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**The Pharmacokinetics of Taurolidine Metabolites in Healthy
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ABSTRACT

Taurolidine is an experimental anti-bacterial and anti-endotoxic compound whose clinical utility as an anti-tumor agent is being investigated in human clinical trials. Taurolidine in aqueous solution exists in equilibrium with taurultam. Taurultam is subsequently transformed to taurinamide. The pharmacokinetic profiles of these metabolites are not well established. In this study, eighteen healthy volunteers were administered 5.0 g of taurolidine in 250 mL of 5% polyvinylpyrrolidone in water over either 2, 1, or 0.5 hour by intravenous infusion in a parallel group design. All subjects noted discomfort at the infusion site, though there were no serious adverse events. T_{max} generally occurred at the end of infusion for taurinamide while that of taurultam was reached before completion of infusion. The taurolidine metabolite taurultam demonstrated a shorter half-life and lower systemic exposure than taurinamide. Shortening of infusion duration increased the C_{max} and AUC of taurultam. Changes in infusion rate did not substantially change the pharmacokinetic parameters of taurinamide.

INTRODUCTION

Taurolidine [TRD] is a small dimeric molecule with bactericidal properties against a broad spectrum of bacteria ranging from anaerobic to aerobic species.^{1, 2, 3} Taurolidine's mechanism of action as an antibiotic agent is associated with a chemical reaction between the active TRD metabolites, taurultam [TRT] and taurinamide [TRM] with the structures of bacterial wall.^{3, 6} In addition, TRD exhibits the ability to neutralize bacterial endotoxins, exotoxins and lipopolysaccharides.^{7, 8, 9} The most widespread clinical application of TRD at present is as a catheter lock solution to reduce the incidence of vascular access-associated blood stream infections. Other clinical applications have included peritoneal lavage for prophylaxis against post-operational bacterial infections in patients with established peritonitis following elective colorectal surgeries, and as an anti-endotoxic agent in patients with systemic inflammatory response syndrome.^{2, 3, 10}

TRD has also been investigated extensively as an experimental anti-neoplastic agent in *in vitro* and *in vivo* studies.^{11, 12, 13, 14} It appears to have a direct effect on various tumor cell lines with a consecutive inhibition in cell growth.^{12, 15} Preclinical investigations have suggested activity against colon, ovarian, and prostate cancer, as well as melanoma, and mesothelioma. Of significance, intra-peritoneal and systemic application of TRD resulted in a reduction of intra- and extra-peritoneal metastases in rodent models, suggesting utility as a chemopreventive agent against metastases.^{11, 16} Indeed, prophylactic, intra-operative peritoneal lavage with TRD for prevention of metastatic diseases has been successfully applied, while intravenous administration of the agent as

the primary treatment of poorly managed malignancies has been currently investigated in clinical trials.^{17, 18}

Despite administration to over 13,000 patients, the pharmacokinetics of TRD metabolites has not been comprehensively characterized in humans. TRD in aqueous solution undergoes rapid conversion to TRT, with smaller amounts of hydroxymethyltaurultam. TRT is subsequently converted to TRM [Figure 1].^{19, 20} Because of these metabolic characteristics, the TRD metabolites are more important pharmacokinetic markers than the parent compound in studying its pharmacodynamic properties including antibacterial and anti-neoplastic repertoire. In this study, the pharmacokinetics of TRD metabolites was investigated in healthy volunteers following intravenous administration of TRD solution.

METHODS

Subjects

Healthy male or female subjects between the ages of 18 and 45 years, between 45 and 100 kg and within 20% of ideal body weight range for body frame, were eligible to participate in the present study. The use of prescription medications and tobacco were exclusion criteria. The study was approved by the institutional review board of Thomas Jefferson University. All subjects gave written informed consent to participate prior to undergoing any study-related procedures.

Study Design

This was an open labeled, three-arm, single dose, parallel study that compared the pharmacokinetics and safety of [1] 5.0 gram [g] taurolidine intravenous infusion over 2 hours [h], [2] 5.0 g taurolidine intravenous infusion over 1 h and [3] 5.0 g taurolidine intravenous infusion over 0.5 h. Taurolidine was prepared as a 2% solution in 250 ml of water and 5% polyvinylpyrrolidone [Kollidon[®] 17, BASF]. Healthy volunteers underwent a screening visit within three weeks of drug administration. Each subject was admitted to the Clinical Pharmacology Research Unit of Thomas Jefferson University Hospital the day before each treatment. Following an overnight fast, they received one of the three treatments. Clinical laboratory tests, electrocardiogram, and vital signs were performed at baseline and at specified intervals post dose. Twenty-four hours after each treatment, subjects were discharged from the unit.

Collection and determination of analyte concentrations

Blood was drawn for TRT and TRM pharmacokinetics predose, and at 5, 15, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 hours postdose. Time zero was the beginning of intravenous infusion. Blood samples were collected in sodium heparin-containing tubes, and immediately [within 40 seconds] mixed with the derivatizing agent 9-fluorenylmethyl-chlorformate [FMOC-Cl] in an acetonitrile and pseudoephedrine processing solution. Samples were incubated at room temperature between 30-45 minutes, followed by freezing at -20⁰C. Analysis was performed by Kansas City Analytical Services [Shawnee, KS] using a validated high performance liquid chromatography [HPLC] method. In addition to the pre-column derivatization, the

method consisted of liquid-liquid extraction, gradient HPLC separation, and fluorescence detection using a 260 nm excitation/340 nm emission cut-off filter. The analytic range for TRT was 20 to 1000 μM and 20 to 900 μM for TRM. At the time of analysis, samples were thawed, combined with additional derivatizing reagent FMOC-Cl, and respective TRT and TRM internal standards. The samples were allowed to react for 10 min, quenched with the addition of taurine, and extracted into an organic solvent. The extracts were reconstituted in mobile phase and subjected to reverse phase HPLC using a 5 μ ODS column. The analytes were detected using fluorescence detection and system calibration was accomplished by weighted linear least-square regression of the weight-normalized peak height ratio [analyte/internal standard] vs. the nominal concentration of analyte. During validation, the correlation coefficient [r] was ≥ 0.995 for TRT and ≥ 0.997 for TRM, respectively. The precision for this assay was 1.3 to 15.95% CV for TRT and 2.3 to 8.5% for TRM, respectively, while accuracy [% of recovery] was 94.9 to 116.3% for TRT and 102.1 to 114.6% for TRM.

Pharmacokinetic Analysis

The apparent clearance [Cl] and volume of distribution [Vd] of TRD metabolites, TRT and TRM, following intravenous infusion of TRD, along with the terminal elimination rate constant [λ_z], and corresponding half-life [$t_{1/2}$], maximum concentration [C_{max}], time to maximum concentration [T_{max}], observed area under the curve [AUC_{0-24}] and area under the curve extrapolated to infinity [$\text{AUC}_{0-\infty}$], were estimated based on whole blood concentration [$\mu\text{g/mL}$] versus time [h] data using non-compartmental methods [WinNonlin 5.01 software; Pharsight, Mountain View, CA].

RESULTS

Demographics

Eighteen healthy volunteers [16 males and 2 females] with a mean age of 30.7 [range 21 to 42], participated in the study. Ten subjects were black, 6 white, one Hispanic and one subject was self-described as mixed race. Detailed demographic data is summarized in Table 1. All subjects completed the study.

Pharmacokinetics

The present study compared the pharmacokinetics of TRD metabolites over 3 different durations of intravenous infusion with parent compound TRD [Tables 2, 3; Figure 2]. Data from the subject in the one hour infusion group who had his infusion rate decreased on account of infusional burning was not included in PK analysis. Estimated clearance and volume of distribution were calculated using the assumption of a 5 gm dose of parent compound. The mean clearance (L/hr) was 124.6 (SD 35.7) for TRT and 16.5 (SD 3.2) for TRM. The mean volume of distribution (L) was 252.9 (SD 132.9) for TRT and 155.1 (SD 32.5) for TRM. Each metabolite is proportional to parent on a molar basis but involves the liberation of water, so the clearance and volume of distribution presented are likely overestimates of actual values. The AUC and C_{\max} of TRT increased, and Cl decreased with decreasing infusion time, suggesting a saturable elimination process. TRM lacked such changes and with the exception of T_{\max} , pharmacokinetic parameters were comparable across different durations of infusion. Due to the limited number of time points during the first hour after the initiation of intravenous infusion, T_{\max} values

should be considered estimates. Maximum concentrations were reached sooner for TRT in the order of 0.5 hr-infusion < 1 hr-infusion < 2 hr-infusion ($p = 0.0017$). The T_{\max} for TRM occurred essentially at the end of infusion while that of TRT appeared generally to be achieved before completing the infusion ($p < 0.05$).

Safety

Safety data on all subjects in the trial is reported. There were no serious adverse effects associated with the administration of taurolidine infusions. No hypotension was noted during drug infusion. All subjects noted burning at the infusion site. Five were graded as mild, twelve as moderate, and one subject in the one hour infusion rate group had severe burning that required a decrease in the rate of infusion. Seven subjects also described a numbness or soreness in the infusion arm or shoulder. Four episodes were ranked as mild and three as moderate. Infusion-related symptoms began within one minute of onset and generally ceased at the end of infusion. Four subjects had mild erythematous streaking at the site of the IV, which also resolved quickly after the end of infusion. Five subjects had facial flushing, of which four were mild and one was moderate. Four of the flushing episodes took place in the 0.5 hr-infusion group and one in the 1 hr group. Other adverse events included single occurrences of headache, epistaxis, and nausea. There were no clinically significant abnormalities in vital signs, electrocardiograms, and clinical laboratory tests except one subject with a single elevated prothrombin time value felt to be possibly related to study drug.

DISCUSSION

TRD was synthesized in 1970s and was originally used as an antibiotic in the prophylactic treatment of intraperitoneal bacterial infections in patients with established peritonitis.^{1, 2, 3} The utility of taurolidine as an anti-tumor agent has been investigated extensively recently.¹⁷ Although intra-operative peritoneal lavage of TRD for prophylactic therapies either as an antibiotic or as an anti-tumor agent against metastatic diseases has been administered clinically, the pharmacokinetics of TRD metabolites after intravenous administration was not well established. Pharmacokinetic characterization of taurolidine metabolites had been hampered by the rapid *in vivo* conversion of TRT to TRM. Key to the present investigation was the development of a sensitive assay and careful attention to derivatizing samples immediately after collection.

Previous analytical studies on animal specimens revealed that TRD exists in equilibrium with TRT, which further reversibly converts to TRM and other degradation products [Figure 1].^{19, 20} In a clinical investigation, Erb et al¹⁹ reported a biphasic elimination of TRT in a model-based analysis after IV administration of 1 gram over one hour in six subjects using a different analytic method. Beta $t_{1/2}$ was reported as 2.2 h and V_d was 162 ± 93 L, which is comparable to the findings reported here [Table 2]. In the present study, intravenous infusion of 5.0 g of taurolidine resulted in a smaller AUC for TRT than for TRM and, conversely, a larger Cl for the former than for the latter [Table 2 and 3]. These findings demonstrate that TRT is an unstable and short-lived metabolite. Prior investigations revealed that the antibiotic action of TRD appeared to be related to action

of active metabolites methylol TRT and methylol TRM [Figure 1] on bacterial cell walls,^{2, 21} while the antitumor activities were likely due to its proapoptotic and antiangiogenic effects on tumor cells.^{17, 18} The present study did not include pharmacodynamic measures to define mechanisms of action of each metabolite.

TRD not only acts as an antibacterial agent to suppress infection but also prevents the growth and spread of tumor cells. In oncology patients, intravenous infusions were reported of up to 20 g/day (1,000 ml of 2% TRD), which were ~4 times more than that examined in the present study, and few clinically relevant drug adverse effects were observed.^{15, 17, 22} Anti-tumor activity has been noted preclinically at micromolar concentrations in many tumor cell lines.¹⁸ These concentrations were demonstrated for both metabolites in the present study. The PK parameters generated in this study will assist in the rational dose and infusion interval selection in future human clinical trials.

Finally, safety data reported here in healthy adults indicate that local reactions including burning at the infusion site, numbness or soreness of the infusion arm and erythematous streaking at the IV site were the most common adverse effects associated with intravenous TRD administration. Systemic clinically relevant drug toxicities were minimal in this study, in accordance with the other prior clinical investigations related to the low toxicity of this agent.¹⁷

In summary, there was no serious adverse events occurred in intravenous administrations of 5 g TRD 2% solution in healthy subjects. Local irritation at infusion sites was

observed although all subjects completed the infusion. The TRD metabolite TRT demonstrated a shorter half-life and systemic exposure than TRM. Shortening of infusion duration increased the C_{\max} and AUC of TRT relative to that of TRM. Characterization of metabolite pharmacokinetics will assist in the further clinical development of TRD.

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Table 1: Demographic characteristics of research subjects

Group	2-h infusion	1-h infusion	0.5-h infusion
n	6	6	6
Age (yrs)	27.7 ± 2.3	30.3 ± 8.0	31.0 ± 7.3
Weight (kg)	60.3 ± 7.9	87.7 ± 14.8	82.5 ± 16.9
Height (cm)	167.9 ± 7.7	167.9 ± 7.7	179.3 ± 10.5
Gender (M:F)	5:1	5:1	6:0

All data are presented as mean ± S.D.

Table 2: Mean Pharmacokinetic Parameters of Taurultam

Duration of infusion <i>hr</i>	n	AUC ₍₀₋₂₄₎ <i>hr*ug/mL</i>	AUC _(0-∞) <i>hr*ug/mL</i>	C _{max} <i>ug/mL</i>	half life <i>hr</i>	T _{max} <i>hr</i>
2	6	34.9 ± 9.6	35.7 ± 9.0	16.0 ± 4.5	1.1 ± 0.3	1.50
1	5	37.3 ± 10.1	40.7 ± 11.2	32.0 ± 16.1	1.2 ± 0.7	0.75
0.5	6	44.8 ± 9.8	51.8 ± 10.6	51.4 ± 12.2	2.1 ± 1.1	0.50
All Groups		38.8 ± 9.8	42.9 ± 11.4	32.0 ± 17.9	1.5 ± 0.9	0.50*

* = median

All data are presented as mean ± S.D.

Table 3: Mean Pharmacokinetic Parameters of Taurinamide

Duration of infusion <i>hr</i>	n	AUC ₍₀₋₂₄₎ <i>hr*ug/mL</i>	AUC _(0-∞) <i>hr*ug/mL</i>	C _{max} <i>ug/mL</i>	half life <i>hr</i>	T _{max} <i>hr</i>
2	6	315.4 ± 46.5	356.5 ± 61.1	53.9 ± 10.8	6.9 ± 1.5	2.00
1	5	233.9 ± 29.4	269.0 ± 35.3	59.4 ± 19.4	6.5 ± 1.4	1.00
0.5	6	271.7 ± 61.4	310.3 ± 67.2	62.6 ± 16.8	6.7 ± 1.2	0.63
All Groups		273.4 ± 55.8	312.7 ± 63.2	57.3 ± 15.3	6.7 ± 1.3	1.00*

* = median . All data are presented as mean ± S.D.

Figure 1: Metabolic disposition of taurolidine

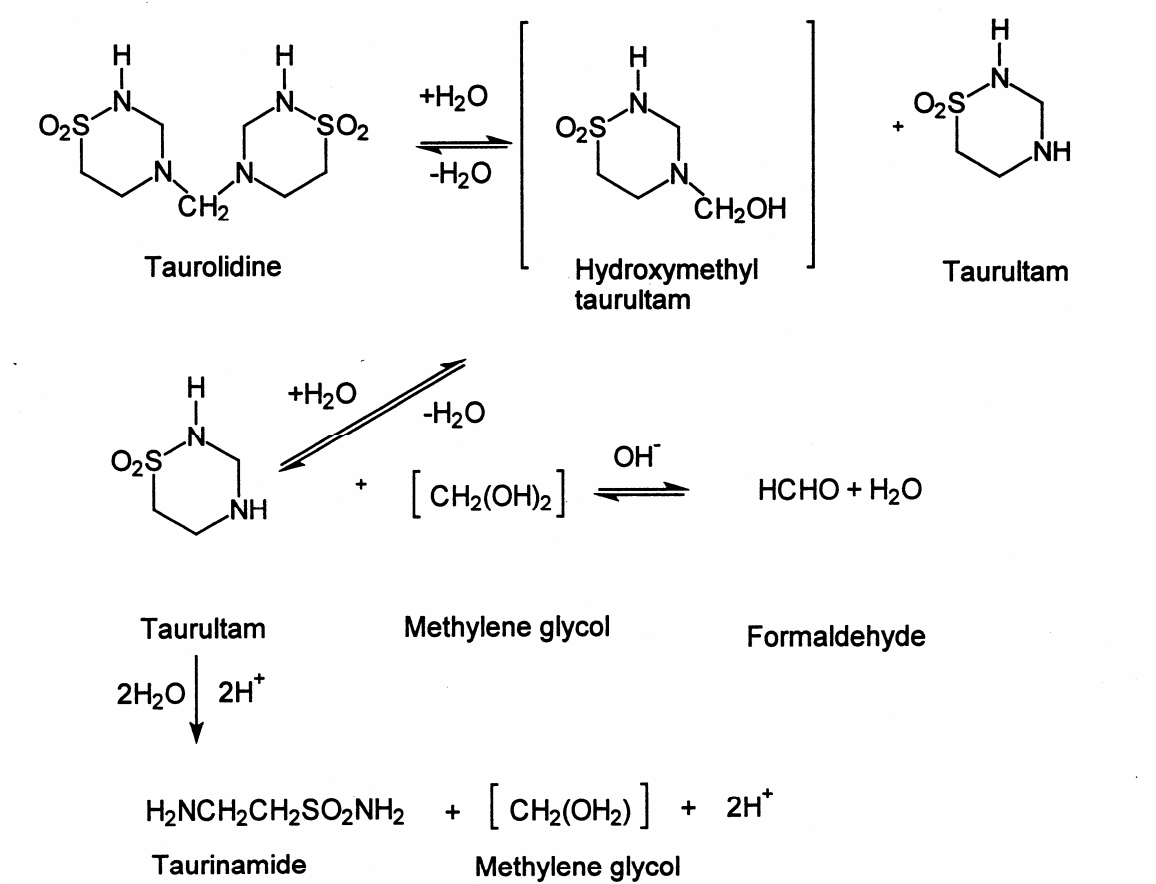


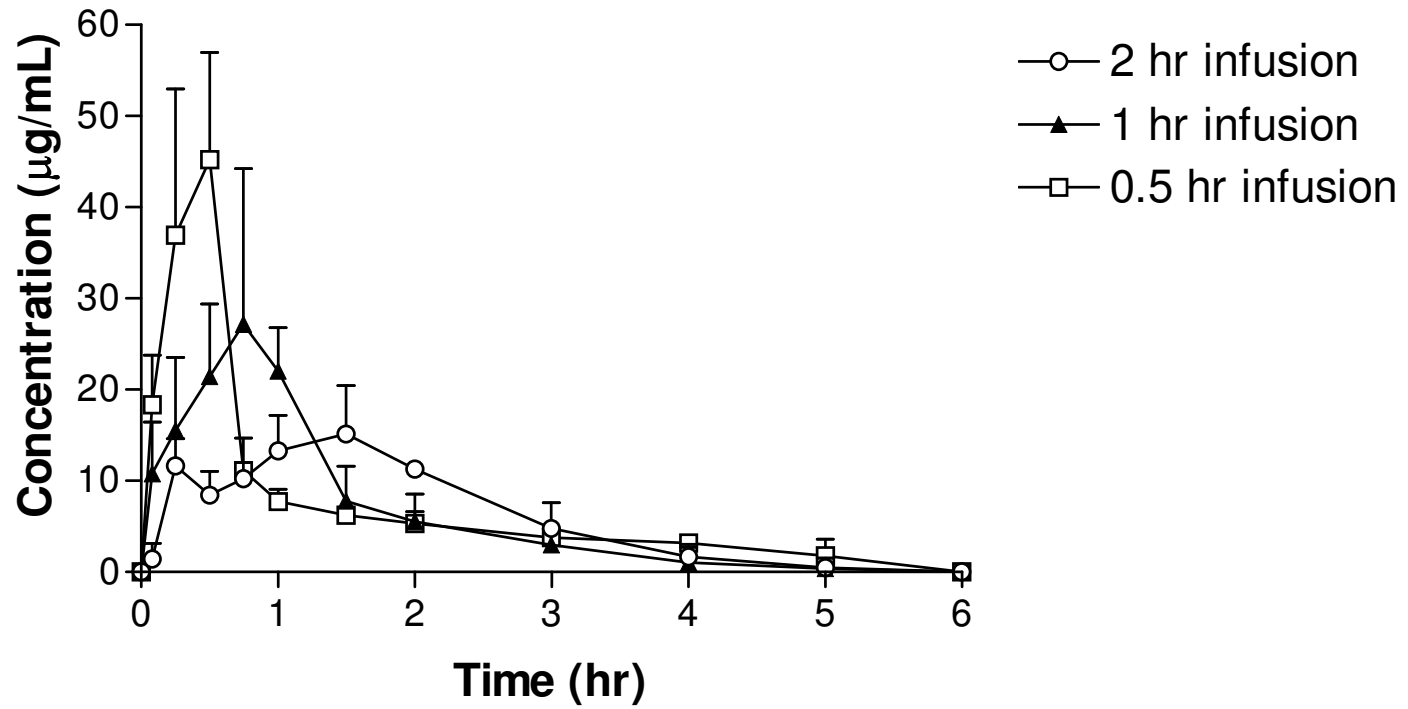
Figure 2: Concentration time curves for taurultam (TRT) and taurinamide (TRM) following intravenous infusion of taurolidine

Figure Legend

Figure 2 Time-concentration relationship of the taurolidine metabolites taurultam and taurinamide in three intravenous infusion groups. Panel (A) 2-, 1- and 0.5-h infusion groups for taurultam (B) 2-, 1- and 0.5-h infusion groups for taurinamide. All data were presented as mean \pm S.D.

Panel A, Figure 2

TRT by Duration of Infusion



Panel B, Figure 2

TRM by Duration of Infusion

