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Tutorial Article

Pharmacological and pharmacokinetic differences between donkeys and horses

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Introduction

Donkeys play a key role in subsistence agriculture and farm work in many parts of the world. Greater populations of donkeys live in developing countries where they rarely receive proper medical assistance. Furthermore, if veterinary care is provided, donkeys tend to be treated as if they were horses, either in developing countries or in the industrialised world.

Many physiological features of donkeys (*Equus asinus*) are different from those of horses (*Equus caballus*). For example, plasma volume is maintained in dehydrated donkeys even when they loose 20% of normal body water, while horses are, by far, less resistant to this challenge (Matthews *et al.* 1997a). Donkeys also appear to possess an increased metabolic capacity for certain drugs, which may be related to differences in cytochrome P450 isoenzymes (Peck *et al.* 1997).

Hence, it is reasonable to expect differences in the disposition of drugs between these species, which may alter dosing intervals (Kinabo and Bogan 1989; Horspool and McKellar 1990; Horspool *et al.* 1994; Mealey *et al.* 1997). **Table 1a,b** summarises the values available for pharmacokinetic variables for drugs in donkeys and the corresponding values for horses. In the absence of specific information, however, it has generally been assumed that distribution and metabolism of drugs in donkeys are similar to those in horses. **Dosage regimens for many drugs are currently being extrapolated, disregarding not only species but breed and individual variation.**

Few drugs have been authorised for use in donkeys and only a limited number of dosage regimens have been properly calculated for specific conditions in this species (**Table 2**). In the UK, for example, **griseofulvin**, **mebendazole** and **permethrin** are the only drugs authorised for use in donkeys (Bishop 1998). **To the best of our knowledge, information about pharmacological/pharmacokinetic aspects of drugs in donkeys has not been recently compiled; hence, a review of this subject and its comparison to that for horses became the impetus for this review.** The clinical implications of such comparison may stimulate clinicians to treat these species correspondingly.

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Antimicrobial drugs

Amikacin

Two similar studies with horses showed inconsistent values for elimination half-life ($T^1/_2\beta$), total body clearance (Cl_B) and apparent volume of distribution (area) (Vd_{AUC}) (Orsini *et al.* 1985; Horspool *et al.* 1994). When comparing these values with those for donkeys (Horspool *et al.* 1994), both studies with horses showed important differences. A dose of 6 mg/kg was recommended either b.i.d. (Orsini *et al.* 1985) or t.i.d. (Horspool *et al.* 1994) for horses and q.i.d. for donkeys (Horspool *et al.* 1994). **If these differences are not considered when treating an infection, rapid clearance of amikacin from donkeys may endanger clinical results.**

Amoxicillin

Oukessou *et al.* (1994) reported that the pharmacokinetics of amoxicillin (15 mg/kg) administered i.v. to donkeys were best described by a 3-compartment model and found that the Vd_{AUC} was 901 ml/kg, with a Cl_B of 333 ml/h/kg. When the same dosage regimen was administered to horses, Monteissa *et al.* (1988) found that the disposition of amoxicillin was best described by a two-compartment model with smaller Vd_{AUC} (490 ml/kg) and Cl_B (239 ml/h/kg) than the corresponding values for donkeys.

With a smaller dose (10 mg/kg) in donkeys, Lavy *et al.* (1995b) found a two-compartment model with a smaller Vd_{AUC} (325 ml/kg) and Cl_B (285 ml/h/kg) than previously reported (Oukessou *et al.* 1994). Using the same dose (10 mg/kg) in horses, a comparable Vd_{AUC} (325 ml/kg) was observed but a

larger Cl_B (340 ml/h/kg) was obtained (Wilson *et al.* 1988). **In spite of lack of consistency, these results indicate generally larger clearance of amoxicillin in donkeys and, hence, the need for a shorter dosing interval.**

A single i.v. injection of sodium amoxicillin (10 mg/kg) to donkeys achieves serumal concentrations greater than 0.5 µg/ml for only 2.5 h (Lavy *et al.* 1995b). Higher doses (15 mg/kg) i.v. extended this time to approximately 4 h, and to 7 h after i.m. injection of the same dose (Oukessou *et al.* 1994). Horses that were injected with amoxicillin sodium at 15 mg/kg i.v. or i.m. maintained concentrations in plasma above 0.5 µg/ml for about 6 and 8 h, respectively (Montesissa *et al.* 1988). Shorter dosing intervals appropriate for this form of amoxicillin may have serious limitations of compliance for donkeys. Together, available pharmacokinetics for sodium amoxicillin, suggest that, to obtain sound clinical results, the dose of amoxicillin should be increased and/or dose intervals shortened for donkeys relative to those factors for horses.

Oukessou *et al.* (1994) stated that absorption half-life ($T^1/2_{ab}$) of amoxicillin sodium (15 mg/kg) administered i.m. to donkeys was half that reported for horses (20.75 mins; Montesissa *et al.* 1988) hence, time to reach the maximum plasma concentration (T_{max}) was shorter (20 mins) in donkeys compared to 41.27 mins in horses. Bioavailability (F) was 13% higher in donkeys (80%) than in horses (67%). However, maximum plasma concentration (Cp_{max}) was similar in both species (approximately 12 µg/ml). Lavy *et al.* (1995b) administered 3 different oil-based products of amoxicillin trihydrate (10 mg/kg) to donkeys and found smaller values for F (25.8 to 45.1%); slower absorption rates ($T^1/2_{ab}$ = 27.4 to 40.0 mins), lower Cp_{max} values (0.81–1.68 µg/ml), later T_{max} (between 45 and 75 mins) and $T^1/2\beta$, of 368.6–518.8 mins. Amoxicillin trihydrate administered to horses at the same dose (10 mg/kg i.m.) was completely absorbed after 24 h (F = 111.91%), with a $T^1/2_{ab}$ of 9.9 mins, a Cp_{max} of 2.17 µg/ml, a T_{max} of 45 mins, and a $T^1/2\beta$, of 1239 mins (Wilson *et al.* 1988). Concentrations greater than 0.5 µg amoxicillin/ml of serum persisted for approximately 24 h in horses (Wilson *et al.* 1988), while 0.4 µg amoxicillin/ml of serum was maintained for only 12 h in donkeys (Lavy *et al.* 1995b), **again suggesting the need for shorter dosing intervals in donkeys**.

Ampicillin

Concentrations of ampicillin in plasma, 4 h after a single i.v. injection of 10 mg sodium ampicillin/kg, were 0.69 and 0.5 µg/ml plasma for horses and donkeys, respectively (Horspool *et al.* 1992). Comparison of standard pharmacokinetic values revealed that only $T^1/2\beta$, was similar between these 2 species. Values for total body clearance and apparent volume of distribution were higher for donkeys than for horses (Horspool *et al.* 1992; Sarasola and McKellar 1992; Sarasola *et al.* 1992) whereas the area under the concentration:time curve (AUC) was lower for donkeys (Horspool *et al.* 1992). **These data suggest that doses of beta-lactams may need to be administered more frequently to donkeys than to horses.**

Gentamicin

This widely used aminoglycoside has been extensively studied in horses. When pharmacokinetics of gentamicin (2.2 mg/kg i.v.) in horses (Bowman *et al.* 1986; Anderson *et al.* 1995; Whittem *et al.* 1996) were compared with corresponding values for donkeys (Miller *et al.* 1994; Welfare *et al.* 1996), no major differences were detected. However, Miller *et al.* (1994) compared their results using **Mammoth asses** with data reported for horses and found a **smaller apparent volume of distribution in Mammoth asses than in horses** and suggested that, to avoid undesirably high circulating concentrations of gentamicin, the **total dose for Mammoth asses should be slightly less than that suggested for horses while maintaining the 8 h dosing interval recommended for horses**. Although, at first, those authors suggested that breed-related differences may exist between Mammoth asses and standard asses in the apparent volume of distribution for gentamicin (Miller *et al.* 1994), no major differences were observed when apparent volume of distribution of the central compartment (Vd_c) for gentamicin in Mammoth asses (Miller *et al.* 1994) and that in standard asses were compared in subsequent studies (Welfare *et al.* 1996).

Norfloxacin

The slow, single i.v. administration of the nicotinate salt of this quinolone (10 mg/kg) produced transient ataxia, strabismus, mild seizures, profuse sweating and tachycardia in donkeys (Lavy *et al.* 1995a). Similar effects have been observed with the administration of some fluoroquinolones to horses (Ramírez 1993). It would appear that i.v. administration of some of these antibacterials to *Equidae* poses a risk that should be considered clinically significant. Norfloxacin nicotinate administered orally to donkeys was poorly absorbed (F = 9.6 and 6.4% for 10 and 20 mg/kg doses, respectively). When administered i.m., bioavailability (F = 31.5 and 18.8% for 10 and 20 mg/kg doses, respectively) was slightly higher. Dose and dosing interval suggested for the treatment of Gram-negative microorganisms in donkeys were 10 mg/kg q.12h or 20 mg/kg q.24h i.m. It must be kept in mind, however, that after multiple i.m. doses, some degree of local swelling must be expected at the injection site, and concentrations of creatinine phosphokinase may be correspondingly 6.7 to 36 fold increased (Lavy *et al.* 1995a).

When comparing the pharmacokinetics of norfloxacin nicotinate (10 and 20 mg/kg) administered i.m. to donkeys (Lavy *et al.* 1995a) with those of norfloxacin-glycine acetate (5 mg/kg) administered to horses (Park *et al.* 1997), longer mean residence time (MRT) and higher F (53%) were obtained for horses. In contrast, T_{max} and C_{max} were similar for donkeys (33 mins and 0.57 µg/ml, respectively) and for horses (22.5 mins and 0.79 µg/ml, respectively) when horses received a dose of 10 mg/kg. These values differed markedly (T_{max} = 67.5 mins and C_{max} = 3.85 µg/ml) when horses received a higher dose (20 mg/kg). **Whether these issues are related to the salt rather than the species, remain to be determined.**

Oxytetracycline

When injected i.v. to horses and donkeys at a dose of 10 mg/kg, oxytetracycline was detected in plasma for up to 96 and 48 h, respectively. Concentrations above 0.5 µg/ml plasma were maintained for 48 h in horses but only for 24 h in donkeys, which reflected a shorter $T^1/_2\beta$ for oxytetracycline in donkeys (387.6 mins) than in horses (777 mins). Horses showed greater AUC in comparison to that for donkeys (223.7 vs. 96.9 µg/ml/h), whereas Vd_C and Cl_B were significantly lower for horses than for donkeys (Vd_C = 49.6 ml/kg and Cl_B = 39.5 ml/kg/h for horses; Vd_C = 150.2 ml/kg and Cl_B = 91.4 ml/kg/h for donkeys). Based on these data, those authors recommended a 48 and 24 h dosing interval for oxytetracycline (10 mg/kg i.v.) in horses and donkeys, respectively (Horspool and McKellar 1990). Faecal concentrations of the drug were not different between the 2 species. A tendency for oxytetracycline to accumulate in the intestinal lumen was observed, possibly due to enterohepatic circulation of the drug. **Horses appeared to be more prone than donkeys to suffer from faecal pastiness after the administration of oxytetracycline** (Horspool and McKellar 1991).

Penicillin G sodium

Horspool and McKellar (1995) found that pharmacokinetics of sodium penicillin G was similar for horses and for donkeys after i.v. injection of approximately 16,000 iu/kg. They suggested that this dose, administered q.6 to 8 h, should suffice to treat susceptible bacterial infections in both species. However, when comparing values obtained by those authors for horses with others in the literature (Firth *et al.* 1986, 1990) for horses receiving 20,000 iu/kg i.v. sodium penicillin G, the former $T^1/_2\beta$, was more than 5 times shorter and the apparent volumes of distribution were slightly smaller.

Oukessou *et al.* (1994) investigated the pharmacokinetics of sodium penicillin G (20,000 iu/kg i.v.) in donkeys. Although they did not publish all the pharmacokinetic data, they stated that penicillin G clearance from the body (393 ml/h/kg) was similar to that reported for horses (510 ml/h/kg) (Firth *et al.* 1986) and recommended that the same dosage regimen for this drug could be used for both species. However, Oukessou *et al.* (1994) found that $T^1/_2\beta$ was 4-fold shorter for donkeys (56 mins) than the value reported for horses (223.2 mins) (Firth *et al.* 1986). The apparent volume of distribution at steady state (Vd_{ss}) was only 18% (84 ml/kg) of the corresponding value calculated for horses (467 ml/kg) by Firth *et al.* (1986). Therefore, an i.v. dose of 20,000 iu/kg of sodium penicillin G could produce concentrations in plasma above 0.5 iu/ml for about 4 h in donkeys (Oukessou *et al.* 1994), whereas in horses concentrations could be maintained above this for approximately 6 h (Firth *et al.* 1986, 1990). **Lack of consistencies and obvious differences in reported values merit further work to establish a suitable dosage regimen for donkeys.**

In either species no penicillin G could be detected in faecal samples or caecal contents following i.v. administration (16,000 iu/kg), suggesting low risk of developing antimicrobial-associated alterations in the gastrointestinal microflora (Horspool and McKellar 1995).

Antiparasitic drugs

Imidocarb

Although 4 doses (4 mg/kg i.m. at 72 h intervals) of imidocarb dihydrochloride effectively eliminated *Theileria equi* from experimentally infected horses, **this drug was lethal when administered either to infected or uninfected donkeys at a dose of 2–4 mg/kg, 1–4 doses, 24–168 h apart** (Frerichs *et al.* 1973). There is no clear explanation for this different degree of toxicity of imidocarb dihydrochloride between species. A further report showed that **the dipropionate salt of the same drug is effective** against *Theileria equi* in donkeys with only minor, transient side effects (Singh *et al.* 1980).

Lasolacid

This agent has been used commercially as a feed additive in the prevention of coccidiosis in broiler chickens and as a growth promoter in ruminants. Sometimes, horses are inadvertently fed with premixes containing lasolacid and the consequences can be fatal. **Horses seem to be more sensitive than donkeys to the lethal effects of lasolacid.** While donkeys survived sequentially increasing single oral doses up to 47.5 mg/kg and 1 donkey given a single oral dose of 57.5 mg/kg died, 1 of 5, 1 of 3, 1 of 3, and 1 of 2 horses died after sequentially increasing single oral doses of 15, 21, 22, and 26 mg/kg, respectively (Hanson *et al.* 1981).

Monensin

This growth promoter that is used in ruminants is quite toxic and even lethal when ingested by *Equidae*. Again, horses seem to be less resistant than donkeys to the deadly action of monensin. Donkeys survived oral dosages of 3 and 5 mg/kg, but died when given a single dose of 10 and 25 mg/kg; meanwhile, 1 of 2 horses and 1 horse died after a dosage of 2 and 3 mg/kg, respectively (Hanson *et al.* 1981).

Triclabendazole

This flukicidal drug is effective for treating *Fasciola hepatica* in horses. Its pharmacokinetics in horses and donkeys have already been described by Kinabo and Bogan (1989). Triclabendazole as such, was not detected in plasma after being orally administrated (12 mg/kg) to horses or donkeys, suggesting high first-pass metabolism as occurs in ruminants (McKellar and Scott 1990). Pharmacokinetic values for triclabendazole sulphoxide in horses and donkeys were quite similar, but those for triclabendazole sulphone were significantly different between species.

TABLE 1a: Pharmacokinetic parameters of different drugs in donkeys (*Equus asinus*) and comparison to their corresponding value in horses (*Equus caballus*)

Species	Dose (ml/kg bwt i.v.)*	Observations	Model best fitting data (compartment)	T½β (min)	AUC (µg/ml/h)	MRT (min)	Vd (ml/kg bwt)	Cl_B (ml/kg/h)	Reference
Amikacin									
D	6	n = 3, (1♂; 2♀) 2–14 years	2	115.8	-	168	156.9_{AUC} 70.3_{C} 150.2_{SS}	58.0	Horspool *et al.* 1994
H	6	n = 3♀, 7–9 years	2	168	-	240	214.9_{AUC} 117.9_{c} 206.6_{ss}	45.2	Horspool *et al.* 1994
H	6.6	n = 6	2	94.2	80.2	-	174_{AUC} 51_{c}	76.6	Orsini *et al.* 1985
Amoxicillin, sodium									
D	15	n = 3	3				901_{AUC}	333	Oukessou *et al.* 1994
D	10	n = 4♂, 2–4 years	2	47.3	20.63	-	325_{AUC} 113_{ss} 81_{c}	285.78	Lavy *et al.* 1995b
H	15	n = 5♂, 5–10 years	2	82.19	63.71	-	490_{AUC} 150_{c}	239	Montesissa *et al.* 1988
Ampicillin, sodium									
D	10	n = 3♂, 8–19 years	2	42.8	24.5	-	499.2_{AUC} 224.8_{c} 422.5_{ss}	418.8	Horspool *et al.* 1992
H	10	n = 3♂, 7–22 years	2	45	42.0	-	279.5_{AUC} 167.6_{c} 210.8_{ss}	240.5	Horspool *et al.* 1992
H	10	n = 4, (3♂; 1♀) 7–21 years	2	43.5	38.4	-	303.5_{AUC} 168.1_{c} 228.0_{ss}	268.2	Sarasola *et al.* 1992
Ascorbic acid									
D	50	n = 4♀	2	201	268.73	-	417.93_{ss} 286.12_{c}	194.89	Elsheikh *et al.* 1997
D	50	n = 4♀ food withheld for 72 h	2	341.4	644.87	-	481.54_{ss} 208.63_{c}	83.27	Elsheikh *et al.* 1997
H	12.5–16.6	300–400 kg	2	546	99	-	540_{ss}	50.4	Löscher *et al.* 1984
H	25.0–33.3	300–400 kg	2	510	165	-	680_{ss}	74.4	Löscher *et al.* 1984
H	8.3–11.1	450–600 kg	2	774	65	-	560_{ss}	33.6	Löscher *et al.* 1984
H	16.6–22.2	450–600 kg	2	522	131	-	650_{ss}	62.4	Löscher *et al.* 1984
H	10 g, pH 7.5	n = 4	2	316.2	186.8	-	-	-	Snow & Frigg 1990
H	10 g, pH 6	n = 6	2	279	188.4	-	-	-	Snow & Frigg 1990
Caffeine									
D	2.5	n = 5, (2♂; 3♀) 3–7 years	-	-	52.0	1260	1060_{ss}	49.4	Peck *et al.* 1997
		Theophyline metabolite	-	-	11.3	-	-	-	Peck *et al.* 1997
		Theobromine metabolite	-	-	4.1	-	-	-	Peck *et al.* 1997
		Paraxanthine metabolite	-	-	2.8	-	-	-	Peck *et al.* 1997
H	2.5	n = 4, (2♂; 2♀) 4–20 years	-	-					
		Theophyline metabolite	-	-	18	-	-	-	Peck *et al.* 1997
		Theobromine metabolite	-	-	6.2	-	-	-	Peck *et al.* 1997
		Paraxanthine metabolite	-	-	2.9	-	-	-	Peck *et al.* 1997
Caffeine, sodium benzoate									
H	0.82–1.8	n = 10, (6♂; 4♀) 16 ± 7 years	2	610.8	20.17	858	649_{ss} 215_{c}	42.7	Schumacher *et al.* 1994
H	2.5	n = 4, (6♂; 3♀) 4–8 years	2	930	63.1	-	454_{c} 887_{AUC}	40.4	Aramaki *et al.* 1991
Flunixin meglumine									
D	1.1	n = 5, (3♂; 2♀) 8–11 years	2	45	38.76	57	50_{c} 85_{ss}	108	Coakley *et al.* 1999
D	1.1	n = 3♀, 7–15 years	2	270	23.63	205.2	171_{ss}	50.27	Cheng *et al.* 1996a
H	1.1	n = 3, (2♂; 1♀) 3–19 years	2	-	58.56	110	65_{c} 117_{ss}	60.6	Coakley *et al.* 1999
H	1.1	n = 6♂	2	202.2	19.34	238.2	70_{c} 317_{AUC}	58	Landoni & Lees 1995
Gentamicin									
D (Ma)	2.2	n = 7, (6♂) 20–26 months;	2 (n = 3)	124.9	34.48	158.97	127.0_{c}	73.2	Miller *et al.* 1994
		1♂, 18 years	3 (n = 4)	50.6	28.49	158.73	88.0_{c}	77.4	Miller *et al.* 1994
D	2.2	n = 6, (3♂; 3♀) 3–6 years	2 (n = 3)	112.34	22.00	128.62	134.20_{c}	100.2	Welfare *et al.* 1996
			3 (n = 3)	47.26	28.41	178.13	102.39_{c}	76.2	Welfare *et al.* 1996
H	2.2	n = 5♀	2 (0–12 h)	241.67	-	-	100.0_{c} 150 $.0_{ss}$	49.8	Bowman *et al.* 1986
			3 (0–168 h)	205.78	-	-	100.0_{c} 1740.0_{ss}	40.8	Bowman *et al.* 1986
H	2.2	n = 5, (4♂; 1♀) 2–6 years	-	130.2	23.75	172.2	270.0_{ss} 310.0_{c}	93.6	Anderson *et al.* 1995
H	2.2	n = 7	2	264	30.8	192	150.0_{c} 240.0_{ss}	71.5	Whittem *et al.* 1996
Guaifenesin									
D	§2600 mg/min (131 mg/kg)	n = 6, (2♂; 4♀) 1–7 years	1	50.4	231	73.2	678_{c}	546	Matthews *et al.* 1997b
H	§2600 mg/min (211 mg/kg)	n = 3, (2♂; 1♀) 6–8 years	1	106.2	688	156.6	794_{c}	313	Matthews *et al.* 1997b
H	§12000 mg/min (134 mg/kg)	n = 9, (4♂; 5♀) 3–12 years	-	79.2	-	-	-	-	Hubell *et al.* 1980

♂ = Male; ♀ = Female; *Single bolus administration except where indicated; †Bioavailability; ‡Possible mistake in units (mg/h/kg) from source; §Administered until recumbency; #Premedication; $_{AUC}$ = Apparent volume of distribution area; $_{c}$ = Apparent volume of central compartment; $_{ss}$ = Apparent volume at steady state; D = Donkey; Ma = Mammoth asses; Min = Miniature; M = Mule; H = Horse.

The sulphoxide and sulphone metabolites of triclabendazole were found in plasma of horses and donkeys 2 h after administration of the parent drug, but those metabolites were detected in plasma of horses for 96 and 168 h, respectively, whereas in donkeys they were detectable for only 72 h (Kinabo and Bogan 1989). For the sulphone metabolite Cp_{max}, AUC and T½β, values were much smaller for donkeys than for horses. However, these

TABLE 1b: Pharmacokinetic parameters of different drugs in donkeys (*Equus asinus*) and comparison to their corresponding value in horses (*Equus caballus*)

Species	Dose (ml/kg bwt i.v.)*	Observations	Model best fitting data (compartment)	$T^1/_2\beta$ (min)	AUC (µg/ml/h)	MRT (min)	Vd (ml/kg bwt)	Cl_B (ml/kg/h)	Reference
Ketamine									
M	2.2	n = 6, 2–7 years xylazine (1.1 mg/kg)#	2	23.3	3900		877_{ss},1140_{AUC}	2034	Matthews *et al.* 1994
D (Ma)	2.2	n = 6, 0.5–2 years xylazine (1.1 mg/kg)#	2	12.4	2592		592_{ss} 911_{AUC}	3060	Matthews *et al.* 1994
H	1 g bolus then 4 g infusion over 30 min	n = 4, 6–10 years xylazine (1.1 mg/kg)#	2	42	-	-	212_c 823_{ss} 1680_{AUC}	1596	Kaka *et al.* 1979
H	2.2	n = 10, 2–9 years xylazine (1.1 mg/kg)# and halothane maintenance	2	65.84	-	-	492_c, 2722_{AUC}	1866	Waterman *et al.* 1987
Ketoprofen									
D	2.2	n = 4, (2♂; 2♀) 4–8 years	2	78	-	39.6	263.10_{ss}	414.1	Oukessou *et al.* 1996
H	2.2	n = 5, (3♂; 2♀) 5–12 years	2	61.2	12.06	45.6	142.30_{ss}	184.72	Owens *et al.* 1995
H	2.2	n = 6♀, 3–11 years	3	98.2	7.44	34.2	164.00_{ss}	288.6	Sams *et al.* 1995
Norfloxacin, nicotinate									
D	10	n = 5♂, 2–4 years	2	208.8	54834	213.9	3340_{AUC} 1934_{ss} 534_c	0.65	Lavy *et al.* 1995a
D	10 i.m.	n = 6♂, 2–4 years †F = 31.5%	2	202.4	17274	273.1	-	-	Lavy *et al.* 1995a
D	10 *per os*	n = 6♂, 2–4 years †F = 9.6%	2	195.6	5262	257.4	-	-	Lavy *et al.* 1995a
D	20 i.m. s.i.d. during 5 days	n = 4♂, 2–4 years †F = 18.8%	2	216.7	20622	308.7	-	-	Lavy *et al.* 1995a
D	20 *per os* s.i.d. during 5 days	n = 4♂, 2–4 years †F = 6.4%	2	158.7	6966	269.7			Lavy *et al.* 1995a
Norfloxacin, glycine acetate									
H	5 i.m.	n = 4♂, †F = 53%	2	404.4	4.36$	313.8	2010_{ss}		Park *et al.* 1997
Oxytetracycline									
D	10	n = 3, 7–18 years	-	387.6	96.9	-	776.5_{AUC} 150.2_c 649.3_{ss}	91.4	Horspool & McKellar 1990
H	10	n = 3♀, 6–21 years	777	223.7	-	-	672.8_{AUC} 49.6_c 348.8_{ss}	39.5	Horspool & McKellar 1990
Penicillin G, sodium									
D	20,000 ui/kg	n = 5, (3♂; 2♀)	2	-	-	-	-	393	Oukessou *et al.* 1994
D	10	n = 3, (2♂; 1♀) 2–14 years	2	31.52	21.91	24.46	357.25_{AUC} 95.91_c 204.53_{ss}	462.86	Horspool & McKellar 1995
H	10	n = 3♀, 7–9 years	2	38.95	22.41	30.07	537.25_{AUC} 165.98_c 362.32_{ss}	514.46	Horspool & McKellar 1995
H	20,000 ui/kg	n = 5	2	223.02	25.03	-	718_{AUC} 337_c	510	Firth *et al.* 1990
H	20,000 ui/kg	n = 5	2	223.2	25.06	-	467_{ss}, 340_c 720_{AUC}	510	Firth *et al.* 1986
Phenylbutazone									
D	4.4	n = 3♂, 7–15 years	2	37.8	19.21	41.4	146.67_{ss}	214.18	Cheng *et al.* 1996b
		Oxyphenbutazone	1	108.6	12.86	-	-	-	Cheng *et al.* 1996b
D	4.4	n = 6, (3♂; 3♀) 3–7 years	2	-	28.3	106.2	242_{ss}	170.3	Mealey *et al.* 1997
D (Min)	4.4	n = 6♀	-	-	12.61	84	212.6_c 545_{AUC}	360	Matthews *et al.* 2001
		Oxyphenbutazone	-	-	9.06	132	-		Matthews *et al.* 2001
H	4.4	n = 4, (2♂; 2♀) 4–20 years	2	-	118.3	216.6	174_{ss}	29.3	Mealey *et al.* 1997
H	4.4	n = 6♀, 3–11 years	-	265	165.16	-	84.4_{ss}	13.32	Sams *et al.* 1997
		Oxyphenbutazone	-	-	42.38	-	-	-	Sams *et al.* 1997
Triclabendazole									
D	12 *per os*	n = 3							
		Sulphoxide metabolite	-	564	100	-	-	-	Kinabo & Bogan 1989
		Sulphone metabolite	-	543.6	63	-	-	-	Kinabo & Bogan 1989
H	12 *per os*	n = 3							
		Sulphoxide metabolite	-	584.4	115	-	-	-	Kinabo & Bogan 1989
		Sulphone metabolite	-	1053.6	594	-	-	-	Kinabo & Bogan 1989

For abbreviations see Table 1a.

differences may be of little therapeutic significance because the sulphone metabolite is generally devoid of anthelmintic activity (McKellar and Scott 1990). **Therefore, similar dosage regimens of triclabendazole could be used for horses or donkeys.** Because bioavailability of the sulphoxide metabolite seems to be lower in *Equidae* than it is in ruminants (McKellar and Scott 1990), a higher dose, i.e. 12 mg/kg *per os*, may be required.

Anaesthetics

Clinically used anaesthetic regimens for donkeys and mules, and comparison of main pharmacological features have already been reviewed (Matthews *et al.* 1997a). In this paper, only the pharmacokinetic studies of anaesthetic drugs performed with donkeys are considered and, when appropriate, the clinical significance of these findings are discussed.

Guaifenesin

Experimentally, it has been shown that i.v. administration of this muscle relaxant to donkeys at a dosage of 2600 mg/min required 11.3 mins (mean) to achieve recumbency, while the same procedure required 39 mins to reach recumbency in horses. Total dose was 131 mg/kg for donkeys and 211 mg/kg for horses. Although mean time to sternal recovery was about twice as long for horses than for donkeys (34 and 15 mins, respectively), mean time to full standing was similar in both species (36 and 32 mins, respectively) (Matthews *et al.* 1997b). **This latter feature may be more a consequence of behaviour, rather than pharmacokinetic differences** (Matthews *et al.* 1997a).

Infusion rates influence the effect of guaifenesin. When this agent was infused in horses at a rate of 12,000 mg/min, mean time to recumbency was 7.8 mins (total dose: 134 mg/kg) with a plasma concentration of 313 µg/ml. Mean time from recumbency to sternal recumbency and to standing were 20.9 and 23.8 mins, respectively (Hubell *et al.* 1980). Changes in rate of infusion of guaifenesin in donkeys have not been studied in detail. However, the pharmacokinetics of guaifenesin in donkeys and in horses, under the same conditions (Matthews *et al.* 1997b), revealed that the AUC was smaller for donkeys than for horses (231 vs. 688 µg/h/ml); Cl_B was faster for donkeys (546 ml/h/kg) than for horses (313 ml/h/kg) and Vd_{AUC} was higher for horses (678 ml/kg for donkeys and 794 ml/kg for horses). Mean residence time was 1.2 h for donkeys and 2.6 h for horses. **Donkeys required only about 60% of the dose of guaifenesin used for horses to produce recumbency, but they cleared it more rapidly** (Matthews *et al.* 1997b).

Ketamine

The pharmacokinetics of this dissociative anaesthetic has been described for horses (Waterman *et al.* 1987; Kaka *et al.* 1979), donkeys and mules (Matthews *et al.* 1994). **Total body clearance of ketamine was greater for Mammoth asses than for horses, while intermediate for mules.** Apparent volume of distribution was smaller for Mammoth asses compared to that for horses and intermediate for mules. Hence $T^1/_2\beta$ was shorter for Mammoth asses than for mules or horses. These differences are consistent under various clinically accepted anaesthetic regimens (Kaka *et al.* 1979; Waterman *et al.* 1987; Matthews *et al.* 1994).

Pharmacokinetic data explain well some clinical observations when short-term anaesthesia is performed in *Equidae*. For example, mean recumbency time after xylazine (1.1 mg/kg i.v.) followed by ketamine (2.2 mg/kg i.v.), was 14, 23 and 24 mins for mules (Matthews *et al.* 1992b), horses (Matthews *et al.* 1991) and Mammoth asses (Matthews *et al.* 1992a), respectively. **Xylazine produced poor sedation in mules as compared to that in horses or Mammoth asses.** This explains why mules regained full standing position with higher circulation concentrations of ketamine than did asses (2.39 µg/ml and 0.42 µg/ml, respectively) (Matthews *et al.* 1994). This same anaesthetic combination in horses (Matthews *et al.* 1991), produced rapid and smooth induction with satisfactory recoveries, as well as some degree of muscular relaxation. In contrast, the quality of anaesthesia was not as good in Mammoth asses (Matthews *et al.* 1992a) and even worse in mules (Matthews *et al.* 1992b), which showed unstable induction to anaesthesia with poor recoveries and even some muscle rigidity.

Interestingly, it appears that equal doses (based on bodyweight) of the anaesthetic combination xylazine+ketamine alone or given along with diazepam and butorphanol, produce anaesthesia of shorter duration in miniature donkeys than in standard donkeys (Matthews *et al.* 2001). Matthews *et al.* (2002) evaluated 3 anaesthetic combinations in miniature donkeys: xylazine + butorphanol + ketamine; xylazine + propofol and xylazine + butorphanol + tiletamine + zolazepam. Using the former 2 anaesthetic combinations, mean recumbency time obtained was approximately only 14 mins. With the latter combination a longer mean recumbency time of 34 mins was achieved. The referred perception of the authors was that recumbency time was noticeably shorter than the one observed in standard donkeys. A more rapid metabolism in miniature donkeys may have accounted for these differences.

TABLE 2: Doses and indications of drugs for donkeys

Drug	Dose	Indication
Acepromazine	2.5 mg/50 kg i.v. followed by 25–50 mg *per os* q. 12h	Laminitis
Acepromazine + Detomidine + Ketamine	1.5 mg/50 kg + (after 30 mins) 1.5 mg/50 kg + (after 5 mins) 110 mg/50 kg i.v.	Field anaesthesia
Clenbuterol	160 µg/kg *per os* q. 12h (maximum dose) 320 µg/kg i.v.	Respiratory disease
Griseofulvin*	10 mg/kg *per os* q. 24h	Ringworm
Ivermectin	200 µg/kg *per os*	Roundworms (in particular *Dictyocaulus arnfieldi*)
Mebendazole*	5–10 mg/kg *per os* 15–20 mg/kg *per os* q. 24h for 5 days	Roundworms *Dictyocaulus arnfieldi*
Permethrin*	0.1 ml/kg by 'pour-on' application	*Culicoides*, lice
Phenylbutazone	500 mg *per os* q. 12h† 500 mg i.v. q. 24h†	Laminitis
Triclabendazole	12 mg/kg *per os*	Fascioliasis

*Drug doses for preparations that have a marketing authorisation for use in donkeys in the UK.
†Based on bodyweight, these doses are slightly higher than that for horses but the optimal dose for donkeys has not been established.
+As pre-anaesthetic agent.
Refer to the text for more information. Adapted from Bishop 1998.

TABLE 3a: Subjective rating for induction and recovery in *Equidae* submitted to different injectable anaesthetic protocols

	Induction of anaesthesia												Recovery from anaesthesia											
Anaesthetic	Rapid, smooth				Slightly prolonged or unstable				Unstable				Satisfactory				Some instability				Unsatisfactory			
combination	M	MA	MD	H	M	MA	MD	H	M	MA	MD	H	M	MA	MD	H	M	MA	MD	H	M	MA	MD	H
X/K*	55	63	NA	100	33	37	NA	0	11	0	NA	0	67	75	NA	100	11	25	NA	0	22	0	NA	0
X/B/K†	67	89	50	83	33	11	50	17	0	0	0	0	100	89	67	100	0	11	33	0	0	0	0	0
X/T-Z‡	44	100	NA	83	44	0	NA	17	11	0	NA	0	22	44	NA	33	33	56	NA	33	45	0	NA	33
X/B/T-Z§	NA	NA	100	83	NA	NA	0	17	NA	NA	0	0	NA	NA	67	50	NA	NA	33	33	NA	NA	0	17

*Xylazine 1.1 mg/kg i.v. followed 3–5 mins later by ketamine 2.2 mg/kg i.v.
†Xylazine 1.1 mg/kg i.v. followed immediately by butorphanol 0.044 mg/kg i.v. and 3–5 mins later by ketamine 2.2 mg/kg i.v., except for MD where xylazine and butorphanol were given together.
‡Xylazine 1.1 mg/kg i.v. followed 3–5 mins later by tiletamine-zolazepam 0.5 mg/kg of each drug i.v.
§Xylazine 1.1 mg/kg i.v. followed immediately by butorphanol 0.044 mg/kg i.v. and 3–5 mins later by tiletamine-zolazepam 0.5 mg/kg of each drug i.v., except for MD to which xylazine and butorphanol were given together.
Values are expressed in %; NA = data not available. M = mules (n = 9); MA = Mammoth asses (n = 9; except for X/K, n = 8); MD = Miniature donkeys (n = 6); H = horses (n = 6).
Data from Matthews *et al.* 1991, 1992a,b, 2002.

TABLE 3b: Subjective rating for muscle relaxation in *Equidae* submitted to different injectable anaesthetic protocols

	Muscle relaxation during anaesthesia											
Anaesthetic	Present				Absent				Absent with rigidity			
combination	M	MA	MD	H	M	MA	MD	H	M	MA	MD	H
X/K*	33	62	NA	83	44	12	NA	17	22	25	NA	0
X/B/K†	89	78	33	83	11	22	33	0	0	0	33	17
X/T-Z‡	100	100	NA	100	0	0	NA	0	0	0	NA	0
X/B/T-Z§	NA	NA	100	100	NA	NA	0	0	NA	NA	0	0

For abbreviations see Table 3a.

Other anaesthetic considerations of clinical relevance using different injectable anaesthetic regimens in *Equidae* are summarised in **Tables 3a,b**, where it is obvious that the combination xylazine (1.1 mg/kg i.v.) plus butorphanol (0.044 mg/kg i.v.) and ketamine (2.2 mg/kg i.v.) **is a better anaesthetic option for mules and miniature donkeys than is xylazine plus ketamine** (Matthews *et al.* 1992b, 2002). Horses and mules responded similarly to the xylazine + buthorphanol + ketamine combination; however, some horses developed muscle rigidity (Matthews *et al.* 1991, 1992b). In Mammoth asses (Matthews *et al.* 1992a), this combination produced some instability during the recovery from anaesthesia and no muscle relaxation was observed in some cases. When ketamine was replaced by tiletamine-zolazepam (0.5 mg/kg of each drug i.v.), **this anaesthetic combination** (xylazine-tiletamine-zolazepam) **produced good quality induction in Mammoth asses and in most horses, but the quality of induction was poor in mules** (Matthews *et al.* 1991, 1992a,b). Muscle relaxation was accompanied by ataxia at recovery from anaesthesia when using this combination; however, it seems that Mammoth asses are less affected than are horses or mules.

Alpha$_2$-adrenoceptor agonists

A 50% increase in the dose of xylazine, or other α_2-adrenoceptor agonists has been recommended to achieve adequate sedation in mules (Matthews *et al.* 1997a). **Donkeys also seem to need larger doses of α_2-adrenoceptor agonist, such as detomidine, to produce adequate sedation and analgesia** (El-Maghraby and Atta 1997; Joubert *et al.* 1999). Alpha$_2$-adrenoceptor agonists are capable of producing atrio-ventricular and sino-atrial blocks in donkeys as in horses (El-Maghraby and Atta 1997; Joubert *et al.* 1999).

Nonsteroidal anti-inflammatory drugs

Flunixin meglumine

In a parallel study using donkeys and horses, Coakley *et al.* (1999) observed that the kinetic disposition of flunixin meglumine (1.1 mg/kg i.v.) in donkeys differed significantly from that in horses with regard to AUC, MRT and Cl_B. The AUC and MRT were significantly less, whereas Cl_B was significantly greater in donkeys, compared with those values for horses. Cheng *et al.* (1996a) also reported greater values for $T^1/_2\beta$ AUC, MRT and Vd_{ss} of flunixin meglumine in donkeys, whereas Cl_B was less than that observed by Coakley *et al.* (1999). These differences could be attributed to changes induced by experimental inflammation in the study by Cheng *et al.* (1996a) donkeys compared to clinically normal donkeys used by Coakley *et al.* (1999). Similar observations were noticed when comparing kinetics of flunixin meglumine in clinically healthy horses (Coakley *et al.* 1999) to those with horses with induced inflammation (Landoni and Lees 1995).

In both donkeys and horses, the MRT of flunixin meglumine in exudate (18.21 and 14.26 h, respectively) was much longer than that in plasma (3.42 and 3.97 h, respectively) but similar to that in transudate (14.33 and 13.19 h, respectively) (Landoni and Lees 1995; Cheng *et al.* 1996a).

Flunixin meglumine appeared more readily in the inflammatory exudate of donkeys (T_{max} = 2.63 h) than in that of horses (T_{max} = 4.0 h) but C_{max} in inflammation exudate was about half the value observed in that from horses (1.3 vs. 2.47 µg/ml), which reflected a larger AUC in horses (35.99 µg/ml/h) than in donkeys (10.26 µg/ml/h) (Landoni and Lees 1995; Cheng *et al.* 1996a). Contrary to what happened in inflammatory exudate, flunixin meglumine appeared more slowly in the inflammatory transudate of donkeys (T_{max} = 6.0 h) than in that of horses (T_{max} = 4.67 h) and C_{max} in transudate in donkeys was almost 2-fold that of transudate in horses (1.09 vs. 0.66 µg/ml); AUC values were similar in both species (13.38 vs. 12.05 µg/ml/h) (Landoni and Lees 1995; Cheng *et al.* 1996a).

Generation of thromboxane B_2 (TXB_2) in donkeys' serum was significantly inhibited (91–77%) from 1 to 12 h after administration of flunixin meglumine but returned to normal by 24 h (Cheng *et al.* 1996a). From 1–12 h about 95–80% inhibition and about 63–55% inhibition at 24 h was observed in horses' serum, whereas values reverted to normal at 48 h (Lees *et al.* 1987; Landoni and Lees 1995). In the inflammatory exudate, prostaglandin E_2 (PGE_2) production was abolished for 8 h in donkeys and horses; at 12 h, inhibition was similar in both species (80 and 95%, respectively). At 24 h, however, less inhibition (54%) was observed in donkeys relative to that in horses (90%). That tendency continued thereafter with 44% inhibition at 32 h in donkeys and 75% at 30 h in horses (Landoni and Lees 1995; Cheng *et al.* 1996a). **Nonetheless, it is important to consider that only a small number of donkeys** (n = 3) **were used in those studies and that the figures could be altered if a larger number of animals were used.**

Dosing intervals for flunixin meglumine in donkeys should be shorter than those recommended for horses. However, multiple dose pharmacokinetic and pharmacodynamic studies should be performed to determine optimal dosing recommendations (Coakley *et al.* 1999). Together, these data suggest that when dosage regimens for flunixin meglumine in these species are determined, particular attention should be paid to the PK/PD data for the inflammatory exudates and transudate.

Ketoprofen

A single dose of ketoprofen (2.2 mg/kg i.v.) produced similar pharmacokinetic values in donkeys and horses, although larger apparent volumes of distribution and clearance values were seen for donkeys compared to those for horses (Owens *et al.* 1995; Sams *et al.* 1995; Oukessou *et al.* 1996). Oukessou *et al.* (1996) speculated that these differences could be due to lower plasma protein binding of ketoprofen in the donkey. This feature may also modify clinical efficacy between the 2 species, a view that requires investigation.

Phenylbutazone

Donkeys eliminate phenylbutazone (PBZ) much faster than do horses, and this is probably due to differences in protein binding of the drug because apparent volume of distribution for PBZ does not differ greatly between these 2 species. It appears that donkeys possess more efficient hepatic biotransformation of PBZ into the pharmacologically active metabolite oxyphenylbutazone (OPBZ) (Cheng *et al.* 1996b; Mealey *et al.* 1997) than do horses (Mealey *et al.* 1997; Sams *et al.* 1997); hence, $T^1/_2\beta$ of PBZ is shorter for donkeys than for horses.

Interestingly, there seems to be breed-related differences on the kinetic disposition of PBZ in donkeys. **Miniature donkeys** (Matthews *et al.* 2001) eliminate PBZ faster than do **standard donkeys** (Mealey *et al.* 1997), which is reflected by shorter MRT in the former breed. Although C_{max} for OPBZ was similar between the 2 breeds, the metabolite appeared in serum sooner in miniature donkeys (0.4 h) (Matthews *et al.* 2001) than in standard donkeys (1.6 h) (Mealey *et al.* 1997). **Hence, miniature donkeys appear to have a higher rate of oxidative hepatic metabolism than do standard donkeys.**

Pharmacokinetic differences for PBZ and OPBZ in exudate and transudate from carrageegan-induced inflammatory sites have been described. Donkeys and ponies exhibited slower elimination rate of PBZ and of OPBZ from exudate and transudate than from plasma. However, distribution of PBZ into the exudate was lower and shorter-lasting in donkeys (maximum concentration = 1.48 µ/ml; time to maximum concentration = 5.33 h) (Cheng *et al.* 1996b) than in ponies (maximum concentration = 12.4 µg/ml; time to maximum concentration = 4.6 h) (Lees *et al.* 1987).

Additionally, important pharmacodynamic differences have also been noticed between equine species using the carrageegan-induced inflammatory model. Prostaglandin E_2 synthesis in donkeys was completely blocked 4 h after the injection of PBZ and 50% after 8 h (Cheng *et al.* 1996b), while in horses, 90% inhibition of synthesis of PGE_2 lasted 12 h, and that of 6-keto-$PGF_{1\alpha}$ was 70 to 85% inhibited for 24 h (Lees *et al.* 1987). Similarly, concentrations of TXB_2 in serum of donkeys were inhibited (33 to 86%) for only 6 h and was almost fully restored at 8 h (Cheng *et al.* 1996b). In ponies, serumal TXB_2-inhibition was 88, 75, 76 and 50% at 4, 8, 12 and 24 h, respectively. By 48 h concentrations of TXB_2 were restored (Lees *et al.* 1987). This kinetic-dynamic behaviour may partially impair the anti-inflammatory effects of PBZ and OPBZ at the target tissue level in donkeys.

There is a clinical perception that, in order to achieve a similar anti-inflammatory effect in both species, higher doses and/or shorter dosing-intervals are required when administering PBZ to donkeys (Cheng *et al.* 1996b; Mealey *et al.* 1997). **However, further studies must determine the optimal dose scheme of PBZ for donkeys to avoid toxicity. Miniature donkeys may require an even shorter dosing interval than do standard donkeys to maintain therapeutic concentrations** of PBZ (Matthews *et al.* 2001). However, it must be considered that OPBZ has pharmacological activity and a higher dose and/or shorter dosing interval may be deleterious. **Therefore, further studies must determine the optimal dose scheme for PBZ in donkeys to avoid toxicity.**

Spinal analgesia

Spinal analgesia is better induced in donkeys by injecting the local anaesthetic agent in the second intercoccygeal space (Shoukry *et al.* 1975), **while the first intercoccygeal space appears to be more accessible in horses** (Grosenbaugh *et al.* 1999). Analgesia, defined as the lack of response to pin-prick in the skin of the perineal area, was achieved in **donkeys** after epidural administration of xylazine (0.35 mg/kg at a concentration of 20 mg/ml) (Makady *et al.* 1991) and **horses** after epidural administration of xylazine (0.17 mg/kg at a concentration of 12.86 mg/ml) (Grubb *et al.* 1992). Time to onset of analgesia was shorter for donkeys (20 mins) than for horses (32 mins), but duration of analgesia was similar for both species (226 mins for donkeys and 204 mins for horses).

Lidocaine (20 mg/ml) produced analgesia in **donkeys** when administered epidurally at a dose of 0.35 mg/kg (Makady *et al.* 1991). **Horses** required 0.22 mg lidocaine/kg at a concentration of 16.64 mg/ml (Grubb *et al.* 1992). Time to onset of analgesia and duration of analgesia with lidocaine were longer for donkeys (10 and 120 mins, respectively) than for horses (4.3 and 87.2 mins, respectively). A single injection of bupivacaine (0.06–0.08 mg/kg in 1 ml dose volume) intrathecally in donkeys, produced analgesia immediately after its administration and lasted for 80 mins (Saleh 1993). The authors are unaware of any literature reports about spinal administration of bupivacaine in horses.

The epidural administration of opioid-base agents to donkeys (Naemi *et al.* 1999) and to horses (Grosenbaugh *et al.* 1999) has failed to provide sufficient analgesia as occurs in other species.

Intrathecal administration of ketamine (1.17 to 1.66 mg/kg in 1 ml dose volume) in donkeys produced analgesia 2 to 3 mins after its injection and lasted for 40 mins (Saleh 1993). No reports of the spinal analgesic effect of ketamine administered intrathecally were found for horses; however, it is known that epidurally administered ketamine (0.8–1.2 mg/kg in a volume of 0.15 ml/kg) significantly reduced the amount of halothane required to maintain anesthesia during pelvic limb stimulation in ponies (Grosenbaugh *et al.* 1999).

Miscellaneous

Ascorbic acid

Ascorbic acid has a role in the formation of connective tissue, but in equine species it is also administered because it supposedly helps the patient withstand physiological and physical stress and improves immune status (Thaxton and Pardue 1984). After i.v. administration, ascorbic acid showed a larger Cl_B, larger AUC, shorter $T^1/_2\beta$ and smaller Vd_{AUC} in donkeys (Elsheikh *et al.* 1997) as compared to those values in horses (Löscher *et al.* 1984; Snow and Frigg 1990). In the former species, food deprivation for 72 h, affected the values for pharmacokinetic variable of ascorbic acid (50 mg/kg i.v.). Although Vd_{ss} was not significantly changed, Vd_c was significantly reduced and there was a 4-fold increase in the distribution of ascorbic acid from the central to the peripheral compartment, as well as a significant decrease in Cl_B accompanied by increased $T^1/_2\beta$ and AUC (Elsheikh *et al.* 1997). The therapeutic relevance of these data is uncertain. Assessment of clinical efficacy derived from the use of ascorbic acid poses a difficult challenge. Additionally, no recommended dose for ascorbic acid in *Equidae* has been universally accepted. These pharmacokinetic reports may help explain clinical differences and better define a dose for this agent.

Caffeine

Pharmacokinetics of the capacity-limited drug caffeine in horses have not been consistent in 3 different experiments (Aramaki *et al.* 1991; Schumacher *et al.* 1994; Peck *et al.* 1997). In parallel trials using horses and donkeys, however, Peck *et al.* (1997) found no significant differences between species for pharmacokinetic values for caffeine and its metabolites theophylline and paraxanthyne, but Cp_{max} of the metabolite theobromine was significantly higher in donkeys. This suggests that some differences may exist between these 2 species in the concentration and/or activity of cytochrome P450 isoenzymes. It remains necessary, however, to clarify if the similar pharmacokinetic profile of caffeine in donkeys and horses was real or it was affected for the small number of animals used in the trials (Peck *et al.* 1997). When comparing the pharmacokinetic data from other studies with horses (Aramaki *et al.* 1991; Schumacher *et al.* 1994) to the corresponding values in donkeys (Peck *et al.* 1997), a larger apparent volume of distribution and a more prolonged MRT was observed in donkeys, which could also be indicative of differences between these species in the rate of hepatic metabolism.

Discussion

To the best of our knowledge data reviewed here represent nearly all the reports about pharmacokinetics of drugs studied in donkeys. **It becomes clear that important differences in pharmacokinetics and pharmacodynamics exist between horses and donkeys and among breeds of donkeys.** However, only a small fraction of the potential investigations has been done. Hence, direct extrapolation of dosage regimens for horses to use in donkeys may impose some danger to the latter species, for example, reduced pharmacological action, poor clinical outcome or a direct toxic effect (Frerichs *et al.* 1973; Singh *et al.* 1980). **The donkey therefore, should not be regarded as a small odd-looking horse, but should be recognised and treated as a species in its own right.**

The donkey is a remarkable equid. As shown, it differs sufficiently from the horse and requires specific pharmacological studies. **In general, it appears that donkeys present fewer adverse drug reactions than do horses and are less sensitive than horses to the majority of vehicles of parenteral preparations.** Nonetheless, there have been some

reports of oil-based formulations or unbuffered solutions or suspensions that cause irritation and tissue damage at the site of injection (Lavy *et al.* 1995a; Bishop 1998). Some aqueous solutions can produce local swelling at the site of injection in donkeys, as was observed with norfloxacin nicotinate (Lavy *et al.* 1995a). Tetracyclines have been associated with severe enterocolitis in horses exposed to stress and this appears to be less common in donkeys (Bishop 1998). Healthy horses suffer more than do healthy donkeys from faecal pastiness after the injection of oxytetracycline (Horspool and McKellar 1991).

Apparently, donkeys have a relative greater capacity than horses to metabolise and/or eliminate drugs. That is supported by the fact that total body clearance values for must of the drugs studied were greater for donkeys than for horses. For example, clearance of phenylbutazone in donkeys is about 5- to 15-fold greater than that in horses (Cheng *et al.* 1996b; Mealey *et al.* 1997). Donkeys may have greater quantities and/or activity of certain P450 isoenzymes than do horses. Hence, **for some drugs that undergo hepatic metabolism, the dose and dosing-interval used for horses may not be appropriate for donkeys** (Peck *et al.* 1997). Both oxytetracycline and phenylbutazone undergo hepatic elimination or enterohepatic re-circulation, and they are metabolised and cleared faster in donkeys than in horses. In contrast, caffeine, a capacity-limited drug, showed similar patterns of elimination in horses and donkeys when comparing serumal clearance of caffeine and its metabolites, theophylline, theobromine and paraxanthine (Peck *et al.* 1997).

In summary, evidence supports the presence of marked differences in drug metabolism, between horses and donkeys, horses and mules (Matthews *et al.* 1994) and horses and ponies (Horspool *et al.* 1992, 1994). These differences emphasise the danger of extrapolating dosage-regimens. Because of the great importance of donkeys in developing countries, it is necessary that the veterinary medical community generate more pharmacological information specifically with, and for, donkeys. Basic pharmacokinetic information is required for commonly used drugs such as α_2-adrenoceptor agonists, i.e. detomidine and xylazine, and for antibacterial agents such as metronidazole and potentiated sulphonamides.

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