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Review Article

Pharmacology and therapeutics in donkeys

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Summary

Therapeutics are often administered to donkeys based on dosage and intervals recommended for horses because very few drugs have donkey-specific label indications. Yet differences between donkeys and horses in drug distribution, metabolism and elimination have been noted for most therapeutic agents studied. These differences can be partially explained by the donkey's unique physiology. Since their ancestors evolved in a desert environment, the modern donkey exhibits qualities that allow them to tolerate dehydration better than the horse and recover more quickly from its effects. Fluid balance and body water compartment partitioning differ from the horse and may have implications regarding drug distribution. Since donkeys are preferential browsers, differences in diet may have influenced evolutionary differences in metabolic disposition of drugs. It is important to acknowledge these differences when designing dose regimes for donkeys based on horse protocols in order to avoid either lack of efficacy or toxicity.

Introduction

Anyone who treats and administers drugs to donkeys (*Equus asinus*) soon realises that they are not merely short horses with long ears. Dosage ranges and dosing intervals of commonly used therapeutic drugs differ significantly from the horse and even within the species itself. There has been little species-specific research done on which to base therapeutic decisions. This is mainly because donkeys have limited economic impact in the major pharmaceutical markets compared to horses, even though they are a major economic factor in developing areas of the world.

DNA evidence suggests that the donkey was first domesticated about 5000 years ago by the nomadic peoples of northern Saharan Africa (Kimura *et al*. 2011). At this time the qualities that allowed for adaptation to the desert climate were exploited and the donkey became an indispensable partner in the survival of these ancient peoples. Even today the donkey continues to function as a working animal in challenging environments. Furthermore, they carry loads at lower net oxygen consumption than man (Yousef and Dill 1969), making them particularly relevant in today's eco-friendly world. These adaptations have been preserved into modern history through selective breeding, with the result that the physiology of the donkey differs from that of its more teleologically-pampered cousin, the horse. These physiological differences result in differences in drug pharmacokinetics and pharmacodynamics between the species which can have a profound effect on the choice of therapeutic agents and dosing regimes. Adaptations to water deprivation can alter volume of distribution, affecting drug absorption; and the donkey's ability to survive on less than optimal forage may have implications regarding the efficiency of biotransformation enzyme systems and thus drug metabolism.

In this article we will first examine what is known regarding the physiological parameters in donkeys which impact pharmacokinetics and pharmacodynamics and how they differ with respect to the horse. This will be followed by a review of the literature regarding specific drug studies in donkeys and how they relate to physiological parameters which affect decisions regarding therapeutics.

Physiology

Since donkeys evolved in a desert environment, they exhibit qualities that allow them to tolerate a certain degree of dehydration without detriment to their physiological wellbeing. Fluid balance and body water compartment partitioning differ from the horse in that the donkey can survive water loss of 30% of its original weight, then consume sufficient water to restore the deficit within minutes. Urine output is lower than that of the horse, even when water is readily available. When water is restricted and heat load increases, faecal dry weight and faecal water loss are reduced (Maloiy 1970). The hind gut serves

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as a reservoir of water similar to that of ruminants (Kasirer-Izraely *et al*. 1994) and plasma volume is maintained in donkeys which have endured up to 20% dehydration (Yousef *et al*. 1970). Taken jointly, these factors have implications on drug distribution that is exquisitely dependent on hydration status.

Evolution in a vegetation-challenged environment has allowed the donkey to thrive on less than optimal forage. Feed efficiency in donkeys is generally regarded to be better than that of the horse although there are no obvious anatomical differences. They are selective grazers and browsers, feeding on a wide variety of forage. It is possible that their ability to thrive, browsing on plants unpalatable to the horse, results from metabolic alterations that may partially explain the donkey's increased rate of metabolism of some drugs.

Pharmacology

Very few drugs are approved for use in the donkey. As a result, most drugs must be administered 'off label'. Drug dosages are most often extrapolated from those determined for horses during the relevant drug approval process. However, the impact of differences in donkey physiology must be considered in light of its effect on pharmacology. The main sources of interspecies variability with respect to drug dosing can be explained by pharmacokinetics and pharmacodynamics. Therefore, a basic understanding of these principles is necessary in order to extrapolate drug therapeutics from horses to donkeys.

Pharmacokinetics

In order for a drug to be therapeutic, it must reach its site of action within a reasonable amount of time and reside there long enough to exert its desired effect. In most cases, this means it must be soluble in an aqueous phase (blood plasma) in order to interact with cell membrane receptors. To access intracellular sites of action, the drug must be sufficiently lipid soluble with the optimal ionisation ratio in order to cross cell membrane barriers. Pharmacokinetics deals with these issues. Bioavailability, distribution, clearance and elimination are pharmacokinetic parameters routinely used to determine dosing regimes and will be briefly described in this article.

Bioavailability

Bioavailability is the rate and extent at which a drug is absorbed from its site of administration and enters the systemic circulation in its original form. It is expressed as a percentage of the value of the same dose of that drug following i.v. administration. Bioavailability is determined from 3 parameters which together describe the rate and extent of drug distribution; peak plasma concentration, time to peak plasma concentration and the total area under the time vs. concentration curve (AUC). The systemic availability of a drug administered by a nonvascular route is determined by comparing the AUC of that drug when a standard dose is administered by both the route in question and i.v.

Distribution

Volume of distribution (Vd) is defined as the apparent volume in which a drug is dissolved. Volume of distribution is dependent on the nature of body compartments and can differ markedly between species. Distribution of a drug depends on properties such as pKa, lipid solubility, molecular size and extent of protein binding. Highly protein-bound drugs will remain in the vascular space. Lipid-soluble, basic drugs can diffuse into body reservoirs such as the equine colon and become trapped by ionisation. The Vd must be known in order to calculate the dose that should be administered to achieve a certain drug concentration in plasma. The hind gut of the donkey serves as a water reservoir, a similar role to that of small ruminants (Kasirer-Izraely *et al*. 1994) which may account for some differences in drug distribution and availability.

Clearance

Clearance is defined as the volume of plasma that is cleared of a drug per unit time. Total body clearance is based on all systems involved in drug elimination (hepatic, renal) acting as a whole. Hepatic metabolism in donkeys has been shown to be more rapid than horses for various drugs such as phenylbutazone (Mealey *et al*. 1997) and guaifenesin (Matthews *et al*. 1997a). Similarly, the active tubular secretion of sulphamethoxasole is apparently greater in the donkey (Peck *et al*. 2002). Since clearance is used to calculate the dose per unit time needed to produce a given steady-state concentration in the plasma, these differences must be taken into account when designing dosing regimes.

Elimination half-life

Elimination half-life ($t_{1/2}$) is the time required for a drug to achieve 50% of plasma concentration. It differs from clearance in that it does not separate the rate of elimination of a drug from its disposition kinetics. However, it is useful in determining dosing intervals.

Knowledge of the differences in pharmacokinetics between horses and donkeys is necessary when extrapolating dosages and dosing intervals for donkey therapeutics from doses recommended for horses. Dosing donkeys must be approached with caution. For drugs in which clearance tends to be more rapid than in horses, it may not be advisable to increase the dosage in order to achieve a longer dosing interval. Increased bioavailability and a smaller apparent Vd for some drugs may predispose to toxicity in donkeys.

Lizarraga *et al*. (2004) have written an excellent literature review (up to 2002) of the pharmacological differences between horses and donkeys. The wealth of published information has not expanded appreciably since then. Among the references on donkey pharmacology cited here, only about 35% have been published since 2002.

Pharmacodynamics

Once a drug reaches its site of action, it must be able to affect cellular processes, either to the benefit of the host or to the detriment of an invading organism (e.g. bacteria, parasites, viruses). How drugs achieve this comes under the purview of pharmacodynamics. Many drugs exert their effect by physically binding with specific cell membrane receptors. This binding causes a conformational change that is transmitted through the cell membrane to trigger intracellular events. If the target receptor is not present on the cell membrane, no amount of drug present will have an effect. Significant inter-species variability between the horse and the dog with respect to location and density of opiod and alpha-2 adrenergic drug receptors in the central nervous system has been demonstrated (Hellyer *et al*. 2003). This could explain some of the differences in behavioural reactions between the two species to opioid administration. It is feasible that similar variability exists between the donkey and horse to explain some of the therapeutic differences.

Other drugs are able to cross cell membranes and affect cellular metabolic processes directly. Physiological differences that convey an evolutionary advantage to the donkey compared to the horse can also affect variability in drug response.

Therapeutics in donkeys

Anaesthetics and sedatives

More studies have been conducted in donkeys to determine effective drug doses for anaesthetics and sedatives than any other drug class. However, most protocols have been adjusted empirically from the limited pharmacokinetic data available. A review of the pharmacological data and differences in response to common sedative and analgesic drugs between donkey and horses will be noted here. Precise dose regimes and their application will be covered in detail elsewhere in this series.

Donkeys appear to metabolise many anaesthetic and sedative drugs differently from horses. Furthermore, different-sized donkeys appear to vary in their metabolic rates, which require compensatory adjustments in drug doses. Miniature donkeys generally seem to require higher drug dosages (Matthews *et al*. 2001, 2002).

Donkeys respond well to most common sedatives. Alpha-2 agonists such as xylazine, detomidine and romifidine have all been shown to be effective in sedation of donkeys at dosages comparable to those of the horse (Matthews *et al*. 1997b). Similar to horses, the addition of an opioid such as butorphanol, has been shown to produce a synergistic effect on the quality and length of sedation (El-Maghraby and Atta 1997; Joubert *et al*. 1999). Acepromazine, alone or in combination with xylazine, also produces effective tranquilisation of donkeys at the dosages recommended for horses (Matthews and Van Dijk 2004).

Effective anaesthesia of donkeys can be challenging in the field. Donkeys metabolise ketamine faster than horses (Matthews *et al*. 1997b). It has been determined that mammoth asses have a smaller apparent Vd and larger total body clearance than horses, which results in a shorter $t^1/_2$ (Matthews *et al*. 1994). Redosing, to prolong anaesthesia, must be approached with caution, since rough recoveries can result (Matthews and Taylor 2000). The combination of ketamine with xylazine and guaifenesin (GKX) is often used in horses to produce extended i.v. anaesthesia. This can also be used effectively in donkeys with the caveat that donkeys are more sensitive to guaifenesin than horses. Guaifenesin produces recumbency in donkeys more rapidly and at a lower dose than horses; but total body clearance is more rapid (Matthews *et al*. 1997a). This has implications for the combination of these drugs for i.v. anaesthesia in donkeys. Proportions commonly used in horses are best adjusted in donkeys. This was borne out in a field study which compared varying proportions of GKX in standard donkeys and found that doubling the ketamine in relation to the other components of the standard horse protocol produced the best results in donkeys (Taylor *et al*. 2008).

The holy grail of donkey field anaesthesia has yet to be attained. Propofol in combination with ketamine has been used for induction of general anaesthesia in donkeys with apparent success (Abass *et al*. 2007). However, propofol may prove to be cost prohibitive in all but miniature donkeys, which are difficult to anaesthetise with most other equine drug combinations. Thiopental alone, or in combination with guaifenesin, is another potential choice for short procedures (<25 min) but apnoea can be a problem (Matthews 2010).

Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been the choice for management of inflammatory pain in horses. Much emphasis has been placed on COX-2 selectivity in order to reduce gastrointestinal side effects and increase the safety margin for chronic pain management. This has shown to be the case in man and is presumed to translate to the horse as well (Kvaternick *et al*. 2007). However, comparison of COX-2 selectivity

TABLE 1: Comparison of pharmacokinetic parameters for nonsteroidal anti-inflammatory drugs between the donkey and horse. For ease of comparison, means have been rounded and where reference values differ, a range has been indicated. References are provided where the definitive values and descriptive statistics can be found. Values and citations pertinent to the horse are in brackets

	Reference(s)	Clearance donkey [horse] (ml/kg bwt/h)	AUC donkey [horse] (µg/ml/h)	MRT donkey [horse] (h)	Vd_{ss} donkey [horse] (ml/kg bwt)	$T^1/_2$ el donkey [horse] (h)	Recommended dose for donkeys (Trawford and Mulugeta 2008)
Phenylbutazone	Matthews *et al*. 2001 Mealey *et al*. 1997 Cheng *et al*. 1996a [Sams *et al*. 1997]	170–215; Minis 360 [13–30]	28.3 [118.3]	0.7–1.7; Minis 1.4 [3.6]	147–242; Minis 213 [84–174]	0.6 [4–6 h]	2.2–4.4 mg/kg bwt q. 12 h Standard; q. 8 h Minis
Ketoprofen	Oukessou *et al*. 1996 [Sams *et al*. 1995]	414 	nd [7.4]	0.66 [0.56]	263 [164]	1.3 [1.5 h]	1–2.2 mg/kg bwt q. 24 h
Flunixine meglumine	Coakley *et al*. 1999 Cheng *et al*. 1996b [Landoni and Lees 1995]	1.78 [1.1]	11–39 [19]	0.9 [1.8]	85–171 [317_{AUC}]	0.75–4.5 [3.4 h]	1.1 mg/kg bwt q. 12–24 h
Meloxicam	Sinclair *et al*. 2006 [Toutain *et al*. 2004]	188 [35]	4.6 [19]	0.6 [9.6]	93 [120–270]	nd [8.5 h]	0.6 mg/kg bwt q. 24 h
Carprofen R(–) R(+)	Mealey *et al*. 2004	2.8 [8.4] 4.9 [37]	266 [83] 149 [22]	70.3 [24] 13.1 [18]	183 [201] 214 [517]	nd[22 h]	0.7 mg/kg bwt q. 24 h
Firocoxib i.v. Oral	Matthews *et al*. 2009 [Kvaternick *et al*. 2007]	239 [37] nd	0.5 [2.3] 0.35 [1.8]	2.9 nd	604 [1695] nd	0.85 [34] 1.5 [30]	None determined

AUC, area under the curve; MRT, mean residence time; Vd_{ss}; steady state volume of distribution; $T^1/_2$ el; elimination half time.

between different NSAIDs in horses is difficult because of inter-laboratory assay variability. Direct comparison is further complicated by the finding that potency determinations are dependent on the level of inhibition at which they are determined (Beretta *et al*. 2005). Significant species differences have been noted in COX-specificity for the same drug in man, horse, dog and cat (Lees *et al*. 2004). Until the work is done, it cannot be assumed that COX-2 selectivity in the horse can translate directly to the donkey.

Table 1 serves as a comparison of pharmacokinetic parameters in donkeys and horses. The table has been compiled from various sources. All of the NSAIDs listed have been subject to use in horses but little research has been conducted in donkeys to determine optimal dosing intervals for maximum efficacy and reduced toxicity. Because of apparent differences in distribution and clearance, extrapolation must be done with care. Little work with the older, commonly used NSAIDs has been done in donkeys. More recent papers focus on newer generation NSAIDs. Meloxicam and firocoxib have been shown to have elimination half-lives in donkeys that are shorter than in the horse (Sinclair *et al*. 2006; Matthews *et al*. 2009). Clearance of carprofen, however, is less in the donkey and the AUC ranges from 3.2–6.7 times longer for the (–) and (+) enantiomers, respectively (Mealey *et al*. 2004). The current recommended dosage is the same for donkeys as in horses (Svendson 2008). However, a longer dosing interval might be considered in donkeys due to potential toxicity concerns. Firocoxib is the most COX-2 selective agent in the horse (Kvaternick *et al*. 2007) but it is cleared much more rapidly in the donkey (Matthews *et al*. 2009). Therefore, the presumed safety advantage may be lost in the requirement for a shorter dosing interval. Further clinical studies with firocoxib in donkeys are warranted.

It should be noted that, in horses, many NSAIDs persist much longer in exudates than in plasma (Lees *et al*. 1986). This seems also to be the case in donkeys with respect to phenylbutazone; however, not to as great an extent as in the horse (Cheng *et al*. 1996a). Thus, NSAIDs may be clinically effective longer than indicated by the respective plasma $t^1/_2$.

Optimum dosing intervals for maximum efficacy and reduced toxicity in the donkey are yet to be determined. With the possible exception of carprofen, the dose may need to be increased and/or dosing intervals reduced. For extended use, animals should be closely monitored for signs of gastrointestinal or renal toxicity.

Opioids

The use of opioids in donkeys has been reported, mainly in association with an α_2 agonist. The addition of butorphanol to detomidine acts synergistically with respect to both sedation and analgesia in donkeys (El-Maghraby and Atta 1997; Joubert *et al*. 1999). Butorphanol combined with xylazine and ketamine produced effective anaesthesia with longer recumbency times (mean 37 min) than xylazine and ketamine alone in mammoth asses (Matthews *et al*. 1992). However, the same combination, in a study involving miniature donkeys, produced variable results, with 5 of 6 animals becoming sternal or responding to stimulation within 10 min of induction to anaesthesia (Matthews *et al*. 2002).

Plasma levels of fentanyl consistent with analgesia in horses were attained in a miniature donkey with a fentanyl patch (Matthews 2010). The donkey did require a larger dose patch than a horse on a mg/kg bwt basis to achieve comparable plasma levels of fentanyl. Analgesic levels

were achieved more rapidly in the donkey and more frequent patch changes were required.

The pharmacokinetics of tramadol, an analgesic with opioid activity, and its metabolites were determined in donkeys after both i.v. and oral administration (Giorgi *et al*. 2009). In man, the analgesic effectiveness of tramadol is primarily determined by its metabolism into the active metabolite M1 which is 300 times more potent at the μ-receptor than the parent drug. In donkeys, the inactive metabolite M2 is produced in greater quantities than M1 which may decrease its analgesic efficacy. Oral availability in donkeys appears to be limited (11.7%). The utility of tramadol for use in donkeys in the field cannot be extrapolated from these data and further work is warranted.

Antimicrobial drugs

The efficacy of any antimicrobial drug therapy regime depends on maintaining drug concentrations above therapeutic levels at the site of infection while limiting systemic levels below that which cause negative side effects. Plasma concentrations of the drug are used as a convenient indicator to determine the dose and dosing interval required to maintain plasma drug concentration within this therapeutic 'window'. **Table 2** lists the implied recommendations for antimicrobial doses and dosing interval relative to the horse.

The aminoglycosides are widely used to manage bacterial infections in horses and can be successfully used in donkeys. However, it appears that many of these drugs may require altered dosing regimes when applied to this species. The pharmacokinetics of gentamicin, after a single i.v. dose in donkeys, were similar to those reported in horses (Welfare *et al*. 1996). However, the disposition of gentamicin in mammoth asses appears to differ, owing to a smaller apparent Vd. This implies that lower doses may be required to avoid toxicity (Miller *et al*. 1994). However, since clearance is the same as in the horse, if a lower dose is administered, a shorter dosing interval may be indicated to maintain therapeutic plasma levels of gentamicin. Administration of a single i.v. dose of amikacin resulted in a shorter elimination half-life in donkeys compared to horses (Horspool *et al*. 1994). Thus, a shorter dosing interval for amikacin is also recommended for donkeys. The same applies for oxytetracycline. To maintain therapeutic plasma concentration the dosing interval should be half that recommended for horses (Horspool and McKellar 1990).

Inconsistencies exist between studies regarding the pharmacokinetics of sodium penicillin G in horses and donkeys (Lizarraga *et al*. 2004). Donkeys appear to have a shorter elimination half-life and smaller apparent Vd following i.v. administration of sodium penicillin G when compared to published data on horses (Firth *et al*. 1986; Oukessou *et al*. 1994). The time to achieve sodium amoxicillin plasma concentrations greater than 0.5 μg/ml following i.v. or i.m. administration was approximately half that reported for horses (Montesissa *et al*. 1988; Oukessou *et al*. 1994; Lavy *et al*. 1995a). The same was reported for amoxicillin trihydrate given i.m. (Lavy *et al*. 1995a). The elimination half-life and apparent Vd after a single i.v. injection of sodium ampicillin were comparable between donkeys and horses, whereas the values for body clearance were significantly higher in donkeys (Horspool *et al*. 1992). Collectively, these data suggest that a shorter dosing interval is required when administering beta-lactam antimicrobials to donkeys but further comparative studies are required to establish a reliable dosing regime.

Sulphonamides and trimethoprim are other antimicrobials commonly used in equine practice due to their broad range of bactericidal activity. The disposition of sulphamethoxazole and trimethoprim after i.v. administration has been investigated in both donkeys and horses (Peck *et al*. 2002). Results from this study demonstrated a faster clearance of trimethoprim and

TABLE 2: Implied recommendations for doses and dosing interval relative to the horse. Citations and values pertinent to the horse are in brackets

Antimicrobials	Reference(s)	Dosage donkeys [horse]	Route
Gentamicin	Welfare *et al*. 1996	2.2 mg/kg bwt q. 8 h [same]	i.v.
Amikacin	Horspool *et al*. 1994	6 mg/kg bwt q. 6 h [q. 8 h]	i.v.
Oxytetracycline	Horspool and McKellar 1990	10 mg/kg bwt q. 24 h [q. 48 h]	i.v.
Na Penicillin G	Horspool and McKellar 1995 [Firth *et al*. 1986]	20,000 u/kg bwt q. 4–6 h [q. 6–8 h]	i.v.
Amoxicillin	Oukessou *et al*. 1994, Lavy *et al*. 1995a	10–15 mg/kg bwt q. 4–6 h [q. 6–8 h]	i.v. i.m.
Ampicillin	Horspool *et al*. 1992	10 mg/kg bwt q. 4–6 h [q. 6–8 h]	i.v.
Sulphamethoxazole/ Trimethoprim	Peck *et al*. 2002	12.5 mg/kg bwt: 2.5 mg/kg bwt q. 8–12 h [q. 8–24 h]	i.v.
Danofloxacin	Kum *et al*. 2009 [Fernández-Varón *et al*. 2006]	>1.25 mg/kg bwt* [1.25 mg/kg bwt q. 24 h]	i.v.
Marbofloxacin	Gonzalez *et al*. 2007 [Carretero *et al*. 2002]	2 mg/kg bwt q. 24 h [same]	i.m.
Norfloxacin	Lavy *et al*. 1995b	10–20 mg/kg bwt q. 12–24 h	i.m.

* Danofloxacin did not achieve effective plasma concentrations in donkeys at 1.25 mg/kg bwt.

sulphamethoxazole in donkeys than in horses. Interestingly, the volume of distribution at steady state (Vd_{ss}) for sulphamethoxazole was the same in both species but the Vd_{ss} for trimethoprim was significantly greater in horses than donkeys. The observed differences in the Vd_s of trimethoprim between species may be attributable to the amount of serum protein binding to trimethoprim (Peck *et al*. 2002). Further, the optimal ratio for both drugs to achieve bactericidal activity is one part trimethoprim to 20 parts sulphamethoxazole (Mandell and Petri 1996). The study conducted by Peck *et al*. (2002) demonstrated a decrease in the optimal drug ratio by 2 h post administration. Thus, a dosing interval more frequent than every 24 h may be indicated.

The pharmacokinetics of the following antimicrobials from the fluoroquinolone class have been reported in donkeys: danofloxacin, marbofloxacin and norfloxacin. Intravenous administration of a single dose of danofloxacin resulted in faster clearance and approximately 3 times the Vd in donkeys when compared to horses (Kum *et al*. 2009). Conversely, marbofloxacin administered i.v. to donkeys was characterised by a longer elimination half-life and slower total body clearance than horses. However, therapeutic indicators were effective for only the *Enterobacteriaceae* in donkeys at the recommended horse dose. Higher effective doses were calculated for both *Staphylococcus aureus* and *Streptococcus* spp. in donkeys (Gonzalez *et al*. 2007). The i.v. administration of norfloxacin nicotinate to donkeys at 10 mg/kg bwt over 45–60 s induced central nervous system signs, including transient ataxia, mild seizures, strabismus, profuse sweating and tachycardia. Multiple oral treatments did not produce any gastrointestinal clinical signs; however, oral bioavailability was low. Intramuscular administration resulted in serum concentrations above that necessary to inhibit most Gram-negative equine bacteria isolates but multiple i.m. doses caused local swelling at injection sites (Lavy *et al*. 1995b). Norfloxacin may not be the best choice of a fluoroquinolone in donkeys.

Anthelmintic drugs

Anthelmintic drugs commonly used for control of endoparasites in equines fall into four main categories: Macrocyclic lactones (e.g. abamectin, ivermectin, moxidectin); benzimidazoles (e.g. fenbendazole, oxfendazole, oxibendazole, triclabendazole); tetrahydropyrimidines (e.g. pyrantel salts); pyrozinoisoquinolines (e.g. praziquantel).

Donkeys and horses share susceptibility to most endoparasites and these drugs have been shown to be effective for the control of natural parasitic infection in donkeys at doses determined for horses (Malan and Reinecke 1979; Taylor and Craig 1993; Trawford and Tremlett 1996; Binev *et al*. 2005; Imam *et al*. 2010). **Table 3** lists some of the common equine anthelmintics currently in use and their specific label indications. Studies regarding the pharmacokinetics of some macrocyclic lactones (Gokbulut *et al*. 2005) and benzimidazoles (Kinabo and Bogan 1989; Gokbulut *et al*. 2006) in donkeys corroborate their use at these dosages despite some apparent differences in absorption and disposition.

The pharmacokinetics of ivermectin in equines have been studied more extensively than any of the other endectocides. Gokbulut *et al*. (2005) compared the plasma pharmacokinetics and faecal excretion of ivermectin to doramectin in donkeys but no direct comparison of either drug with the pharmacokinetics in horses has been made within a single controlled study. Two similar studies in horses, using the same dose rate and route of administration (Gokbulut *et al*. 2001; Gokbulut *et al*. 2010), yielded conflicting results. The discrepancy was attributed to differences in breed and diet between the horses in the 2 equine studies (Gokbulut *et al*. 2010). Comparison of pharmacokinetic parameters for oral administration of ivermectin in donkeys to that of Gokbulut *et al*. (2001) in horses, gave the impression that gastrointestinal absorption was greater and drug persistence longer in the donkey. However, the opposite appears to be the case when the same values for the donkey are compared to those of the 2010 horse study. It is possible that any equine inter-species variation in the pharmacokinetics of ivermectin is overridden by variations between individual animals and their management.

Similar comparisons involving benzimidazoles suggest that they appear to be less readily absorbed from the gastrointestinal tract of the donkey than the horse.

TABLE 3: Anthelmintics commonly used to treat endoparasites in donkeys

Class	Example	Indications	Dose*
Macrocyclic lactones	Ivermectin	Roundworms, lungworm (*D. arnfieldi*)	0.2 mg/kg bwt *per os*
Benzimidazoles	Fenbendazole	Roundworms	30–60 mg/kg bwt *per os* or 7.5 mg/kg bwt *per os* for 5 days
	Oxfendazole	Roundworms, lungworm	10 mg/kg bwt *per os*
	Triclabendazole	Flukes (*F. hepatica)*	12 mg/kg bwt *per os*
Tetrahydropyrimidines	Pyrantel pamoate	Roundworms	19 mg/kg bwt *per os*
		Tapeworm (*A. perfoliata*)	38 mg/kg bwt *per os*
Pyrozinoisoquinolines	Praziquantel†	Tapeworm	1–2.5 mg/kg bwt *per os*

* Trawford and Mulugeta 2008. † Several oral preparations are approved for use in horses that combine praziquantel and one of the macrocyclic lactones. Each has a unique dosage within the stated range.

Fenbendazole and its metabolites were not detectable in the plasma of donkeys at any time following treatment of donkeys with fenbendazole (50 mg/ml). This may account for fenbendazole's reported lack of efficacy against naturally-acquired lungworm (*Dictyocaulus arnfieldi*) infection (Taylor and Craig 1993).

In contrast, the same dosage and route of administration in horses resulted in low, detectable levels of fenbendazole and its sulphoxide and sulphone metabolites in plasma (McKellar *et al*. 2002). However, when fenbendazole's sulphoxide metabolite (oxfendazole) is administered orally to donkeys, plasma disposition is similar to that of horses. Gut transit times for both fenbendazole and oxfendazole appear to be longer in donkeys (Gokbulut *et al*. 2006) than in horses (McKellar *et al*. 2002) with the caveat that diet may have had influence over the outcome between the 2 separate studies.

The disposition of triclabendazole in donkeys (n = 3), indicated for the treatment of *Faciola hepatica* in equines, was compared to that of 3 horses and 3 ponies in a study by Kinabo and Bogan (1989). When given orally at a dosage of 12 mg/kg bwt, Cmax, AUC and half-life appeared to be shorter for the donkey group but the dosage is that recommended by the Donkey Sanctuary (Trawford and Mulugeta 2008).

Conclusion

Few drugs used in donkeys have dosages based on evidence. A review of the literature reveals some guidelines for commonly used therapeutics. The logical reference point continues to be the horse, realising that drugs may have lesser or more profound effects and/or duration of effect. In most cases, larger doses and/or shorter dosing intervals will be required but there are important exceptions. In the absence of published data or clinical experience, one should start with a conservative dosing regime and titrate to effect while monitoring clinical signs.

Authors' declaration of interests

No conflicts of interest have been declared.

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