INFLUENCE OF CIMETIDINE ON ORAL DIAZEPAM ELIMINATION WITH MEASUREMENT OF SUBSEQUENT COGNITIVE CHANGE

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In a double-blind crossover design, the effect of cimetidine on oral diazepam pharmacokinetics and an evaluation of cognitive function change was studied in seven healthy volunteers. Subjects randomly received placebo or cimetidine 300 mg orally every 6 h for a total of five doses prior to diazepam 10 mg. A significant increase in diazepam elimination half-life from (mean $\pm$ s.e. mean) 66.9 ± 21.4 to 89.6 ± 22.5 h ($P = 0.006$) and area under the plasma concentration-time curve from 5.06 ± 1.47 to 8.93 ± 1.88 $\mu\text{g ml}^{-1}$ h ($P = 0.028$) was observed indicating a probable cimetidine induced inhibition of diazepam hepatic metabolism. Digit symbol substitution and visual analogue scales were used to measure the effect of an alteration of diazepam kinetics on cognitive function. An enhancement of pharmacological effect as reflected in digit symbol substitution scores and visual analogue scale measurements was not observed.

Introduction

Cimetidine, widely prescribed for the treatment of duodenal ulcer and other hypersecretory states, is reported to inhibit the metabolism of several drugs metabolized by the hepatic mixed function oxidase system (Somogyi & Gugler, 1982). Benzodiazepines reported include chlordiazepoxide (Desmond *et al.*, 1980), diazepam (Klotz & Reimann, 1979) and desmethyldiazepam (Klotz & Reimann, 1980). It is suggested that cimetidine may inhibit microsomal *N*-dealkylation and hydroxylation of these agents.

Because both cimetidine and diazepam are widely prescribed, often concomitantly, an interaction between these agents is of clinical importance if an alteration in pharmacokinetic parameters results in an enhancement of pharmacologic effect. This study was designed to evaluate the effect of pretreatment with cimetidine on the pharmacokinetics of orally administered diazepam and to evaluate the effect of cimetidine pretreatment on cognitive function in normal healthy volunteers.

Methods

Seven volunteers (four males, three females) ranging from 21 to 26 years of age were studied. Subjects were excluded if a history of hepatic, renal, respiratory or gastrointestinal disease existed. Volunteers were non-smokers, were not taking other medications and

conformed to the Metropolitan Life Insurance height-weight tables. Alcoholic beverages were not consumed a week prior to or during the treatment course. Each volunteer had a normal history and physical exam, CBC and SMA-17 profile prior to entry into the study. The SMA-17 profile was repeated before the second treatment phase.

Using a double-blind crossover design, subjects were randomly selected to receive diazepam preceded by cimetidine or an identically appearing placebo. A one month interval elapsed between the two study periods. Cimetidine (Tagamet®) 300 mg and placebo tablets were administered every 6 h for a total of five doses with the last dose administered 30 min prior to a diazepam (Valium®) 10 mg tablet given with 150 ml of water 3.5 h after a standardized breakfast. Food was withheld until 2.5 h post-diazepam administration.

Prior to diazepam administration, a single blood sample was collected for cimetidine steady-state concentration analysis. Diazepam blood samples were obtained from an indwelling venous cannula. Samples were collected immediately prior to diazepam administration and at 10, 20, 30, 40 and 50 min, 1, 2, 4, 6, 9, 12, 24, 48, 72 and 96 h. Patency of the indwelling cannula was maintained with a dilute heparin solution (Naranjo *et al.*, 1980). After 12 h remaining samples were obtained by venipuncture.

Diazepam plasma concentrations were analyzed

according to the oral two-compartment pharmacokinetic model (Kaplan *et al.*, 1973). The following parameters were obtained: Absorption half-life ($t_{1/2}$ abs), distribution half-life ($t_{1/2}\alpha$), elimination half-life ($t_{1/2}\beta$), total plasma clearance (CL), apparent volume of distribution of the central compartment (V_1) and total apparent volume of distribution (V_β). Plasma concentrations were fitted by the NONLIN computer program (Metzler *et al.*, 1974) to the function $C_{p(t)} = Ae^{-\alpha(t-t_0)} + Be^{-\beta(t-t_0)} - Ce^{-ka(t-t_0)}$. Absorption lag time is represented by the symbol t_0 . CL was calculated from the dose divided by the area under the time concentration curve from zero to infinity ($AUC_{(0\rightarrow\infty)}$). The trapezoidal method was used to measure $AUC_{(0\rightarrow\infty)}$. Since diazepam is reported to be rapidly and completely absorbed (Kaplan *et al.*, 1973), complete absorption was assumed. Diazepam plasma concentration analysis was performed using high pressure liquid chromatography (Skellern *et al.*, 1978). Three diazepam tablets of the same lot number used in the study were analyzed with this method to verify dosage accuracy.

In an attempt to objectively measure the effect of diazepam on cognitive function, digit symbol substitution (Wechsler, 1955) tests were used to measure the ability of a subject to sustain concentration or attention. Digit symbol substitution tests were administered 1 h and 0.5 h prior to diazepam administration and at 45, 75, 135 and 375 min after administration. Estimates of subjective feelings were recorded using a five item battery of visual analogue scales (Aitken, 1969). The five scales estimated feelings in the following dimensions: (1) drowsy-alert, (2) mentally-slow—quick-witted, (3) lethargic-energetic, (4) well-coordinated—clumsy and (5) tense-relaxed. Printed visual analogue scales were marked immediately following digit symbol substitution.

Pharmacokinetic data were analyzed using the two-tailed paired difference *t*-test. Visual analogue scale measurements and digit symbol substitution scores were analyzed using a repeated measures analysis of variance. $P = 0.05$ was accepted as the minimal level of significance.

Results

The content of the diazepam tablets assayed by a modification of the USP XX method was 11.2, 9.9 and 11.0 mg. This was within USP limits for diazepam content of tablets designated as meeting the USP specification.

Cimetidine steady-state plasma concentrations obtained 0.5 h after the last cimetidine dose ranged from 0.4 to 1.0 $\mu\text{g/ml}$ with a mean plasma concentration of 0.7 $\mu\text{g/ml}$.

Pharmacokinetic parameters derived from diazepam time-concentration profiles are presented in Table 1. Changes in diazepam elimination characteristics occurred in all subjects with a mean increase from 66.9 h mean $t_{1/2}\beta$ following placebo to 89.6 mean $t_{1/2}\beta$ after cimetidine ($P = 0.006$). A significant difference ($P = 0.028$) in $AUC_{(0\rightarrow\infty)}$ was observed following cimetidine. Although a trend toward decreasing CL was observed with cimetidine, statistical significance was not achieved.

The total number of digit symbol substitutions completed in the cimetidine and placebo pretreatment groups did not differ significantly during any time of test administration (Figure 1). No significant differences were observed in subjective evaluation of feelings in the five visual analogue scale categories.

Discussion

The results of this study employing an oral dosage form demonstrated a significant increase in diazepam elimination half-life and area under the plasma-concentration curve in seven volunteers pretreated with cimetidine.

Although a change in pharmacokinetic parameters reflecting a decrease in diazepam elimination was observed, significant differences in digit symbol substitution scores and volunteer subjective evaluation of cognitive function with visual analogue scales were not demonstrated.

This study was unable to detect a significant change in diazepam pharmacological effect as assessed by

Table 1 Diazepam pharmacokinetic parameters (mean $\pm$ s.e. mean) of a single oral 10 mg diazepam dose in seven healthy volunteers.

Variable	Placebo	Cimetidine	P value
$t_{1/2}\alpha$ (h)	2.17 $\pm$ 0.660	3.03 $\pm$ 0.868	NS
$t_{1/2}\beta$ (h)	66.9 $\pm$ 21.4	89.6 $\pm$ 22.5	0.006
V_1 (l/kg)	2.11 $\pm$ 0.358	1.65 $\pm$ 0.378	NS
V_β (l/kg)	2.99 $\pm$ 0.453	2.27 $\pm$ 0.340	NS
CL (ml/min)	53.0 $\pm$ 16.8	26.5 $\pm$ 6.98	NS
$AUC_{(0\rightarrow\infty)}$ ($\mu\text{g ml}^{-1}$ h)	5.06 $\pm$ 1.47	8.93 $\pm$ 1.88	0.028
$t_{1/2}$ abs (h)	0.360 $\pm$ 0.125	0.254 $\pm$ 0.039	NS

Figure 1 Digit symbol substitution scores (mean $\pm$ s.e. mean) $\circ$ cimetidine, $\bullet$ placebo.

digit symbol substitution and visual analogue scales after cimetidine pretreatment. However, these findings should be interpreted with the knowledge that extra-polation of results from a single dose study may not be applicable to actual clinical situations where multiple dosing is utilized. The true clinical relevance of the alteration of diazepam pharmacokinetics by cimetidine can only be accurately assessed following the measurement of cognitive function in

subjects receiving cimetidine in addition to long-term full therapeutic doses of diazepam.

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