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Pharmacokinetics of Buspirone following Oral Administration to Rhesus Monkeys

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Abstract

Pharmacokinetics of buspirone and its active metabolite, 1-pyrimidinyl piperazine (1-PP) following oral administration were assessed in rhesus monkeys at doses used in chronic toxicology studies. The study was conducted over four periods in three male and three female rhesus monkeys. In the first three periods, buspirone hydrochloride solution was administered in a randomized manner by oral gavage at doses (expressed as buspirone free base) of 12·5, 25 and 50 mg kg^{-1} once a day on days 1 and 7 and twice a day on days 2–6. In the last period, all monkeys received 25 mg kg^{-1} buspirone as a single daily dose for 7 days. Serial plasma samples were collected for analysis of buspirone and 1-PP on days 1 and 7 in the first three periods and on day 7 in the last period for assessment of single dose and steady-state pharmacokinetics.

Inter-animal variability in the pharmacokinetics of buspirone was high. Examination of C_{min} vs time plots revealed that the steady state was attained by day 7 except for one monkey who demonstrated much higher C_{min} values. For buspirone, dose proportionality was concluded for both C_{max} and AUC on day 1 but not on day 7. The accumulation factor on day 7 for buspirone was nearly 5 for C_{max} and 7 for AUC when compared with day 1. For 1-PP, dose proportionality was concluded except for C_{max} in male monkeys on day 7. In contrast to buspirone, 1-PP showed less than 2-fold accumulation in C_{max} and AUC values on day 7 compared with those on day 1. Exposure at a dose of 25 mg kg^{-1} once daily was in between the 12·5 mg kg^{-1} and 25 mg kg^{-1} twice-a-day regimens.

These results document dose-dependency in the steady-state pharmacokinetics of buspirone in rhesus monkeys.

Buspirone is a non-benzodiazepine anxiolytic drug effective in the treatment of generalized anxiety disorder (Goldberg & Finnerty 1979; Rickels et al 1982). Its efficacy is equivalent to that of benzodiazepines, although, unlike some benzodiazepines, buspirone is not noted for the development of tolerance or of a sequence of withdrawal symptoms upon discontinuation of therapy (Rickels et al 1988). In addition, it is not habit-forming and does not significantly impair psychomotor performance (Oritz et al 1987). The average effective oral dose of buspirone is 20 mg daily in divided doses with a maximum dose of 60 mg daily in divided doses. Although orally administered buspirone is well absorbed, its oral bioavailability is only about 4% due to extensive presystemic elimination and less than 1% of the dose is excreted unchanged in urine as intact buspirone (Gammans et al 1986). The average human exposure to one of its pharmacologically active metabolites, 1-pyrimidinyl piperazine (1-PP) is about 12-times higher than to buspirone (Gammans et al 1986).

Rhesus monkey was used as the non-rodent species for long-term safety evaluation of buspirone. This study was carried out to assess the pharmacokinetics and dose proportionality of buspirone and its active metabolite 1-PP in the rhesus monkey. The doses administered were those used in a 1-year toxicity study in which no adverse effects were seen at 25 mg kg^{-1} daily for 1 year. Higher doses produced CNS-related clinical signs, altered haematological and serum chemistry parameters, and organ weight changes. However, there

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were no drug-related morphological tissue changes at any doses given to monkeys. In the 1-year study, the mid (50 mg kg^{-1} daily) and high (100 mg kg^{-1} daily) doses were administered as two divided doses daily while the low (25 mg kg^{-1} daily) dose was administered as a single daily dose. The same dosing conditions were used in this pharmacokinetic study. The low dose was administered as one single dose daily in order to assess exposure to rhesus monkeys under the conditions used in the 1-year toxicity study and also as two divided doses daily in order to assess dose proportionality in the pharmacokinetics of buspirone.

Materials and Methods

Test drug and formulation

Buspirone hydrochloride (purity 99·7%) was dissolved in deionized water for oral dosing. Dosing solutions were prepared weekly on the day before day 1 of each dosing session. Dosing solutions were based on free-base equivalents of buspirone and were prepared by dissolving appropriate amounts of buspirone hydrochloride in 300 mL of deionized water to yield 10, 20 and 40 mg mL^{-1} buspirone for periods 1–3. The dosing solution for period 4 was prepared by dissolving an appropriate amount of buspirone hydrochloride in 1200 mL of deionized water to yield 10 mg mL^{-1} buspirone. All dosing solutions were stored in amber bottles at approximately 5°C until use. Samples of dosing solutions were stored at −15°C for analysis of buspirone.

Animals

Rhesus monkeys, 4·0–5·2 kg, obtained from either Sierra Biomedical Inc. (Sparks NV) or Laboratory Animal Breeders and Services (Yemassee, SC), were surgically implanted with a chronic venous catheter equipped with a subcutaneous vascular access port for blood collection. The monkeys were held in quarantine before their assignment to the study. Four days before dosing period 1, animals received a physical examination including haematology and serum-chemistry analyses and were selected for use based on acceptable health. Each monkey was identified by a unique number indicated by a permanent body tattoo. The animals were individually housed in stainless steel cages. The monkeys were fed LabChows Certified Primate Chow Brand Animal Diet 5048 (Purina Mills, Inc.) daily and were provided with free access to filtered water by an automatic system. As part of the test facility's primate enrichment program, the diet was supplemented with washed, fresh produce twice a day (this included a fruit and a vegetable).

The monkeys were controlled by the rope/pole and collar method of restraint to facilitate animal handling and performance of the technical procedures. On each day of dosing, animals were restrained in primate chairs for the period of dosing and until collection of the 4-h sample was complete, at which time they were returned to their individual cages. The rope and collar and cage restraint was used for all subsequent sample collections. At the conclusion of the in-life portion of the study, the monkeys were released to the test facility's general animal population.

Treatment administration

Buspirone was administered orally to the monkeys via gavage for seven days in a four-way crossover design. There was a two-week washout period between dosing periods. Three male and three female monkeys were treated in a randomized manner with either the high, mid or low dose of buspirone during periods 1, 2 and 3. In periods, 1–3, buspirone was administered at doses of 12·5, 25 and 50 mg (free base) kg^{-1} once a day on days 1 and 7 and twice a day on days 2–6. On days 1 and 7 only the morning dose was administered in order to assess the single-dose and steady-state pharmacokinetics of buspirone. In dosing period 4, buspirone was administered at a dose of 25 mg (free base) kg^{-1} once a day for 7 days to all animals. Doses were calculated based on the pre-treatment body weight and on dose volumes of 1·25 mL kg^{-1} per treatment. Following dosing, the gavage tube was flushed with 15 mL of deionized water.

Blood sample collection

Serial blood samples were collected in vacutainers containing K_3EDTA as the anticoagulant. Each blood volume was approximately 1·5 mL. Samples were collected before dosing and at 0·25, 0·5, 1, 2, 4, 6, 8, 12 and 24 h post-dose on days 1 and 7 in periods 1–3. In addition, predose blood samples were collected on days 3–6. In the last period, serial blood samples were collected predose and at 0·25, 0·5, 1, 2, 4, 6, 8, 12 and 24 h post-dose on day 7 only. Blood samples were processed to obtain plasma by centrifuging at 2500 *g* for 20 min at 5°C within 1 h of collection. Plasma samples were stored at −15°C until analysis.

Plasma sample analysis

Plasma samples were analysed for buspirone and 1-PP by liquid chromatography and atmospheric pressure ionization tandem mass spectrometry (LC-

API/MS/MS). Deuterated analogues of buspirone and 1-PP were used as internal standards. Briefly, buspirone, 1-PP and their deuterated analogues were extracted from rhesus monkey plasma using C18 solid-phase extraction cartridges and eluted with 3% ammonium hydroxide in acetonitrile. The eluate was taken to dryness using nitrogen, reconstituted with mobile phase and analysed by LC-API/MS/MS. The lower limit of quantitation (LLQ) was established at 0·1 ng mL^{-1} for buspirone and 0·2 ng mL^{-1} for 1-PP. The standard curves were linear over a range of 0·1–15 ng mL^{-1} and 0·2–25 ng mL^{-1} for buspirone and 1-PP, respectively. Quality control samples spiked to various concentrations with buspirone and 1-PP in rhesus monkey plasma were prepared and stored along with the study samples to assure sample stability during shipment and storage.

Pharmacokinetic evaluation

Plasma concentration–time data were analysed by non-compartmental pharmacokinetic methods (Riegelman & Collier 1980; Gibaldi & Perrier 1982). The highest observed concentration and the corresponding sampling time were defined as C_{max} and t_{max}, respectively. The elimination half-life ($t_{½}$) was estimated from $t_{½} = \ln 2/\lambda$ where λ is the slope of the regression line that best fitted the terminal portion of the log-linear concentration–time curve. The area under the concentration–time curve to the last >LLQ sampling time point ($AUC_{0\text{-}T}$), was calculated by a combination of the trapezoidal and log-trapezoidal rules. For the day-1 analysis, $AUC_{0\text{-}T}$ was extrapolated to infinity and is reported as AUC_{INF}. The extrapolated area was determined by dividing the last observed >LLQ concentration by λ. For the day-7 analysis, AUC over the dosing interval was reported as AUC_{TAU}. For treatments in periods 1–3, the dosing interval was 12 h while for the treatment in the last period, the dosing interval was 24 h. For 1-PP, AUC ratio was reported as the AUC of 1-PP divided by AUC of buspirone and was corrected for differences in the molecular weight. In the calculation of AUC ratio, AUC_{INF} was used on day 1 and AUC_{TAU} was used on day 7.

Statistical methods

The period and carry-over effects induced by the crossover design were assumed to be negligible due to the small sample size. Pharmacokinetic parameters from the fourth period were not included in the statistical analysis. The predose (C_{min}) concentrations were plotted vs time to check the attainment of steady state. C_{max} and AUC values were analysed to evaluate the effect of dose, day, gender and several interactions by an analysis of variance with repeated measures. The analyses were carried out using PC SAS, Version 6.1. For analysis of dose proportionality, C_{max} and AUC values were analysed using weighted linear regression with 1/dose as the weight. Nonlinearity was inferred by testing for model lack-of-fit (LOF) F statistic on the model without intercept. If statistically significant nonlinearity was found, the dose proportionality test was not pursued. If the LOF statistic was not significant, dose proportionality was concluded if the intercept was not statistically significantly different from zero. The accumulation ratio was obtained by dividing the slope of the AUC-vs-dose relationship on day 7 by the slope on day 1. Significant accumulation was concluded if the accumulation ratio was significantly larger than 1.

Results

Dosing-solution and plasma-sample analysis

Analysis of dosing solutions indicated that concentrations of buspirone were within 8% of the nominal concentration. Therefore nominal concentrations were used in the calculation of actual dose administered. Plasma standard curves had r^2 values of at least 0·998. The overall between- and within-day variability (%CV) of quality-control samples was within 7·7%. The mean observed concentration of the quality-control samples deviated by less than 7·9% from the nominal concentrations. The overall data along with the analysis of shipping quality control samples suggested that the samples were stable during shipment and storage and the assays were suitable for pharmacokinetic evaluation.

Animal observations

At the low and mid doses, there were no apparent drug-related effects. However, at the high dose, animals showed flushed faces, lethargy and blank stares periodically during the 7 days of dosing. The drug-related adverse effects became especially severe during period 2. In this period, the animals receiving the high dose showed mild effects such as lethargy and ataxia on day 2 of dosing and more marked adverse effects by day 3 of dosing. After receiving the fourth 50 mg kg^{-1} dose, the male monkey (No. 1) exhibited, in addition to the previously observed effects, loss of muscular control,

followed by a seizure and loss of consciousness, at approximately 30 min after dosing. After the seizure, the animal remained lethargic with a flushed face. Muscular control was slow to return and at 6 h post-dose the animal still had poor hand-eye coordination and was lying on the bottom of the cage. During the next 6 h post-dose, the animal remained in the same spot without eating and was unresponsive to stimuli. The female animal (No. 4) receiving the high dose in period 2 did not experience a seizure, but was flushed, lethargic and had tremors shortly after the fourth dose. Due to these adverse events, buspirone dosing was discontinued in these two animals for the remainder of period 2. A blood sample was obtained at approximately 12 h post-dose from these animals for analysis of buspirone and 1-PP. These animals received their buspirone doses in periods 3 and 4 as planned.

Pharmacokinetics of buspirone and 1-PP

Plasma concentrations of buspirone increased as the dose increased, with peak concentrations generally occurring within 1 h. Examination of predose plasma concentrations on days 3, 4, 5, 6 and 7 at each dose revealed that steady state was reached by day 7, except for monkey No. 1 who showed very high plasma concentrations of buspirone compared with other monkeys. No formal statistical analysis was performed. Pharmacokinetics of buspirone on day 1 and day 7 are therefore referred to as single-dose and steady-state pharmacokinetics, respectively. Inter-animal variability in the plasma concentrations of buspirone was quite high with concentrations differing by as many as 26-fold and coefficients of variation for AUC as high as 143% between the three animals of the same gender and at the same dose level.

Mean (s.d.) pharmacokinetic parameters for buspirone are shown in Table 1. Mean (s.d.) plasma concentration vs time plots at all dose levels are illustrated in Figures 1 and 2 for male and female monkeys, respectively. The analysis of variance indicated that the dose effect, day effect and dose-day interaction were significant for both C_{max} and AUC of buspirone. Since there was no gender effect, the data were pooled across gender for assessing the dose proportionality in the pharmacokinetics of buspirone. Dose proportionality was concluded for both C_{max} and AUC on day 1. Pharmacokinetics of buspirone was dose-linear but not proportional for both C_{max} and AUC on day 7. The accumulation ratios for buspirone on day 7 were approximately 5 for C_{max} and 7 for AUC_{TAU} (Table 4). Terminal elimination half-life ranged

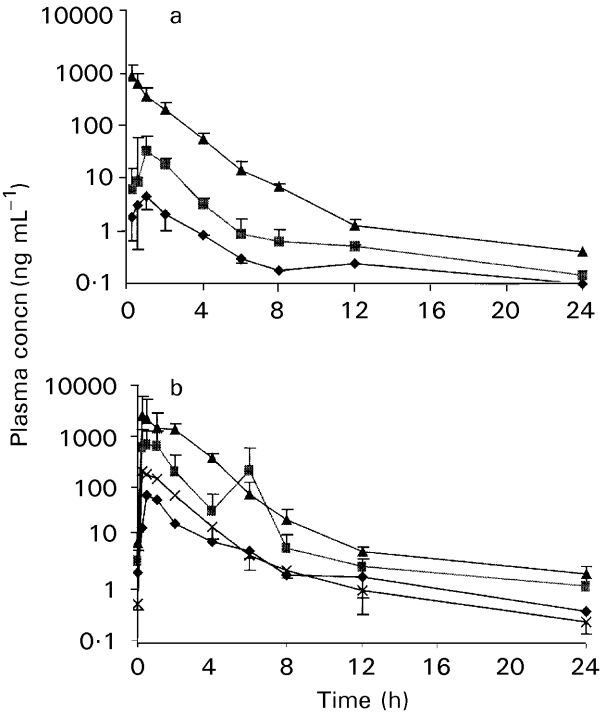

Figure 1. Mean (s.d.) plasma concentration-time profiles of buspirone on days 1 (a) and 7 (b) in male rhesus monkeys following oral doses of 12·5 (◆), 25 (■) or 100 (▲) mg kg^{-1} twice daily or 25 mg kg^{-1} once daily (×).

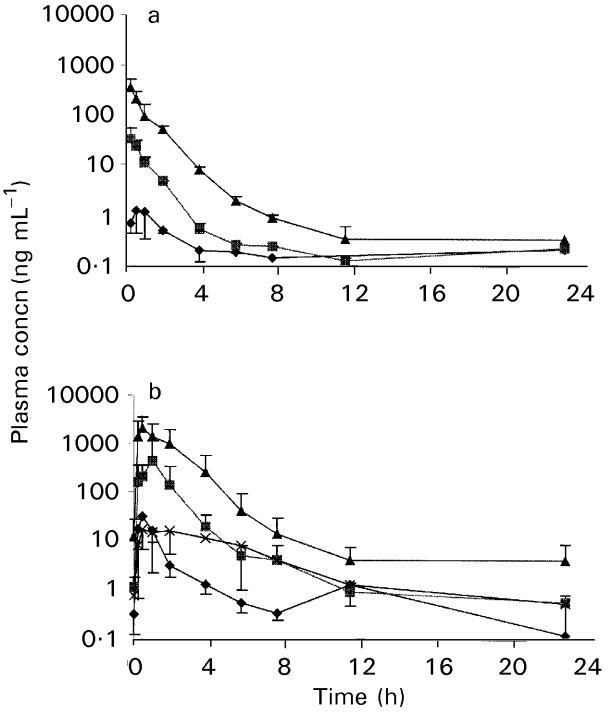

Figure 2. Mean (s.d.) plasma concentration-time profiles of buspirone on days 1 (a) and 7 (b) in female rhesus monkeys following oral doses of 12·5 (◆), 25 (■) or 100 (▲) mg kg^{-1} twice daily or 25 mg kg^{-1} once daily (×).

Table 1. Pharmacokinetic parameters of buspirone in rhesus monkeys.

Dose ($mg\,kg^{-1}\,day^{-1}$)	Gender	Single dose (day 1)		Steady state (day 7)	
		C_{max} ($ng\,mL^{-1}$)	AUC_{INF} ($ng\,h\,mL^{-1}$)	C_{max} ($ng\,mL^{-1}$)	AUC_{TAU} ($ng\,h\,mL^{-1}$)
25	M	4·82 (2·13)	10·1 (6·15)	71·3 (83·7)	140 (142)
	F	1·22 (0·75)	3·16 (0·82)	33·6 (38·5)	39·5 (32·3)
50	M	33·1 (49·7)	71·9 (103)	1031 (779)	1781 (1890)
	F	33·9 (35·2)	33·8 (23·5)	572 (598)	733 (833)
100	M	867 (872)	1194 (1141)	4988, 1734[a]	7533, 3826[a]
	F	357 (335)	346 (282)	3209, 965[a]	7250, 1592[a]
25[b]	M	ND	ND	209 (329)	405 (561)
	F	ND	ND	27·4 (1·99)	106 (48·1)

Values are presented as mean (s.d.); n = 3. [a]n = 2, individual values are reported. [b]Administered as a single daily dose; all others administered in two divided doses. ND = not determined.

Table 2. Pharmacokinetic parameters of 1-PP in rhesus monkeys.

Dose ($mg\,kg^{-1}\,day^{-1}$)	Gender	Single dose (day 1)		Steady state (day 7)	
		C_{max} ($ng\,mL^{-1}$)	AUC_{INF} ($ng\,h\,mL^{-1}$)	C_{max} ($ng\,mL^{-1}$	AUC_{TAU} ($ng\,h\,mL^{-1}$)
25	M	121 (50·7)	772 (444)	161 (46·1)	962 (181)
	F	96·6 (35·3)	439 (70·5)	134 (45·0)	587 (254)
50	M	256 (84·6)	1742 (964)	449 (71·7)	2545 (654)
	F	334 (162)	1266 (189)	303 (146)	1537 (434)
100	M	920 (334)	5686 (2183)	1248, 952[a]	8411, 5790[a]
	F	558 (309)	2910 (1110)	922, 879[a]	6540, 3858[a]
25[b]	M	ND	ND	252 (91·1)	2100 (822)
	F	ND	ND	157 (71·4)	1204 (340)

Values are presented as mean (s.d.); n = 3. [a]n = 2, individual values are reported. [b]Administered as a single daily dose; all others administered in two divided doses. ND = not determined.

from less than 1 h to 23 h. The long $t_{1/2}$ is most probably a reflection of lack of adequate data points in the terminal elimination phase. Exposure of buspirone at the $25\,mg\,kg^{-1}$ once-daily dose was generally in between that at the $12{\cdot}5\,mg\,kg^{-1}$ twice-daily and $25\,mg\,kg^{-1}$ twice-daily dose levels.

Mean (s.d.) pharmacokinetic parameters for 1-PP are shown in Table 2. Mean (s.d.) plasma 1-PP concentrations vs time plots are shown in Figures 3 and 4 for male and female monkeys, respectively. Plasma concentrations of 1-PP also increased in relation to dose, with peak concentrations generally occurring within 1–2 h. Predose plasma concentrations on days 3, 4, 5, 6 and 7 indicated that steady state was probably reached by day 7. Inter-animal variability in the plasma concentrations of 1-PP was much less compared with that for buspirone. The analysis of variance indicated that the gender and dose effects were significant for C_{max}, and the dose and gender-dose interaction were significant for AUC. Hence, dose proportionality in the pharmacokinetics of 1-PP was analysed separately by gender. Pharmacokinetics of 1-PP was found to be dose proportional except for C_{max} values in male monkeys on day 7. On day 7, C_{max} values in male monkeys were dose-linear but showed a non-zero intercept indicating lack of dose proportionality. The accumulation ratios for 1-PP on day 7 were less than 2 for both C_{max} and AUC. The terminal elimination half-life for 1-PP was generally around 5 h. Plasma concentrations of 1-PP at the $25\,mg\,kg^{-1}$ once-daily dose were in between those at the $12{\cdot}5\,mg\,kg^{-1}$ twice-daily and $25\,mg\,kg^{-1}$ twice-daily dose levels.

Exposure to 1-PP was always greater than to buspirone. The AUC ratios (Table 3) of 1-PP to buspirone were highest at the low dose on day 1. As the dose increased, the AUC ratios of 1-PP to buspirone decreased from a mean of 184 to 17·4 in male monkeys and 333 to 46·9 in female monkeys on day 1. The AUC ratios at steady state were always lower than those after the single dose and decreased as the dose increased. At steady state, the mean AUC ratios decreased from 30·0 to 3·1 in

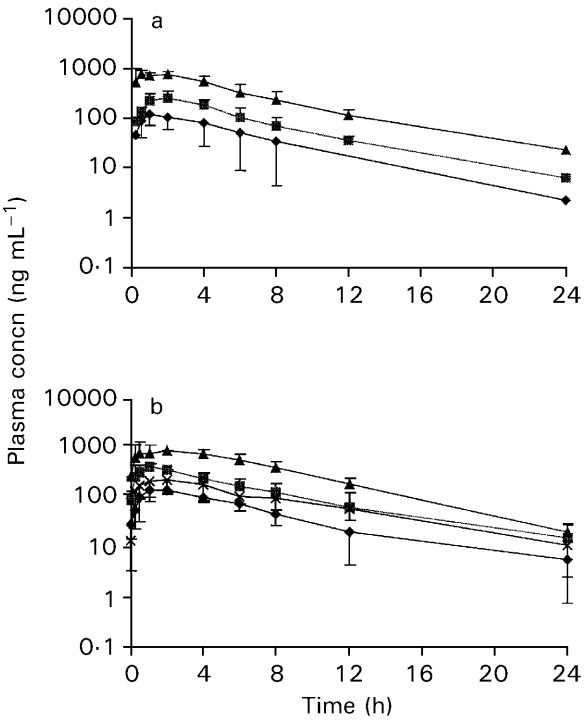

Figure 3. Mean (s.d.) plasma concentration-time profiles of 1-PP on days 1 (a) and 7 (b) in male rhesus monkeys following oral doses of 12·5 (◆), 25 (■) or 100 (▲) mg kg^{-1} twice daily or 25 mg kg^{-1} once daily (×).

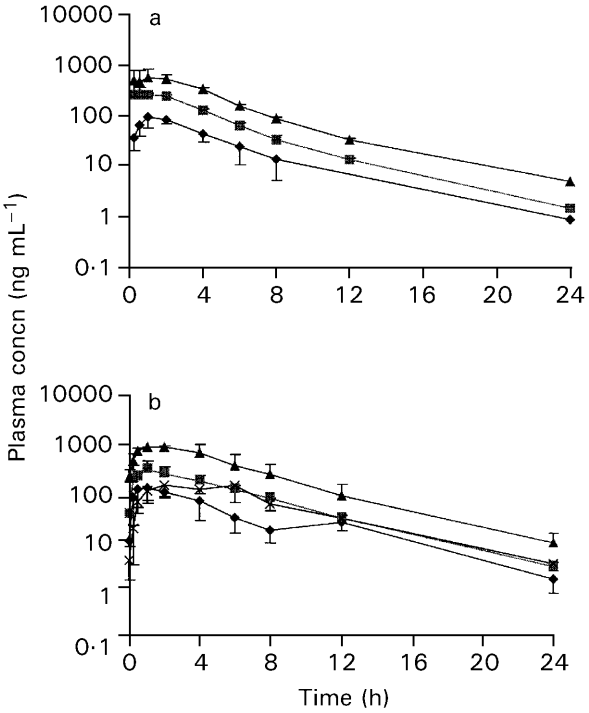

Figure 4. Mean (s.d.) plasma concentration-time profiles of 1-PP on days 1 (a) and 7 (b) in female rhesus monkeys following oral doses of 12·5 (◆), 25 (■) or 100 (▲) mg kg^{-1} twice daily or 25 mg kg^{-1} once daily (×).

Table 3. 1-PP : buspirone AUC ratios.

Dose (mg kg^{-1} day^{-1})	Gender	Single dose (day 1)	Steady state (day 7)
25	M	184 (43·1)	30·0 (23·2)
	F	333 (44·8)	50·5 (36·7)
50	M	166 (124)	8·9 (9·8)
	F	143 (129)	9·3 (6·1)
100	M	17·4 (11·2)	2·62, 3·55[a]
	F	46·9 (51·5)	2·12, 5·69[a]
25[b]	M	ND	33·8 (23·5)
	F	ND	34·0 (24·5)

Values are presented as mean (s.d.); n = 3. [a]n = 2; individual values are reported. [b]Administered as a single daily dose; all others administered in two divided doses. ND = not determined.

Table 4. Assessment of accumulation between day 1 and day 7 for buspirone and 1-PP.

Parameter	Gender	Day 1 slope vs dose	Day 7 slope vs dose	Accumulation ratio
Buspirone				
C_{max}	M and F	7·59	34·80	4·59
AUC	Combined	9·52	63·40	6·66
1-PP				
C_{max}	M	10·30	12·40	1·21
	F	6·41	9·730	1·52
AUC	M	63·50	79·20	1·25
	F	33·00	58·10	1·76

male monkeys and 50·5 to 3·9 in female monkeys. AUC ratios at the 25 mg kg^{-1} once-daily dose were comparable to the 12·5 mg kg^{-1} twice-daily dose.

Discussion

Buspirone is well absorbed after oral administration, but is subject to extensive first-pass metabolism. The metabolism of buspirone has been studied in the rat, monkey and human. Large inter-subject variability in the pharmacokinetics of buspirone has been observed in humans (Barbhaiya et al 1994) which can be attributed to its variable first-pass metabolism in the gut and liver. Buspirone is known to be a substrate for the enzyme CYP3A4 which is found in abundance in the gut (Watkins et al 1987). A recent study has documented a large increase in the plasma concentrations of buspirone when co-administered with CYP3A4 inhibitors

erythromycin and itraconazole (Kivisto et al 1997). In addition, our work with human liver microsomes indicates that the metabolism of buspirone is inhibited by inhibitors of CYP3A4 but not by inhibitors of CYP1A2, CYP2A6, CYP2B, CYP2C9, CYP2D6 and CYP2E1 (data on file, Bristol-Myers Squibb Company). Overall data suggests that buspirone is a substrate for CYP3A4. Large inter-animal variability, similar to that observed in humans, was found in the pharmacokinetics of buspirone in rhesus monkeys.

At the high dose, drug-related adverse events were observed. The monkey that showed the most severe adverse events had plasma concentrations several times higher than the other two male monkeys on day 1. The maximum plasma concentration of buspirone in this monkey on day 1 was 1810 ng mL^{-1} compared with 90·2 ng mL^{-1} and 700 ng mL^{-1} in the other two monkeys. Such high concentrations of buspirone were not observed in the female monkey who also showed drug-related adverse events at the high dose in period 2. It appears that there is also a large inter-animal variability in the tolerability to this drug in rhesus monkeys.

In humans, buspirone shows a nearly dose-proportional increase in AUC after a single dose. Such a dose proportional increase in AUC was also observed after a single dose in rhesus monkeys but not at steady state. This suggests that the first-pass metabolism of buspirone may be saturable at steady state at toxicological doses. This nonlinearity in the pharmacokinetics of buspirone also led to accumulation at steady state which could not be predicted based on the single-dose pharmacokinetics.

1-Pyrimidinylpiperazine (1-PP) is an active metabolite of buspirone. In pharmacological models in which buspirone is active, 1-PP is 1–20% as potent as buspirone (Gammans et al 1983). In man, plasma concentrations of 1-PP are 5–10 times higher than those of buspirone. In this study also, exposure to 1-PP was greater than buspirone. In contrast to buspirone, inter-animal variability in the pharmacokinetics of 1-PP was rather low and pharmacokinetics was generally proportional to dose. Accumulation ratios for 1-PP at steady state were less than 2. Because of the dose-proportional pharmacokinetics of 1-PP and lack of dose proportionality in the pharmacokinetics of buspirone, AUC ratios of 1-PP : buspirone decreased as the dose increased. AUC ratios also decreased at steady state relative to single dose.

In the last period, all monkeys received 25 mg kg^{-1} of buspirone as a single dose daily. This dose was administered to simulate the dosing conditions in the 1-year toxicity study. In man AUC_{TAU} (TAU = 8 h) for buspirone at the maximum therapeutic dose of 20 mg three times daily is approximately 10 ng h mL^{-1} (data on file, Bristol-Myers Squibb). In the present study, AUC_{TAU} (TAU = 24 h) of buspirone at the lowest toxicological dose (25 mg kg^{-1} daily) was 405 ng h mL^{-1} in male monkeys and 106 ng h mL^{-1} in female monkeys, indicating sufficient multiples of exposure relative to man. Consistent with the nonlinearity observed in the pharmacokinetics of buspirone in rhesus monkeys, the exposure to buspirone at the 25 mg kg^{-1} daily dose was greater than the exposure at the 12·5 mg kg^{-1} twice-daily dose. It is speculated that the presystemic metabolism of buspirone may be saturated when the total 25 mg kg^{-1} dose is administered as a single dose vs two divided doses.

In summary, the pharmacokinetics of buspirone in the rhesus monkey appeared to be similar to that in man. There was a large inter-animal variability. Exposure to buspirone increased more than in proportion to dose at steady state.

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