Interspecies Scaling of Tebufelone Pharmacokinetic Data and Application to Preclinical Toxicology

Charles A. Cruze,[1] Gary R. Kelm,[1,2] and Michael P. Meredith[1]

Received January 9, 1995; accepted January 24, 1995

Purpose. Retrospective application of allometric scaling techniques to tebufelone, a nonsteroidal antiinflammatory agent, in order to better understand the systemic exposure relationships between the doses administered to the species used in toxicology studies and the doses given to human subjects and patients in clinical studies. ***Methods.*** Non-compartmental estimates of tebufelone's total body volume of distribution during the terminal phase (V_z) and clearance (CL) obtained from intravenous dosing to rat, monkey, dog, and human were allometrically scaled to body weight, and body weight and brain weight, respectively. AUCs determined from single or multiple dose pharmacokinetic studies and from preclinical toxicology studies were plotted versus dose adjusted for bioavailability and divided by allometrically scaled clearance to produce an allometric relationship suggesting a non-linear increase in AUC with dose across the four species. ***Results.*** Segmental linear regression analysis of this relationship indicates a change point associated with an AUC of approximately 2,300 ng-hr/mL. Elevations in serum levels of various liver enzymes or associated signs of hepatic toxicity occur in some, but not all of the animals exposed for more than three weeks in repeat dosing studies at the actual dose that this represents. ***Conclusions.*** The analysis suggests that doses producing tebufelone plasma levels above a certain threshold AUC and duration of exposure to parent tebufelone are associated with increased risks of hepatic effects. Whether this is because metabolic shifts occur at these doses cannot be determined from these data.

INTRODUCTION

Tebufelone, 1-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-5-hexyn-1-one (Figure 1), is a nonsteroidal antiinflammatory agent for which clinical development has been terminated. In repeated dose toxicology studies, tebufelone doses of 5 mg/kg were considered to be no observable adverse effect doses for rat, dog and primate. Doses of 15 mg/kg and above resulted in dose related increases in relative and absolute liver weights in all three species. Elevations in various liver enzymes or associated signs of hepatic toxicity occur in some, but not all of the animals exposed for more than three weeks in repeat dosing studies at 15 mg/kg or higher. As with other NSAIDs, higher doses produced toxicities in the kidney or gastrointestinal tract. In multiple dose clinical trials of four or twelve weeks, dosages of 50 to 200 mg were associated with reversible, asymptomatic, marked (>8X upper limit of normal) elevations of serum alanine amino transferase (ALT) and aspartate amino transferase (AST) in several patients. Similar elevations were observed in two of five patients who received a 400 mg dose for four weeks.

In order to better understand the systemic exposure relationships between the doses administered to the species used in toxicology studies and the doses given to human subjects and patients in clinical studies, we have retrospectively applied allometric scaling techniques to tebufelone (1,2,3,4,5).

MATERIALS AND METHODS

Drug

Tebufelone from several lots prepared at the Miami Valley Laboratories of the Procter & Gamble Co., Cincinnati, OH, or at its subsidiary, the J. T. Baker Chemical Co., Phillipsburg, NJ was used in the various preclinical and clinical studies. Purity was greater than 97% in all cases.

Intravenous Studies

Rats, dogs, monkeys and humans were dosed intravenously with tebufelone. The human subjects were given a 25 mg dose (~0.36 mg/kg), rats and monkeys were given 2 mg/kg and dogs were given 2.5 mg/kg. Additional studies in dogs incorporated intravenous doses of 1, 5, and 10 mg/kg. See Table 1 for study identification.

The vehicles used for drug administration were a phospholipid emulsion in the rat and dog studies and a mixed solvent vehicle in the monkey and human studies. Intravenous dosing was in the antecubital vein of humans, in the femoral vein of monkeys and dogs, and in the jugular vein of ras. In the case of humans, monkeys, and dogs, serial blood samples were collected from the vein contralateral to the one used for dosing. For the rats, groups of three rats were sacrificed at scheduled collection intervals, and blood was collected from the vena cava. In all studies, blood was collected at prescheduled times up to 72 hours after dosing (24 hours for rats). Actual postdosing sampling times were recorded. Plasma was obtained by centrifugation and stored frozen until the time of analysis.

Oral Studies

Single and multiple oral dose pharmacokinetic studies were conducted in rats, primates and humans. Oral doses were administered to rats and primates by gavage as a fine suspension in 1% methyl cellulose. The solid dosage forms employed in the human studies consisted of a granulated solid dispersion in hard gelatin capsules (AI01) and a self-emulsifying lipid solution in soft elastic gelatin capsules (AI09).

Single doses of 2 (WKS-61) and 10 mg/kg (MEL-011) and once daily multiple doses (28 days) of 5, 15, and 50 mg/kg (MD-1) were administered to rats. Groups of three rats were sacrificed at scheduled time points to obtain blood from the vena cava in the single dose studies. Plasma concentration-time profiles were determined in rats over a 24

[1] The Procter & Gamble Company, Miami Valley Laboratories, P.O. Box 398707, Cincinnati, Ohio 45239-8707.

[2] To whom correspondence should be addressed.

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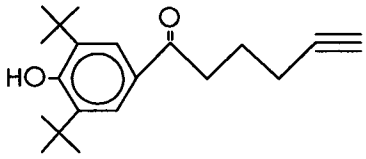

Fig. 1. Chemical structure of tebufelone.

hour period following the last dose of the multiple dose study. Plasma was obtained by centrifugation and stored frozen until the time of analysis.

The dosages employed in a single-dose monkey study were 5, 15, 25, and 100 mg/kg (HPSE 410). Serial blood samples were collected at scheduled times up to 72 hours after dosing. Following a wash out period of approximately four weeks, the same animals were used in a multiple dose study. They were dosed once daily for 26 days (HPSE 414), at the same dose level that the animals had been given in the single dose study. An additional group, dosed at 50 mg/kg was included in the multiple dose study. Periodic trough samples (blood collection just prior to the next dose) were collected during this period, and blood was sampled at scheduled intervals up to 72 hours after the last dose on day 26. Trough plasma concentrations were measured on days 8, 15, 22, 28 and 91 in a six-month primate study (HPSE 424) and a terminal plasma concentration-time profile (24 hour) was also obtained in this study. Plasma was obtained by centrifugation and stored frozen until the time of analysis.

In man, single doses administered ranged from 5 to 800 mg (AI01). In a multiple dose study, 200 to 1000 mg was administered once daily for two weeks (AI09). In both studies, serial blood samples were collected at scheduled times up to 96 hours following the last dose. Plasma was obtained by centrifugation and stored frozen until the time of analysis.

Plasma Analysis

Plasma samples were assayed for tebufelone at Oneida Research Services Inc. (Whitesboro, NY) using a capillary GC/MS/MS method with a stable isotope internal standard and selective reaction monitoring (6). The intravenous rat study was conducted early in the tebufelone development program, and samples were analyzed by GC-MS methods (7).

Pharmacokinetic Analyses

Non-compartmental pharmacokinetic analyses were employed to estimate the pharmacokinetic parameters for tebufelone after oral and intravenous dosing (8). The terminal rate constant (λ_z) was determined by log-linear regression of the terminal time points of the plasma concentration-time curve (selected by inspection of a log-linear plot). Area under the plasma concentration-time curve (AUC) was calculated according to Equation 1:

$$AUC_{0-\infty} = AUC_{0-t_{last}} + \frac{C_{t_{last}}}{\lambda_z} \quad (1)$$

$AUC_{0-t_{last}}$ to the last point (t_{last}) at which concentrations were detectable ($C_{t_{last}}$) were calculated using the trapezoidal rule. Tebufelone total clearance (CL/F) was calculated by dividing the administered dose by the AUC, and apparent volume of distribution (terminal phase) (V_z/F) was determined by dividing CL/F by λ_z. Bioavailability (F) in the several species was estimated by the ratio of dose corrected oral AUC to intravenous AUC. This estimation involved comparison of population AUCs since intravenous studies were not always conducted in the animals/subjects receiving oral doses.

Allometric Scaling of Pharmacokinetic Parameters

Allometric parameters for volume of distribution (V_z) were obtained by fitting V_z parameters obtained from non-compartmental pharmacokinetic analyses of the single intravenous dosing studies (Table I) and mean body weight (W) to Equation 2 using log-log regression.

$$V_z = a_1 W^{x_1} \quad (2)$$

Where a_1 and x_1 are the allometric constant and power coefficient, respectively.

The allometric parameters for clearance (CL) were determined as a function of both body weight and brain weight (BW):

$$CL = a_2 W^{x_2} BW^{y_2} \quad (3)$$

The parameters of Equation 3 were fit to the clearance values determined from single intravenous dose pharmacoki-

Table I. Body Weight and Pharmacokinetic Parameters for Intravenous Tebufelone

Species	Study	Body[a] wt. (kg)	Brain wt.[b] (kg)	Dose[c] (mg)	AUC[d] (ng-hr./mL)	CL(tot) (mL/min)	V_z (L)	$T_{1/2}$ (hr)
Rat	WKS-61	0.2	0.00150	0.4	799	8.34	2.04	2.82
Monkey	HPSE336	4.7	0.05328	10.0	2097	79.5	248	36.0
Dog	HPSE246	12.3	0.06531	30.7	1318	388	998	29.7
Man	AI04A	72.9	1.59339	25.0	579	720	2218	35.6

[a] Mean body weight of species participating in the intravenous pharmacokinetic studies.
[b] Brain weight estimated based on Mordenti and Chappell (6).
[c] Dose in mg used in intravenous pharmacokinetic dosing studies.
[d] Pharmacokinetic parameters—AUC, CL, V_z and $T_{1/2}$ calculated from intravenous pharmacokinetic studies.

netic studies in the four species using Marquardt-Levenberg non-linear curve fitting techniques.

If we assume monoexponential decay (a single compartment model is often adequate to describe dosing interval kinetics although it may not be applicable to the total plasma concentration curve), elimination of drug is described by Equation 4. Substituting Equations 2 and 3 for volume of distribution and clearance, respectively, into Equation 4 and rearranging, yields Equation 5.

$$C = \frac{F \cdot D}{V} \exp\left(-\frac{CL}{V} \cdot t\right) \tag{4}$$

Where C = concentration, F = bioavailability (F = 1 for intravenous dosing), D = dose, t = time, V = volume of distribution.

$$\frac{C}{\frac{F \cdot D}{a_1 W^{X_1}}} = \exp\left(-\left(a_2/a_1\right) \cdot W^{(x_2 - x_1)} \cdot BW^{y_2} \cdot t\right) \tag{5}$$

Plasma concentration data obtained from the intravenous pharmacokinetic studies in the four species were normalized for dose and volume of distribution, and time was adjusted according to the methods of Boxenbaum (3,4,9). The expression for plasma concentration in Equation 5 applies to all species. Its time component is expressed in units of physiological time and reflects the fraction of plasma cleared over a life-time of the species assuming constant drug input.

Similarly, AUC is a function of bioavailable dose and clearance (Equation 6). Thus, substituting for clearance (Equation 2) in Equation 6 yields Equation 7.

$$AUC = \frac{F \cdot D}{CL} \tag{6}$$

$$AUC = \frac{F \cdot D}{(a_2 W^{x_2} \cdot BW^{y_2})} \tag{7}$$

Segmented Regression Analysis

Area under the curve determined from single or multiple dose pharmacokinetic studies and from the toxicology studies was plotted versus dose adjusted for bioavailability and divided by allometrically scaled clearance according to Equation 7. A two-phase segmented-linear regression analysis was conducted to determine the change point of the resultant curve (10). Regression parameters and the change point ($\hat{X}_c$) in Equation 8 were estimated using weighted least squares due to variance heterogeneity of AUC across the range of adjusted dose. The regression used the weights $w_i = 1/\sigma_i^2$, where σ_i^2 is the variance of the ith AUC.

$$Y_i = AUC_i = \alpha + \begin{cases} \beta_1(AUC' - \hat{X}_c) + \epsilon_i, \text{ for } \hat{X}_c > AUC' \\ \beta_2(AUC' - \hat{X}_c) + \epsilon_i, \text{ for } \hat{X}_c \leq AUC' \end{cases} \tag{8}$$

where AUC' = Allometric identity for AUC (F dose/(allometric clearance)), Equation 7, $\hat{X}_c$ = change point (dose when slope of response changes), α = point of intersection when dose = $\hat{X}_c$, β_1 = slope of line for dose < $\hat{X}_c$, β_2 = slope of line for dose ≥ $\hat{X}_c$, ϵ_1 = random error term with variance σ_i^2.

RESULTS AND DISCUSSION

Intravenous Studies

Mean body weights of animals and humans participating in the intravenous dosing studies are given in Table I. Brain weights for the study subjects were estimated by interpolation of data from Mordenti(4) for mean W of the study population. Administered dose (mg) and calculated pharmacokinetic parameters for these intravenous dosing studies are also presented.

Equation 2 was used to model the volumes of distribution (V_z) obtained from the single dose intravenous pharmacokinetic studies in the four species (Table I) as a function of body weight using linear regression. Equation 3 was used to model clearance values obtained from those studies as a function of body weight and brain weight using Marquardt-Levenberg non-linear fitting techniques. The resultant expressions for volume of distribution and clearance are presented as Equations 9 and 10, respectively:

$$V_z = 22.78 \cdot W^{1.237} \qquad R^2 = 0.976 \tag{9}$$

$$CL = 0.436 \cdot W^{1.816} \cdot BW^{-0.819} \qquad R^2 = 0.987 \tag{10}$$

While exponents for volume of distribution often tend to cluster near 1,(2,3,4,11) there are notable exceptions to this generality (5,12,13). The exponent for tebufelone's volume of distribution was greater than 1 (1.237), indicating that the volume per body weight increases with body size. This might reflect additional binding to tissues or depoting in fat with increasing size. Tissue or protein binding estimates were not obtained in these studies; therefore, volumes were not corrected for protein binding. Since V_z is dependent on λ_z, estimates of λ_z and V_z made based on studies conducted early in development programs may have underestimated λ_z because of sensitivity limits of early analytical methods. While these explanations might reduce the volume exponent nearer to 1, it is still probable, based on tebufelone's lipophilicity,(14) that the exponent will still be greater than 1.

Total clearance, rather than intrinsic clearance, was used as the pharmacokinetic parameter for scaling. For some compounds, especially those eliminated primarily by renal filtration, clearance can be scaled as a function of body weight. Although tebufelone's clearance could be characterized as a function of body weight, when substituted into Equation 5, this single parameter approach did not predict the kinetic behavior as well as clearance parameterized as a function of both brain weight and body weight.

Boxenbaum was among the first to suggest that clearance of drugs eliminated primarily by Phase I oxidative processes could be best described by a two power function incorporating both body weight and brain weight. In this way, clearance of the compound is adjusted to the maximum

clearance potential for the compound over the life span of the organism (3,4,11,12). This approach has been applied primarily to low clearance drugs. Tebufelone is eliminated predominately by oxidative metabolism in all four test species, but at low doses, it is a high clearance drug. However the incorporation of the additional brain weight parameter provided a good empirical fit to these data, and since the four species of interest were used in this empirical approach, the data can be generalized over the range studied.

The allometric parameters for volume of distribution and clearance were substituted into Equation 5, and the dose, plasma concentrations, and observation times for each species were allometrically scaled according to Equation 5. The resultant scaled plasma profile is shown in Figure 2.

There is a good fit of the allometrically scaled data for intravenous tebufelone (r = 0.99) across all four species to a triexponential equation using Marquardt-Levenberg techniques. This suggests similar handling and disposition of the drug by rat, dog, monkey and man. Though the scaled data were derived using allometric fits of pharmacokinetic parameters determined by non-compartmental pharmacokinetic analyses, the curve displays distinct poly-exponential characteristics. This poly-exponential behavior was also noted in the individual intravenous dosing studies in the four species. It can be explained in the allometrically scaled data if the various volumes of distribution associated with a multicompartment pharmacokinetic model all scale to a similar allometric exponent. This type of behavior has been previously reported (12,15).

Area Under Curve Considerations

With the exception of drugs which irreversibly bind to or destroy receptors or tissues, the pharmacokinetic measures of importance with regard to toxicity are average steady state concentration, Cmax and AUC.[3,4,6,25] Maximum concentration tends to be more important for acute toxicity and overdose situations, e.g., barbiturate intoxication or cardiac arrest following lidocaine overdose.

Often chronic toxicity is related to total systemic exposure. The average steady state plasma levels or dosing interval AUC are the pertinent pharmacokinetic measures of the total exposure. Since the toxicities noted with tebufelone were both dose and time dependent, exposure relationship based on AUC should be the most relevant comparisons for interspecies comparisons.

Area under the curve data are plotted in Figure 3, according to Equation 7, as a function of bioavailable-dose divided by allometrically scaled clearance. A plot of AUC versus its allometric identity (F · Dose/allometric-clearance) should be linear if clearance and bioavailability remain constant. As shown in Figure 3, this linear relationship is maintained only at low doses, suggesting a change in clearance or bioavailability across the four species studied. Increased bioavailability is an unlikely explanation. A more likely explanation is decreased clearance. Since all four species clear tebufelone by oxidative metabolism, it is possible that one or more pathways for clearance become saturated at higher doses or after repeated dosing.

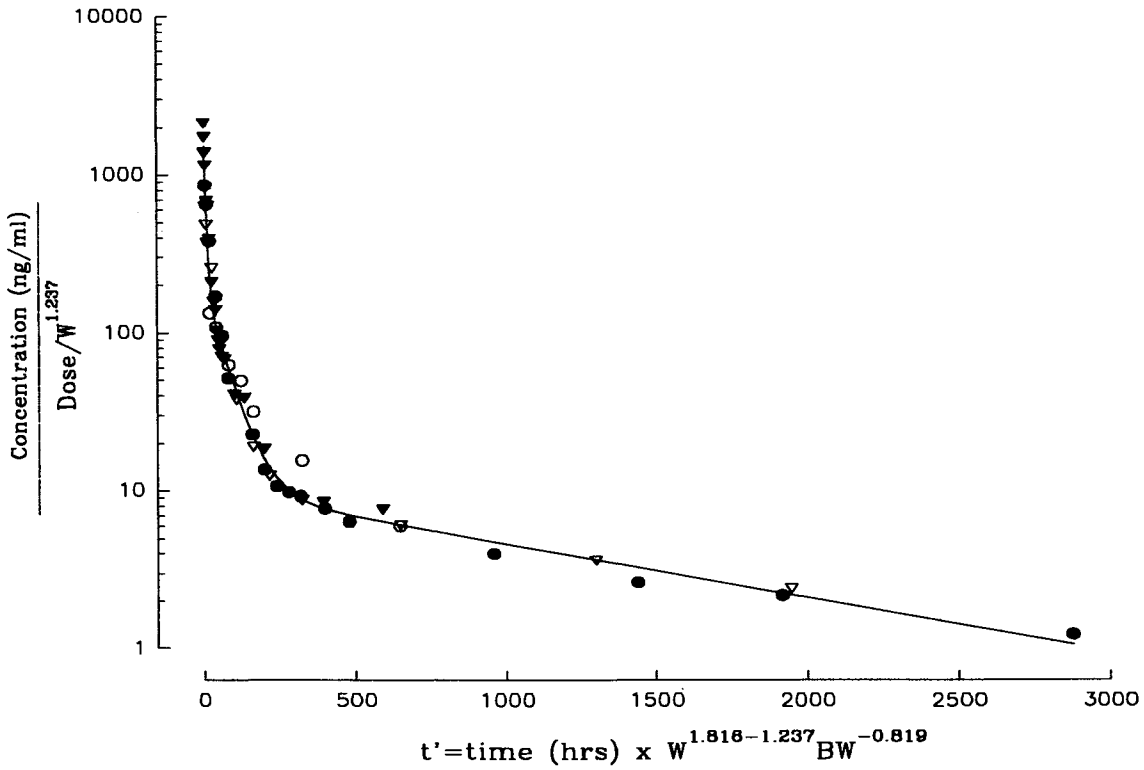

Fig. 2. Allometrically scaled plasma profiles of tebufelone in rat ○, dog ●, monkey ▽, and man ▼ following intravenous dosing of tebufelone. Plasma concentrations obtained from intravenous pharmacokinetic studies in the four species were adjusted for concentration and time according to Equation 5. Non-linear regression yielded the following triexponential equation: $C = 1864e^{-1.58t'} + 190e^{-0.0165t'} + 10.16e^{-0.00079t'}$ with an R = 0.99.

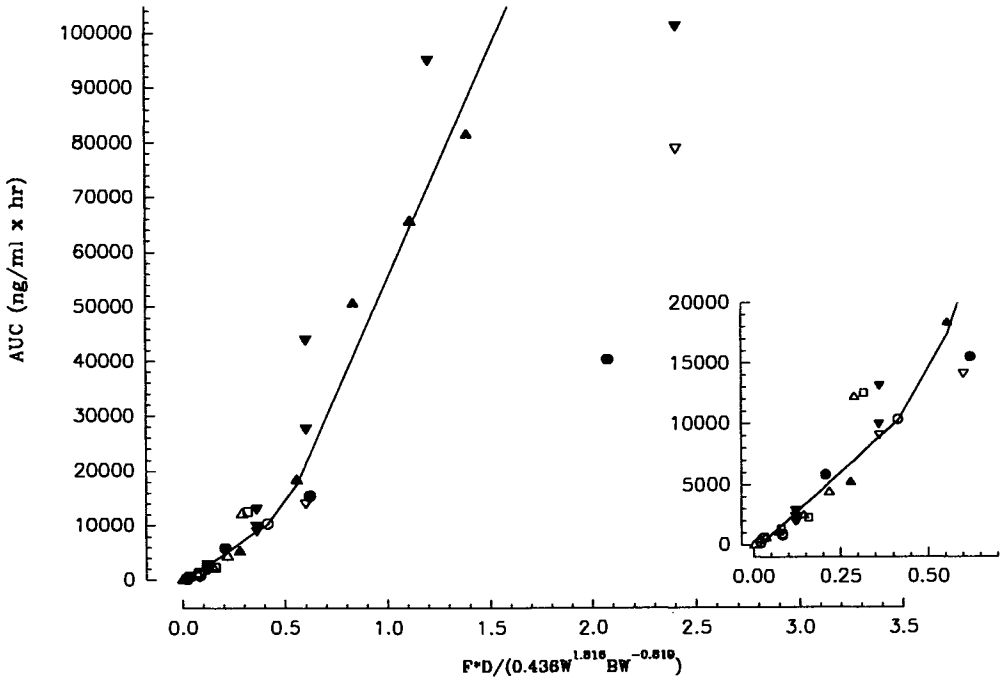

Fig. 3. Area under the curve measurements from rat single dose single ○, rat multiple dose ●, monkey single dose ▽, monkey multiple dose ▼, dog single dose □, human single dose △, and human multiple dose ▲ pharmacokinetic and toxicology studies versus F dose/Allometric Clearance. The inset is the portion of the curve between 0 and 0.6 on the x scale. The fit is described in the text.

Segmented linear regression analysis (Equation 8) indicated that this change point corresponds to X = 0.496 and AUC = 12,321 with slopes before and after the change points of 25,848 and 84,493, respectively (Equation 11), which are significantly different from each other ($p < 0.001$).

$$\hat{AUC}_i = 12{,}321 + \begin{cases} 25{,}848 \cdot (AUC' - 0.496), \text{for } 0.496 > AUC' \\ 84{,}493 \cdot (AUC' - 0.496), \text{for } 0.496 \leq AUC' \end{cases} \quad (11)$$

The change-point at 0.496 is associated with area under the curve measurements near 12,300 ng-hr/mL. Elevations in serum levels of various liver enzymes or associated signs of hepatic toxicity occur in some, but not all of the animals exposed for more than three weeks in repeat dosing studies at the actual dose that this represents. This change-point represents approximately 200-400 mg for humans, 14-20 mg/kg for rats, 12-14 mg/kg for primates, and 14-19 mg/kg for the dog.

Three points, X-values > 2, are outliers. Two points, represented by the triangles, were from primate studies and are the 100 mg/kg single and multiple dose groups. Data from these studies indicate the probability of a limited time window for drug absorption as it passes through the GIT. Under these dosing conditions, AUCs obtained with the 100 mg/kg dose were equivalent with those obtained with 50 mg/kg (unpublished data). The bioavailability adjustments that we made for allometric scaling would not apply to these data since that dose behaved more as a 50 to 60 mg/kg dose, instead of 100 mg/kg. If, however, 50 to 60 mg/kg were used as the dose, these points would fall on the line. For these reasons, the 100 mg/kg data were excluded form the segmented regression analysis.

The third point that is not consistent with the rest of the data is from a multiple dose rat study. This point was also excluded from the analysis. At lower doses, the bioavailability of oral tebufelone in the rat approaches unity, but at higher doses, there are limited data for comparison. Further, in other studies in the rat, tebufelone has been shown to induce P450 enzyme systems which may be responsible for its metabolism. Either of these factors would result in lower observed AUCs.

This analysis does not allow us to draw any conclusions about possible mechanisms or association with the toxicities observed. Tebufelone metabolite profiles were not identified and followed in these studies. No attempt has been made to scale any metabolite pharmacokinetic data. The analysis does suggest that doses producing tebufelone plasma levels above a certain threshold AUC and duration of exposure to parent tebufelone are associated with increased risks of hepatic effects. Whether this is because metabolic shifts occur at these doses cannot be determined from these data.

CONCLUSIONS

We demonstrated that the intravenous plasma profile of tebufelone could be allometrically scaled across rat, dog, monkey and man. Tebufelone's volume of distribution was described by a simple power function of body weight. Total clearance was best described by a two power function incorporating both body weight and brain weight.

A plot of AUC measurements obtained from single and multiple dose studies versus its allometric equivalent re-

vealed a curve with two linear segments having distinct slopes suggesting a change in clearance at higher doses. Doses or AUCs exceeding the intersection point on this curve are associated with hepatic toxicity or elevated plasma levels of hepatic enzymes in the toxicology species. No causality can be assigned based on data presented herein.

APPENDIX

Summary of Study Information Used to Derive the AUC versus Adjusted Dose (D') Relationships

Species	Study ID	Study Type[a]	W (kg)	BW (kg)	Dose (mg)	Dose (mg/kg)	AUC (ng-hr/mL)	D'	F
Rat	WKS-61	SD-IV	0.2	0.0015	0.4	2	799	0.08	1
Rat	WKS-61	SD-IV	0.2	0.0015	0.1	0.5	173	0.02	1
Rat	WKS-61	SD-og	0.2	0.0015	0.4	2	904	0.08	1
Rat	MEL-01	SD-og	0.2	0.0015	2	10	10300	0.42	1
Rat	MD-1	og,qdx28d	0.2	0.0015	1	5	5830	0.21	1
Rat	MD-1	og,qdx28d	0.2	0.0015	3	15	15500	0.62	1
Rat	MD-1	og,qdx28d	0.2	0.0015	10	50	40200	2.08	1
Monkey	HPSE336	SD-IV	4.7	0.0533	10.0	2.13	2100	0.13	1
Monkey	HPSE410	SD-og	4.7	0.0533	23.5	5	2040	0.12	0.41
Monkey	HPSE410	SD-og	4.7	0.0533	70.5	15	9100	0.36	0.41
Monkey	HPSE410	SD-og	4.7	0.0533	117.5	25	14100	0.60	0.41
Monkey	HPSE410	SD-og	4.7	0.0533	470	100	78900	2.41	0.41
Monkey	HPSE414	og,qdx26d	4.7	0.0533	23.5	5	2450	0.12	0.41
Monkey	HPSE414	og,qdx26d	4.7	0.0533	70.5	15	13200	0.36	0.41
Monkey	HPSE414	og,qdx26d	4.7	0.0533	117.5	25	27800	0.60	0.41
Monkey	HPSE414	og,qdx26d	4.7	0.0533	235	50	95100	1.20	0.41
Monkey	HPSE414	og,qdx26d	4.7	0.0533	470	100	101000	2.41	0.41
Monkey	HPSE424	og,qdx26w	3.3	0.0374	16.5	5	2910	0.12	0.41
Monkey	HPSE424	og,qdx26w	3.3	0.0374	49.5	15	10000	0.36	0.41
Monkey	HPSE424	og,qdx26w	3.3	0.0374	82.5	25	44100	0.60	0.41
Dog	HPSE246	SD-IV	12.3	0.0653	30.7	2.5	1320	0.08	1
Dog	HPSE246	SD-IV	12.3	0.0653	12.3	1	626	0.03	1
Dog	HPSE246	SD-IV	12.3	0.0653	61.5	5	2300	0.16	1
Dog	HPSE246	SD-IV	12.3	0.0653	123	10	12500	0.32	1
Man	AI04	SD-IV	72.9	1.5934	25.0	0.34	579	0.03	1
Man	AI01	SD-po	72.9	1.5934	5	0.07	29	0.00	0.26
Man	AI01	SD-po	72.9	1.5934	50	0.69	446	0.02	0.26
Man	AI01	SD-po	72.9	1.5934	100	1.37	613	0.04	0.26
Man	AI01	SD-po	72.9	1.5934	200	2.74	1060	0.07	0.26
Man	AI01	SD-po	72.9	1.5934	400	5.49	2470	0.14	0.26
Man	AI01	SD-po	72.9	1.5934	600	8.23	4380	0.22	0.26
Man	AI01	SD-po	72.9	1.5934	800	10.97	12200	0.29	0.26
Man	AI09	po,qdx14d	72.9	1.5934	200	2.74	5210	0.28	1
Man	AI09	po,qdx14d	72.9	1.5934	400	5.49	18300	0.56	1
Man	AI09	po,qdx14d	72.9	1.5934	600	8.23	50600	0.83	1
Man	AI09	po,qdx14d	72.9	1.5934	800	10.97	65700	1.11	1
Man	AI09	po,qdx14d	72.9	1.5934	1000	13.72	81500	1.39	1

[a] po = per oral, og = oral gavage, SD = single dose, qd = daily, d = days, w = weeks, IV = intravenous.

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