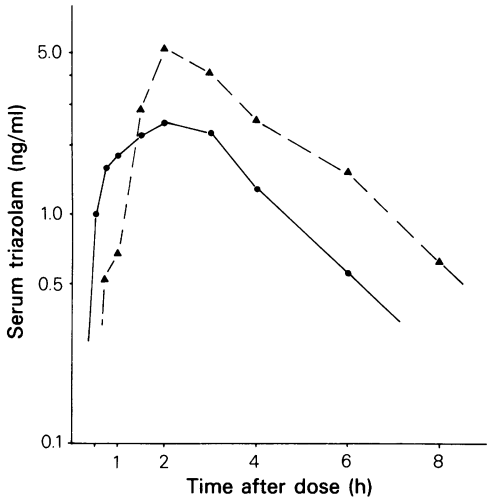

Figure 1 Serum concentrations of triazolam in a representative subject after administration of a single 0.5 mg dose in the control state (●) and during isoniazid coadministration (▲).

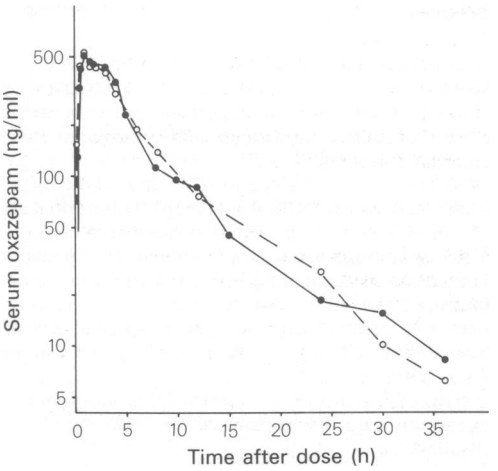

Figure 2 Serum concentrations of oxazepam in a representative volunteer after a single 30 mg dose of oxazepam administered in the control state (●) and during isoniazid coadministration (○).

the peak serum oxazepam concentration, apparent volume of distribution, elimination half-life, or apparent total clearance (Table 1, Figure 2).

Discussion

Coadministration of therapeutic doses of INH caused a significant prolongation in the elimination half-life of the triazolobenzodiazepine derivative triazolam, and significantly increased total area under the serum concentration curve due to a reduction in apparent oral clearance. The findings suggest that INH impairs the hepatic capacity for microsomal oxidation of triazolam, which is biotransformed to at least two hydroxylated metabolites that are rapidly conjugated and excreted (Eberts *et al.*, 1981). The prolongation of triazolam half-life attributable to INH averaged about 30%, whereas the mean increase in AUC and mean reduction in apparent oral clearance more than 40%. Thus a major manifestation of impaired triazolam oxidation by INH, as well as with old age (Greenblatt *et al.*, 1983) or cimetidine coadministration (Abernethy *et al.*, 1983a) is reduced first-pass hepatic extraction, leading to increased systemic availability of the oral dose. This is consistent with physiologically-based mathematical predictions for a drug such as triazolam having an intrinsic hepatic clearance averaging about 30 to 35% of hepatic blood flow (Wilkinson & Shand, 1975). The increase in triazolam AUC attributable to INH is analogous to administration of a higher dose of triazolam, and might increase dose-dependent manifestations of central nervous system depression.

In contrast to triazolam, INH caused no significant alteration in the kinetics of a single dose of oxazepam, a benzodiazepine derivative metabolized mainly by glucuronide conjugation. Several other factors known to impair hepatic microsomal oxidation, such as old age, cirrhosis, cimetidine, and disulfiram, similarly have minimal influence on the clearance of drugs biotransformed mainly by glucuronide conjugation (Abernethy *et al.*, 1983b; Greenblatt, 1981; Greenblatt *et al.*, 1982). The findings emphasize the differential control of drug oxidation and conjugation.

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