Lack of Pharmacokinetic Interaction Between Cimetidine and Tirilazad Mesylate

Joseph C. Fleishaker,[1,2] Laura K. Hulst,[1] and Gary R. Peters[1]

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INTRODUCTION

Tirilazad mesylate {21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methyl-pregna-1,4,9(11)-triene-3,20 dione-methanesulfonate} is a novel 21-aminosteroid membrane lipid peroxidation inhibitor. In animal models, the efficacy of tirilazad has been demonstrated for the prevention of ischemic neuronal damage due to head trauma, subarachnoid hemorrhage, spinal cord injury, and stroke (1).

Tirilazad mesylate pharmacokinetics after single-dose administration to healthy male volunteers are linear at dosages from 0.25 to 2.0 mg/kg (2). The apparent elimination half-life following single doses ranges from 3.7 hr (2) to approximately 30 hr (3,4). A mean terminal half-life of 35 hr is observed following the last dose of a multiple-dose regimen (5). The large differences in half-life between single- and multiple-dose administration are due primarily to assay insensitivity at low concentrations. The majority of tirilazad is recovered in the feces as various metabolites (6). The metabolic profile of tirilazad in man has not yet been elucidated, but tirilazad is likely to be hydroxylated on the steroid nucleus, as is common for other steroids (7). One reduced metabolite, U-89678 {21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16-methyl-pregn-1,9(11)-diene-3,20-dione(5α,16α)-}, has been identified in several animal species (D. G. Kaiser, personal communication), and has been found to exhibit activity similar to that of tirilazad in a mouse head injury model (E. D. Hall, personal communication).

Patients with head injury and other acute neurological trauma often suffer from stress ulcers, which require treatment with antacids and/or H_2-receptor antagonists, such as cimetidine. Cimetidine inhibits the hepatic oxidation of many compounds, mainly through inhibition of cytochrome P-450 (8,9). Cimetidine may also decrease liver blood flow, but the evidence for this is somewhat controversial (10). Since tirilazad mesylate is highly metabolized and it has a medium to high extraction ratio (4), it is possible that cimetidine may affect the pharmacokinetics of tirilazad when these compounds are coadministered.

This study was designed to assess the pharmacokinetic interaction between cimetidine and tirilazad in healthy volunteers following single-dose administration of tirilazad mesylate and multiple-dose administration of cimetidine.

MATERIALS AND METHODS

This study was conducted at Harris Laboratories, Inc., Lincoln, NE, after approval by the local Institutional Review Board. Sixteen healthy young male volunteers (seven nonsmokers, nine smokers) were enrolled in the study after providing written informed consent. The age range of the subjects was from 20 to 49 years (mean, 37.0 years) and their weights ranged from 58.5 to 106 kg (mean, 83.2 kg). Of the smokers, only three smoked the equivalent of ≥20 cigarettes/day. Subjects received no known enzyme inducing agents for 30 days prior to the study, no medications during the 7 days prior to study, and no alcohol for 2 days prior to and during the study. During the course of the study, subjects received no medications other than those specified in the protocol.

Subjects received the following treatments in a balanced two-way crossover design: (A) 300 mg cimetidine every 6 hr on study days 1–4 and 2.0 mg/kg tirilazad mesylate sterile solution (1.5 mg/ml) on Day 2 and (B) 2.0 mg/kg tirilazad mesylate sterile solution on Day 2. Subjects also received 0.5 mg/kg indocyanine green (CardioGreen) on day 2 of each study phase. Two weeks separated day 1 of each study period.

Cimetidine was administered orally at 0700, 1300, 1900, and 0100 on study days 1–4 for treatment A only. Indocyanine green (ICG) was administered as a 5-sec IV bolus at 0800 of each study phase. Subjects were required to fast from 2200 of day 1 until 0900 of day 2. Tirilazad mesylate was sterile filtered and prepared using a 1:1 dilution and infused IV at approximately 0830 over 10 min using an IVAC infusion pump.

Venous blood samples (7 mL) were collected into heparinized vacutainers immediately prior to drug dosing and again at 12, 15, 20, 30, and 40 min and at 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 60.0, and 72.0 hr after the start of tirilazad administration. Plasma was harvested from the samples after centrifugation and frozen until analyzed. Determinations of tirilazad mesylate and U-89678 were performed by HPLC (11). Plasma concentrations are reported as nanograms per milliliter of tirilazad mesylate and nanograms per milliliter of U-89678 base. Standard curves for tirilazad mesylate and U-89678 were linear over the range of 5 to 5000 and 5 to 1000 ng/mL for the parent compound and metabolite, respectively. Coefficients of variation were less than or equal to 6.8 and 4.1%, respectively.

Venous blood samples (3 ml) were collected into heparinized vacutainers immediately prior to and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, and 20 min after ICG administration. Plasma was harvested from the samples after centrifugation and frozen until analyzed. Determinations of ICG were performed by HPLC (10). Standard curves for ICG were linear

[1] Clinical Pharmacokinetics and Clinical Research Units, The Upjohn Company, Kalamazoo, Michigan 49007.
[2] To whom correspondence should be addressed at Clinical Pharmacokinetics Unit, 7215-24-2, The Upjohn Company, Kalamazoo, Michigan 49007.

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over the range of 0.25 to 30 μg/mL. Coefficients of variation were less than or equal to 7.5%.

Venous blood samples (7 mL) were collected into heparinized vacutainers immediately prior to and 1, 2, 24, 48, and 72 hr after the 0700 administration of cimetidine on day 2. Determinations of cimetidine were performed by modifications to a published HPLC procedure (12). Standard curves for cimetidine were linear over the range of 0.05 to 5.0 μg/mL. Coefficients of variation were less than or equal to 7.6%.

Pharmacokinetic parameters were determined by noncompartmental techniques (13). The terminal elimination rate constant (λ_z) was determined by linear regression of the terminal portion of the log concentration–time profile. The terminal half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Area under the plasma concentration–time curve (AUC) was determined by trapezoidal rule and extrapolated to infinity. Area under the first moment curve (AUMC) was determined in an analogous manner. Systemic clearance (CL) of tirilazad and ICG was calculated as Dose/AUC. Mean residence time (MRT) was equal to AUMC/AUC-T/2, where T is the infusion duration. Volume of distribution (V_{ss}) following the iv dose of tirilazad was calculated as CL · MRT. Hepatic blood flow (Q) was calculated as $CL_{ICG}/(1 - HCT)$, where CL_{ICG} is ICG systemic clearance and HCT is the hematocrit (14). Effects of treatment on tirilazad mesylate pharmacokinetic parameters were assessed separately using analysis of variance (ANOVA) for a crossover design, with significance assumed at $P < 0.05$.

RESULTS

Sixteen patients were enrolled in and completed this trial. The most frequent medical event observed in this study was discomfort at the inject site (stinging, burning). Four volunteers also had signs of physical irritation at the injection site. No clinically important changes in vital signs or laboratory parameters were observed in this study.

Mean tirilazad mesylate plasma concentrations are depicted in Fig. 1. Tirilazad mesylate pharmacokinetic parameters are summarized in Table I. There were no significant differences between treatments in tirilazad pharmacokinetic parameters.

Mean plasma concentrations of U-89768 are shown in Fig. 1; pharmacokinetic parameters derived for this metabolite are shown in Table I. Plasma concentrations of the metabolite generally reached the limit of quantitation by 60 hr after dosing; this resulted in an apparent terminal half-life of approximately 24 hr. There was no significant effect of cimetidine administration on the pharmacokinetics of this metabolite.

Mean liver blood flow values were 1219 ± 220 and 1309 ± 268 mL/min following administration of ICG in the presence and absence, respectively, of cimetidine coadministration. The difference was not statistically significant.

DISCUSSION

Tirilazad mesylate is a 21-amino steroid and is likely to be subject to oxidative metabolism characteristic of steroids. Presently, the evidence for this is indirect. Multiple-dose phenytoin administration reduces plasma concentrations of both tirilazad mesylate and U-89678 in man (J. C. Fleishaker, unpublished results), probably via induction of cytochrome P-450. The cytochrome P-450 isozymes responsible for oxidation of tirilazad mesylate have not yet been elucidated, but it appears the IIIA family, which is inducible by phenobarbital (7) and phenytoin (15,16), is important in the metabolism of tirilazad. Cimetidine is likewise a potent inhibitor of IIIA4 (9), so that an interaction between tirilazad and cimetidine was deemed possible.

However, the results of this study show that cimetidine

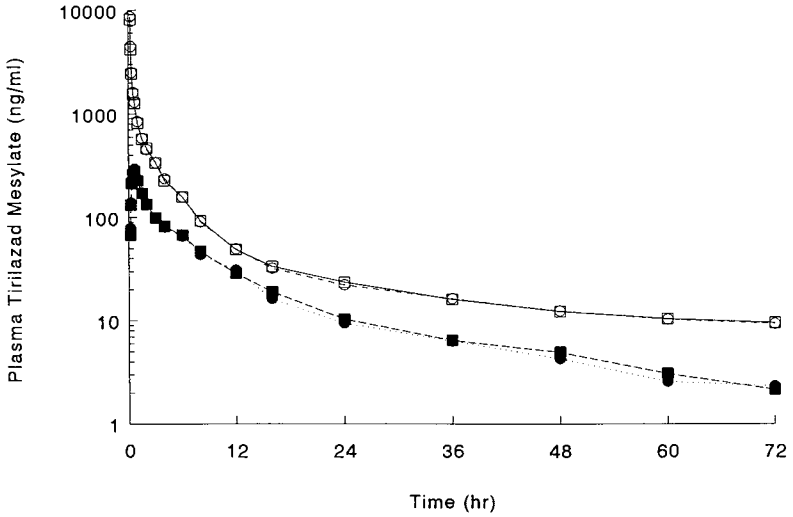

Fig. 1. Mean plasma concentrations of a tirilazad mesylate (open symbols) and U-89678 (filled symbols) following the administration of 2.0 mg/kg tirilazad mesylate in the presence (□) and absence (○) of concomitant cimetidine treatment (1200 mg/day).

Table I. Mean Apparent Tirilazad Mesylate and U-89678 Pharmacokinetic Parameters Following the Administration of 2.0 mg/kg Tirilazad Mesylate and 2.0 mg/kg Tirilazad Mesylate + 1200 mg/day Cimetidine to 16 Healthy Male Volunteers

Parameter	Treatment	
	Tirilazad	Tirilazad + cimetidine
	Tirilazad mesylate	
AUC (ng · hr/mL)	6134	5911
	(1485)[a]	(1418)
CL (L/hr)	28.1	29.2
	(5.29)	(6.73)
C_{inf} (ng/mL)[b]	8697	8136
	(2594)	(2170)
V_{ss} (L)	447	437
	(76.8)	(147)
$t_{1/2}$ (hr)	35.3	31.5
	(6.50)	(5.18)
	U-89678	
AUC (ng · hr/mL)	1577	1654
	(1077)	(1112)
C_{max} (ng/mL)	300	282
	(202)	(170)
$t_{1/2}$ (hr)[c]	23.8	27.4
	(16.7)	(15.0)

[a] Standard deviation in parentheses.
[b] Concentration at the end of 10 min of infusion.
[c] Apparent half-life.

treatment has no apparent effect on tirilazad pharmacokinetics. The reason for the lack of interaction between tirilazad and cimetidine is not clear but may be related to the observation that tirilazad is a medium- to high-extraction ratio compound (2,4), so that changes in tirilazad metabolism due to cimetidine would have to be large, of the order of a two- to threefold reduction, to affect tirilazad mesylate clearance substantially (13). Cimetidine has also been reported to reduce hepatic blood flow, which would in turn decrease the clearance of a compound such as tirilazad. However, in this trial, cimetidine had little effect on hepatic blood flow. Cimetidine plasma concentrations were consistent with previous reports with similar total daily doses (17,18), so that, if an interaction was likely to occur between cimetidine and tirilazad mesylate, it should have been observed.

The statistical analysis of the tirilazad mesylate pharmacokinetic data was complicated by the observation of significant group effects in CL, V_{ss}, $t_{1/2}$, and λ_z. Group effects consisted of 10 to 20% differences between groups in these parameters. Further examination of the treatment effects within groups shows similar trends for treatment effects for CL, $t_{1/2}$, and λ_z in both groups. Due to the minor degree of the group effects, the initial analysis of variance was considered valid.

Cimetidine had no apparent effect on U-89678 pharmacokinetics. No effect of cimetidine on the formation rate of the metabolite is likely, since this metabolite is formed by reduction. However, due to the structural similarity of tirilazad and U-89678 and similar effects of phenytoin on blood levels of tirilazad and U-89678, it is possible that tirilazad and U-89678 share common metabolic pathways that would be inhibited by cimetidine. Without data obtained after the administration of this metabolite, it is impossible to explain the apparent lack of effect on U-89678 pharmacokinetics.

Consistent with previous results (4) the observed half-life of U-89678 was less than or similar to that of the parent compound. Assay insensitivity prevents the accurate determination of the true terminal elimination half-life, which must be equal to or greater than that of the parent compound (13). The results of this study were also consistent with those of the previous single-dose study (4), which show that the AUC for the metabolite is ≤25% of that for tirilazad mesylate.

In conclusion, these results suggest that no pharmacokinetic interaction occurs between tirilazad mesylate and cimetidine. Thus, from a pharmacokinetic standpoint, coadministration of cimetidine and tirilazad mesylate in neurological trauma patients will likely have no serious consequences.

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