Medicines

5

5.1 Introduction and nomograms

For the use of medicines for specific body systems or conditions, see the relevant chapters. For example, anthelmintics are discussed in Chapter 17 Parasitology and ocular therapeutics in Chapter 9 Ophthalmology.

Calculation of body weight (nomograms)

In any situation where drug doses need to be calculated, it is essential to be able to calculate the bodyweight of working equids accurately. If there is access to a weigh scale or bridge this is always preferable. Unfortunately this is not usually available.

There are a number of published calculations for estimating the weight of equids (Carroll and Huntington 1988 and Svendson 2008). However, remember that working equids often have low body weight in relation to their height or length compared with the sample populations that the calculations were made from, so take care in interpreting these calculations.

The equation used by Caroll and Huntington (1988) correlated well with the body condition score charts that they used: weight (kg) = $\frac{\text{girth}^2 \times \text{length (cm)}}{11900}$

5.2 Responsible medicine use

A veterinary qualification allows the legal right to dispense medication to animals. Although the levels of training required to dispense may vary between countries, veterinary undergraduate courses guarantee the teaching of pharmacological principles to an advanced level.

> As a veterinarian, set the standard of excellence for responsible medicine use in the working environment.

The dispensing of medication carries great responsibility. This is often forgotten or overlooked due to the frequency with which medicines are prescribed. The following paragraphs briefly describe some important considerations on this aspect.

Know the basic pharmacological principles of the medication

When administering a drug to an animal, there is an obvious responsibility that it should:

a) reach the affected area, and
b) be effective for the purpose required – a concept known as pharmacokinetics.

Although this concept sounds simple it encompasses five main principles which should be applied when choosing a drug regime:

1. Absorption How quickly will the drug leave the site of administration and get into the bloodstream? Is this appropriate for what is trying to be achieved? For example, to stop a per-acute anaphylactic reaction where the animal could die within minutes, an instantaneous effect is required, thus choose intravenous (IV) administration over oral (PO) or intramuscular (IM). On the other hand, if a drug needs to be absorbed more slowly and/or maintain effective concentrations in the body over a period of hours or days, intramuscular or oral drugs are best.

2. Distribution How rapidly will the drug reach the site of action and how long will it stay there? Drugs reach highly perfused organs (such as the kidneys and lungs) relatively quickly regardless of administration route, whereas they take longer to reach the skin, skeletal muscle and some other organs. Be aware how long effective drug concentrations will persist in the blood (the 'half-life'), as this may dictate how often the drug must be administered over a 24-hour period – once (SID), twice (BID), three (TID) or four times (QID).

3. Metabolism Be aware of how drug metabolism or 'breakdown' occurs for different substances, as this can alter the effectiveness. The majority of medicines are metabolised in the liver but some are metabolised in the kidneys, lungs or gastrointestinal system. Older animals or those with liver pathology may metabolise compounds more slowly than a young, healthy animal. This may have an effect on how fast the drug will work; for example, some drugs are administered in the form of a 'pro-drug' which first must be activated by liver metabolism. Consider whether long-term usage may have a negative effect on the liver or kidneys.

4. Excretion What goes in must come out. Medical compounds will be eliminated from the body either in the original form or as metabolites and it is important to know the routes. Most drugs are excreted through the kidneys although some are eliminated through the gastrointestinal system. Gaseous anaesthetics exit through respiration. Some drugs are excreted in milk; a very important consideration if a mare is lactating as metabolites could have side effects on the foal. The route of excretion also dictates the drug efficacy. Animals which are dehydrated or suffering from anuria may develop a toxic build-up of metabolites if they cannot excrete the drug through the urine.

5. Drug Interactions Interactions may be desirable with positive effects for the animal or undesirable with negative effects. An example of a positive interaction would be using smaller doses of two drugs which have a more profound effect when used in combination, e.g. combining an alpha-2 agonist (detomidine) and an opioid (butorphanol) to give a greater depth of sedation than a single larger dose of the alpha-2 alone would produce.

   In the case of undesirable effects there are two possibilities. The first is that some drugs interact, resulting in inactivation of them both, e.g. combining flunixin meglumine and gentamicin in the same syringe causes precipitation and inactivation. Secondly, certain drugs interact with a negative effect, e.g. if intravenous potentiated sulphonamides (sulphadiazine with trimethoprim, or sulphadoxine with trimethoprim) are administered to horses that have been sedated with the alpha-2 agonist drug detomidine, there is a risk of death from heart arrhythmia (Stack and Schott 2011).

The above has been included as something to think about. It is beyond the scope of this manual to cover the pharmacodynamics of all drugs used in equine practice so reference should be made to pharmacological texts when necessary. Moreover, the data sheet which accompanies most drugs should have pharmacokinetic information.

The table below shows the common drug administration routes and some pharmacodynamic considerations for the use of each route.

Drug administration routes

See Section 4.1 for a full description of each route of administration.

Table 5.2.1 shows the pharmacodynamic considerations for various drug administration routes, outlining the main routes of administration of drugs for equids along with the absorption rates for each route, advantages of the route and any precautions that should be noted and stated to the owner.

Route	Absorption	Advantages	Precautions
Oral (PO) – direct, drench gun, stomach tube	+/- Variable, as must first pass through the gastrointestinal tract. Not possible for all drugs	Owner convenience (compliance), cheap, safe	Liquid may enter lungs Diarrhoea if gut flora upset Lack of absorption due to diet/other complications No guarantee animal will eat medication Depends on owner compliance of timing and correct administration
Intramuscular injection (IM)	+++	Good if drug unsuitable for IV use but a relatively fast onset of action is required	Requires a trained administrator Extreme pain and necrosis if drug is not meant for IM injection route Not > 20 ml/site Animal may show resistant behaviour if used for long term Injection sites may fibrose after time Accidental IV injection can be dangerous
Subcutaneous injection (SC)	++	Good for less soluble suspensions	Large volumes will not disperse Pain/irritation may result Poor absorption if animal is dehydrated

Route	Absorption	Advantages	Precautions
Intravenous injection (IV)	+++++ Immediate	Good for emergency situations or large volumes (absorption bypassed)	Risk of injection into carotid artery when attempting jugular vein injection, always check before injecting More skills required than other routes Systemic reaction/death if drug not suitable for IV Little time to act if adverse reaction or overdose Requires slow injection over 5–10 seconds Not suitable for owner administration
Topical	++	Easy compliance Good where systemic use may have side effects, e.g. steroids	Animal may lick/bite medication off Some preparations harmful to humans and require the use of gloves in application Absorption into skin of equids with hair cover may be variable

Table 5.2.1 The rate of absorption, advantages and precautions of different routes of drug administration.

Owner compliance

As a veterinarian, ensure that any dispensed drugs are adequately packaged and clearly labelled with the owner's name, drug name and instructions for use. Even in illiterate communities there are ways to devise instructions using pictures and symbols. Many community-based health programmes have successfully adopted this method (Hanson 1995, Daghio et al. 2010). If drugs are not dispensed in the correct packaging there is a risk they will be misused or accidentally consumed by children, with potentially devastating effects. Always ensure the owner thoroughly understands the prescription, how often it is to be given and any side effects to look out for.

It is very important to give precise and clear instructions when dispensing drugs to owners.

State:
- The prescribing veterinarian's name and contact details
- The owner's name and contact details
- The identification of the intended animal
- The dose rate – so the owner understands how much of the drug to give
- The dosing interval – so the owner understands how often to give the drug
- 'For animal treatment only'
- 'Not for use in food production animals' (if required)
- 'For external use only' with topical products
- Any necessary warnings and special storage instructions
- The date of supply and expiry date if applicable

- Ensure the owner knows how to administer the drug – the best way to ensure this is to get the owner to administer the first treatment under direct observation.

Ensure that the owner understands if a drug is not to be used in animals intended for human consumption. Although the owner may not be intending to slaughter their equid for consumption, the drug may inadvertently be given to other livestock and owners must be made aware of potential consequences. If there are risks to humans from inadvertent consumption of the drug, these must also be explained to the owner.

Owner compliance is perhaps one of the biggest limiting factors in successful recovery of sick animals.

There is a reliance on owners to carry out instructions once a consultation is finished. It is important to have owners report on the progress of treatment. If there is not a good relationship with the owner the outcome will most definitely be poor compliance, resulting in poor animal welfare.

Figure 5.2.1 Developing good communication and rapport with owners is fundamental to a successful outcome.

Be aware of the wider consequences of medication.

Knowledge of pharmacology brings with it a broader understanding of the potential negative effects of drug usage, not just on the individual animal but on the surrounding human and animal populations, and the environment. Take note of the following guidance to limit the negative effect.

- Always prescribe the full course. There are many examples of drug resistance, particularly in antibiotics and antiparasitics, and it is the responsibility of a veterinarian to avoid contributing to this as much as possible. Even if paraprofessionals, owners or markets

contribute to drug resistance in the locality, veterinarians should be setting the best standard, to avoid such practices. Use any available opportunity to guide government, paraprofessionals, pharmacists, other veterinarians and owners towards appropriate drug use.

- Always administer the correct dose. Overdosing can result in damaging side effects and toxicity, whereas under-dosing will encourage resistance and compromise animal welfare if it does not have the required effect. Body weight can be estimated using a simple tape measure. There are a number of nomograms published for calculating the body weight of horses and donkeys (Carroll and Huntingdon 1988, Svendson 2008).
- Never administer a drug unnecessarily. Veterinarians worldwide are unfortunately exposed to pressure from owners to administer medicines to animals against their better scientific judgement. Experience, confidence and having a good vet/owner relationship will soften the effect of such pressure. Remember, neither the animal's welfare, or in some cases the environment, will benefit from unnecessary treatments. Often drug resistance is the unfortunate result of over-prescription.
- Think about the food chain. Although not quite as pertinent in equine medicine as with production animal medicine, always be conscious of where the drugs prescribed may end up. Owners could use dispensed drugs for other livestock, and then consume the meat or milk without adequate withdrawal periods. A good example is the antibiotic metronidazole; banned in food-producing animals for its carcinogenic properties but often prescribed in equids. Other drugs, such as diclofenac, have resulted in devastation in local wild animal populations due to veterinary use in domestic animals (Oaks et al. 2004).
- Take care when administering drugs that have not been licensed for equids – there may be unpredictable results due to variations in absorption, metabolism and excretion compared to that in the species which the drug is licensed for. Also some drugs are toxic to equids.

The above examples only touch on the moral and ethical debates that may be encountered in daily practice. Capacity building of local paraprofessionals poses an opportunity for working equid veterinarians to emphasise the importance of responsible drug use in the community; leading by example is the first step.

Always store drugs properly, maintaining the cold chain of those drugs for which this is required (see Figure 5.2.2).

Figure 5.2.2 Ensure proper storage of drugs in mobile services.

5.3 Antibiotics

Rational use of antibiotics

Antibiotics are used to treat infections caused by bacteria.

Antibiotics have no effect on other pathogens (including viruses). However, secondary bacterial infection is a common consequence of tissue damage from other causes.

There has been an increased awareness in recent years of the need for rational use and effective choice of antibiotics, given the escalation of bacterial resistance (Hollis and Wilkins 2009) and concerns over drug residues in consumable animal products and the environment.

Before dispensing any antibiotic therapy, consider the following:

Does bacterial infection actually exist, and is antibiotic treatment warranted?

Knowledge of pharmacological principles (see Section 5.2 of this chapter – Responsible medicine use) will help when making this decision; however, the use of antibiotics in superficial wounds or as single doses is unjustifiable. Superficial infections are usually due to commensal organisms which will be flushed away by adequate washing with water and careful attention to wound cleaning. 'One-off' dosages of antibiotics will usually not satisfy the pharmacological conditions necessary to overcome a bacterial infection, and will only encourage resistance. Look for alternatives in these situations.

An increase in body temperature alone does not amount to a diagnosis of bacterial infection! Body temperature can be affected by environmental heat, working conditions, stress, pain, non-infectious inflammatory conditions and viral infections.

Where is the infection and how long has it been present?

Consider where the infection is in the body and whether antibiotics may penetrate the area. For example, antibiotics will not penetrate a walled-off superficial abscess so their use in this case is unnecessary.

Which bacteria are likely to be involved and which antibiotics are they likely to be sensitive to?

It may be possible to make an informed guess about which bacteria are the most likely cause of an infection, even without advanced diagnostics. Normal skin flora such as Staphylococcus aureus will be present in most traumatic skin wounds, whilst respiratory infections commonly involve Streptococcus species. Septic infections and toxaemias will most likely involve gram negative bacteria. Be aware of which antibiotics treat which types of bacteria and choose accordingly (see 'indications' under each antibiotic type in the following pages and other reference texts).

What dosage, frequency and administration route will ensure appropriate antibiotic concentrations at the site of infection?

As discussed earlier in this section, the formulation of a drug influences how quickly it enters the bloodstream and acts at the point of infection. Some antibiotics are formulated as 'long-acting' preparations, meaning they release slowly from the injection site and last for 48–72

hours. The duration of action may be affected by infection, inflammation or other pathology which may compromise the drug's metabolism, so shorter acting antibiotics are preferred whenever possible.

When deciding the frequency of administration required, consider the 'half-life' of the antibiotic in question, as this determines the inter-dosing interval (once per day – SID, twice per day – BID, three times per day – TID or four times per day – QID).

> If medication is not dosed according to the recommended frequency it will not combat the infection due to bacterial multiplication between dosages.

What adverse effects could arise from using antibiotics?

Decide whether the benefits of antibiotic therapy outweigh the risks. Equids are prone to drug reactions (e.g. procaine penicillin), and the use of IV potentiated sulphonamides have been known to cause fatal cardiac arrhythmias if used with the sedative detomidine (Stack and Schott 2011; see Section 7.1).

Additionally, equids are sensitive to changes in their gastrointestinal flora, to the extent that the use of antibiotics may cause diarrhoea and colic due to proliferation of potentially fatal pathogenic bacterial species such as Salmonella and Clostridia.

> Always weigh up the potential harm versus benefit of administering antibiotics in each situation to avoid unnecessary administration.

Consider the specific needs of the equid being treated.

Different animals have different pharmacokinetics which may influence which antibiotics are appropriate. For example, not all antibiotics used in adult horses are safe to use in neonatal foals – e.g. tetracyclines can result in flexor tendon laxity in foals. Similarly, horses with liver disease/liver failure can have greatly altered hepatic metabolism which can affect the pharmacokinetics of drugs. Antibiotics may have different pharmacokinetics in donkeys compared to horses (Lizarraga et al. 2004, Grosenbaugh et al. 2011).

Clinical use of commonly available antibiotics

Due to variations in availability of antibiotics in different countries the following list is certainly not exhaustive. Useful references are the review article by Haggett and Wilson (2008) on the use of antimicrobials in horses, and the paper by Grosenbaugh et al. (2011) on therapeutics in donkeys. Antibiotic formulations and their dose rates, which are suitable for equids, vary widely, so refer to recent texts and reliable formularies as well as the manufacturer's data sheets for specific dose rates for the preparation.

Procaine penicillin (Beta-Lactam)

Penicillins are part of the Beta-Lactam antibiotic group which act on enzymes in the bacterial cell wall. They are generally broad-spectrum, safe, effective drugs of low cost. Procaine penicillin is the white formulation for intramuscular use only. Refer to a formulary for IV and oral penicillin preparations for equids which may be available locally.

Indications

- Streptococcal spp. infections (first choice for equine respiratory infections), e.g. Streptococcus equi spp. equi infections (Hollis and Wilkins 2009)
- Anaerobes such as Clostridial spp., the obvious examples being tetanus (Section 16.1) or malignant oedema (Section 14.9)
- Adverse penicillin reactions are quite common in many species (including humans) especially after multiple doses. In equids they react to the procaine binder of the drug, and the chance of this occurring is greatly exacerbated if the penicillin is injected into the bloodstream by mistake (see Section 4.1. Drug administration techniques). Also the availability of procaine in the body is increased if the drug is overheated.

What does an adverse penicillin reaction look like, and how can this be managed?

An adverse penicillin reaction will usually occur as soon as, or shortly after, penicillin administration.

In many cases the animal may have had a number of previous doses of penicillin without incident and the reaction will occur due to the cumulative effects of the drug over time. The animal will appear hypersensitive, with a range of signs including excessive muscle twitching/shaking, high head carriage, snorting, rigid stance, wide eyes and other manic behaviours. In severe reactions, collapse, seizures and death may occur – often within minutes.

Be warned that these reactions can be extremely violent, and ensure human safety if attempting any treatment. Although there is no antidote, adrenaline and intravenous corticosteroids can be given if it is possible to get access to a vein. Often the best thing to do is leave the animal in a quiet, dark place to recover, where it has minimal opportunities to further injure itself.

The potential severity of a penicillin reaction emphasises the importance of good IM injection technique.

Owners must be made aware that a penicillin reaction has occurred. Emphasise that the animal should never be given penicillin or penicillin derivatives in the future. Note the reaction in veterinary records so that other veterinarians are aware of it.

Cephalosporins (Beta-Lactam)

Cephalosporins were developed in the 1950s due to concern over penicillin resistance in Staphylococcus spp. They have the same mechanism of action as penicillins. They are grouped into 'generations'. The more recent generations (3rd and 4th) should be used cautiously to avoid development of antibiotic resistance. They would not be considered a first-line antibiotic choice except in extremely ill animals. There are many different formulations available; if using them be aware of the dose rate and frequency.

Indications

- Gram +ve Staphylococcus species
- Some Gram -ve species such as Pasteurella (lung infections)
- Pseudomonas spp. (often associated with green-coloured pus) are resistant
- Not as effective against anaerobes as penicillin

Aminoglycosides (Gentamicin)

Aminoglycosides act by penetrating bacterial cells and disrupting protein synthesis, ultimately resulting in bacterial death. Besides being an injectable drug (usually IV), gentamicin is also suitable for intra-articular injection and is found in many topical eye preparations.

Aminoglycosides are important for the treatment of gram negative infections. If using gentamicin be aware that it is not as broad spectrum as some other antibiotics and must be used responsibly – never start a course unless sure the animal will be re-visited for subsequent injections for at least 3 days. It is administered only once daily (SID).

Streptomycin, another aminoglycoside, is commonly mixed with penicillin as 'Pen-Strep'; this combination product is formulated for ruminants. However, the streptomycin concentration in this mixture is not effective in equids, therefore its use is not recommended in this species.

Indications

- Gram -ve bacteria, including Pseudomonas
- Endotoxaemia from species such as E. coli species
- Staphylococcus spp. infections
- Salmonella and Brucella spp. are resistant
- Do not use in suspected anaerobic infections – aminoglycosides require oxygen for action.

> All aminoglycosides are nephrotoxic; carefully consider their use in dehydrated animals or those with suspected kidney or urinary problems, and weigh up the potential harm to the animal versus the benefit of using aminoglycosides in these cases.

Potentiated sulphonamides (Trimethoprim-Sulphur)

These drugs act on folic acid metabolism, disrupting nucleic acid synthesis in the bacteria. Sulphonamides are beneficial for a number of conditions as they penetrate the blood-brain-barrier and achieve high concentrations in liver, kidney and lung tissues. The action of potentiated sulphonamides is reduced in the presence of pus.

Although easily absorbed from the equine digestive tract, sulphonamides can be associated with causing diarrhoea (see Section 11.5). Therefore, be sure to advise the owner when dispensing oral tablets. If using IV, ensure slow injection as hypotension and collapse can occur – never use IV with detomidine as fatal cardiac arrhythmia can occur (Stack and Schott 2011).

Indications

- Gram +ve staphylococcus and streptococcus infections
- Some anaerobic infections including C. perfringens, Fusobacterium and Bacteroides
- Some Gram -ve strains of E. coli and Pastuerella (lung and gastrointestinal tract infection)
- Do not use in serious Clostridial infections such as malignant oedema
- First choice for infections of the skin, central nervous system and mammary/testicular tissues (mastitis, encephalitis) due to its ability to cross barriers and penetrate other tissues

Tetracyclines (Oxytetracycline)

Tetracyclines are bacteriostatic (they stop bacterial replication rather than kill the bacteria) and act via interference with bacterial protein synthesis. They are effective in most tissues. Injectable forms are recommended in equine medicine, as the absorption of oral products can be unreliable

and has been associated with diarrhoea. Rapid IV injection can result in hypotension and collapse so inject slowly.

Long-acting cattle formulations are not licensed in equids and are contra-indicated as they can cause severe local irritant reactions and muscle necrosis in this species.

Indications

- Broad spectrum: effective against many Gram +ve, Gram -ve and anaerobic bacteria
- Good for tissue penetration due to high lipid solubility
- Some ability to get into mammary tissue
- Less effective against Staphylococcus, E. coli or Pseudomonas
- Reports of success in treating flexural limb deformities in foals (Haggett and Wilson 2008)
- Never use the long-acting cattle formulation (20%) in equids and advise paraprofessionals of the same (only use 10% or 5% in equids).

Macrolides (Erythromycin/Tylosin)

Macrolides are associated with potentially fatal colitis in adult equids so their use is not recommended.

Indications

- Rhodococcus equi ('rattles') treatment of foals in specialist paediatric treatment centres (see Section 18.1)

Metronidazole

Metronidazole is a unique drug which has specific action against anaerobic bacteria and protozoal infections.

It has little effect on Gram +ve and Gram -ve aerobic bacteria. It has good absorption from the digestive tract so is most often seen as an oral preparation.

Metronidazole is effective at penetrating those hard to reach places, such as anaerobic infections in bone, abscesses and the CNS. Alternatively, penicillin or cephalosporin-resistant infections can be treated with metronidazole, such as penicillin-resistant Clostridium spp. and malignant oedema cases.

Indications

- Penicillin-resistant anaerobic bacteria Clostridium spp., Fusobacterium, B. Fragilis
- Do not use in tetanus cases as penicillin is the prefered antibiotic for the treatment of C. tetani (see Section 16.1)
- Protozoal Giardia and Trichomonas spp.
- Polymicrobial infections with suspected beta-lactam resistant anaerobes such as peritonitis and pleuro-pneumonia
- Use is prohibited in food-producing animals due to carcinogenic (cancer-causing) properties, so ensure, when dispensing this drug, that the owner understands it is solely for use in equids.

Summary of commonly used antibiotics in working equine practice

Below are tables showing reported dose rates for horses (Table 5.3.1), donkeys (Table 5.3.2) and mules (Table 5.3.3).

(SID = every 24 hours, BID = every 12 hours, TID = every 8 hours, IV = intravenous, IM = intramuscular, PO = per os (orally), SC = subcutaneous)

Horses

Trade name	Dose	Route	Frequency
Procaine penicillin	22,000 IU/kg	IM only	BID for 5 days
Cephalosporins	2.2–4.4 mg/kg 2.2 mg/kg 5–10 mg/kg – foal septicaemia	IM IV/SC/IM IV/SC/IM	SID BID TID/BID
Gentamicin	6.6 mg/kg	IV	SID
Trimethoprim-sulpha	15–24 mg/kg 24–30 mg/kg	IV slowly PO	TID/BID BID
Oxytetracycline	5–10 mg/kg	IV	BID
Erythromycin (Foals only!)	20–25 mg/kg	PO	every 6–8 hours
Metronidazole	15 mg/kg – Clostridial enteritis 20 mg/kg – anaerobic infections 20 mg/kg	PO PO/per rectum IV	TID TID TID

Table 5.3.1 Dose rates for use of antibiotics in horses (Haggett and Wilson 2008).

Donkeys

Trade name	Dose	Route	Frequency
Procaine penicillin	20,000 IU/kg	IM only	BID/SID for 5 days
Cephalosporins (cefquinome – 4th generation)	1 mg/kg	IV	BID
Gentamicin	2.2 mg/kg	IV	TID
Trimethoprim-sulpha	2.5–12.5 mg/kg	IV	TID/BID (or SID)
Oxytetracycline	10 mg/kg	IV	SID (or every 48 hours)

Table 5.3.2 Dose rates for use of antibiotics in donkeys (Miller et al. 1994, Welfare et al. 1996, Widmer et al. 2009, Grosenbaugh et al. 2011).

Mules

Trade name	Dose	Route	Frequency
Procaine penicillin	20,000 IU/kg	IM	–
Kanamycin	7.45–8.73 mg/kg	IV	BID
Oxytetracycline	15 mg/kg	IV	–

Table 5.3.3 Dose rates for use of antibiotics in mules (Muhammed et al. 2003, Reichmann et al. 2008).

5.4 Non-steroidal anti-inflammatory drugs (NSAIDs)

Clinical features of NSAIDs

NSAIDs work to relieve pain, inflammation and fever which result from tissue injury, inflammation and/or infection.

Why do we want to control inflammation?

Inflammation is the body's natural response to injury. However, if this inflammatory response is excessive or prolonged, it can result in pain, loss of function, depression and anorexia. See Section 15.1 for a further explanation of the inflammatory process.

Management of inflammation is therefore an important means of helping the body heal as well as relieving pain.

Inflammation in working equids is often a result of chronic stress and injury to the body (Figure 5.4.1). It is for this reason that a holistic approach is necessary for the long-term relief of pain – anti-inflammatory drugs alone are not sufficient. Refer to Chapter 3 for an in-depth look at pain management principles which should be adopted along with the use of any pain relieving drugs.

Figure 5.4.1 An example of a clinical condition where NSAIDs would form an important part of the treatment approach.

How do NSAIDs control pain and inflammation?

The inflammatory process is well described in pharmacology and physiology texts. The explanation below is a simplified overview. In order to understand how NSAIDs work, it is necessary first to remember the five clinical signs of acute inflammation:

1. Heat Increased blood flow
2. Redness Blood accumulation
3. Swelling Accumulation of exudate
4. Pain Sensitisation of nerve endings
5. Loss of function Pain, vascular disturbances

Blood supply is a key component of the inflammatory process.

> When injury occurs, the body responds by increasing blood supply to the area, as blood carries substances which help fight infection and heal tissues.

Chemical mediators responsible for the inflammatory process belong to the eicosanoid family, of which Prostaglandin (PG) is a member. Prostaglandins have many roles in the body (see adverse effects of NSAIDs below); however, during the inflammatory process, they work to cause vasodilation and nerve sensitisation. This makes it an important player in the five signs of acute inflammation.

Prostaglandin = vasodilation and nerve sensitisation

NSAIDs therefore work to decrease the production of prostaglandin and other inflammatory mediators, thus decreasing the signs of inflammation and pain. Prostaglandins are produced as a result of the COX-1 pathway.

> NSAIDs work to block the synthesis of cyclo-oxygenase, thus resulting in decreased prostaglandin production.

Are there any side effects of the use of NSAIDs in equids?

As mentioned previously, prostaglandins have many roles in the body so the side effects seen clinically often relate to decreased production or inhibition of natural prostaglandins.

- Gastrointestinal Prostaglandins protect the intestinal mucosa; therefore diarrhoea and gastrointestinal ulceration are two of the most common side effects seen in equids if NSAIDs are used in high dosages or for long periods of time. Be cautious when prescribing NSAIDs to an animal showing signs of gastrointestinal disease such as diarrhoea or melena (digested blood in faeces). This ulcerogenic effect is even greater in foals so ensure the correct dose is given for as short a time as possible in young foals. Treating foals less than 1 week old concurrently with omeprazole whilst on the NSAIDs will reduce the risk of forming ulcers.
- Renal Dehydrated animals have been shown to develop acute renal failure with therapeutic doses of NSAIDs. Always try to correct dehydration before administering NSAIDs; for example, before giving flunixin meglumine in a colic case.

- Plasma protein binding NSAIDs bind to proteins in order to move around the body; however, so do drugs such as gentamicin and sulphonamides. If treating a case with one of these antibiotics together with NSAIDs, be aware that the gentamicin may not be as effective, or may require a slightly longer course.
- Masking effects of anti-inflammatory drug use Pain can work as a protective mechanism to stop the animal further injuring itself. The best example is in lameness where an equid may take weight off the injured limb. Another example is the masking of cardiovascular effects seen with flunixin meglumine administration in colic cases. Removal of the pain response with drugs may cause further damage if the animal subsequently works to full capacity or the owner works it harder thinking it is cured.

NSAIDs must never be used in isolation – aim for full owner compliance in management of painful conditions.

Common NSAIDs used in working equids

Phenylbutazone (PBZ)

PBZ is available as IV or PO formulations, with the oral powder/tablet form often used at a low dose for chronic inflammatory conditions of working equids, particularly lameness. Despite being effective and relatively cheap, PBZ has a very narrow safety margin so ensure never to exceed the recommended dose rates below:

Horse Days 1–2: 4.4 mg/kg BID then as for chronic inflammation. For chronic inflammatory cases: 2.2 mg/kg BID, then SID after the first 5 days – this is a very effective dose rate for safe use over longer periods; however, remain aware of side effects with long-term use.

Donkey Donkeys metabolise PBZ 5–15 times faster than horses (Cheng et al. 1996a, Lizarrago et al. 2004), so a dose rate of 4.4 mg IV followed by twice-daily dosing of oral PBZ at 4.4 mg/kg is acceptable. Aim to achieve the lowest dose rate possible; 2.2 mg/kg orally BID may be adequate.

Flunixin meglumine

This NSAID is commonly used for visceral pain with its action thought to be comparable to many opioid analgesics without the negative side effects. Flunixin meglumine is anti-endotoxic at lower dose rates (refer to pharmacological texts for more information). Flunixin meglumine is normally given IV for instantaneous action in extreme cases, at the following dose rates:

Horses 1.1 mg/kg SID–BID (anti-inflammatory) or 0.25 mg/kg every 6–12 hours (anti-endotoxic)

Donkeys Again, donkeys metabolise flunixin meglumine at a faster rate than horses and will require a higher dosing frequency, but the same dose rate (Cheng et al. 1996b, Coakley et al. 1999)

Mules The same dose rate and frequency as for horses (Coakley et al. 1999)

Dipyrone

This is used primarily for its anti-spasmodic and analgesic properties in treating colic in equids. It has a fast onset of action and short clinical effect. Its anti-pyretic, anti-thrombotic and anti-inflammatory properties are poor.

Check the formulation before use, as dipyrone is often combined with other agents (e.g. dipyrone and hyoscine N-butylbromide); always check the dose and route of administration before use. Do not exceed the recommended dose.

Do not give IM, as this will result in localised tissue reactions. Do not use with phenothiazine ataractics (e.g. chlorpromazine) as this may cause hypothermia. Dipyrone may cause blood dyscrasia, hepatitis, nephropathy, colic and diarrhoea. There is an ulcerogenic action on the GI tract as a result of prostaglandin inhibition. Potential renotoxicity and hepatotoxicity is weak. Do not use if there is known hypersensitivity. See Table 5.4.1 for reported dose rates (Lees and Higgins 1985).

Acetylsalicylic acid (aspirin)

Although a good anti-inflammatory, the dose rates required for this effect in horses (10–100 mg/kg) are too large to be of any real practical use.

Aspirin is used at 10 mg/kg and is also a useful antithrombotic.

Diclofenamic acid (diclofenac)

Historically used as an anti-inflammatory in production animal medicine, this drug is now widely banned due to its adverse environmental effects in the food chain (Oaks et al. 2004).

The use of diclofenac is increasing in Africa, but should be discouraged.

Others

Meclofenamic acid, Ketoprofen, Carprofen may be available in some countries. Check manufacturer's recommendations for use of these drugs.

> The use of ibuprofen cannot be recommended as there is insufficient data for its use in equids.

Donkeys and Carprophen Donkeys require a reduced dosing rate to horses as they metabolise this NSAID more slowly than horses (Coakley et al. 1999).

Donkeys and Ketoprofen A higher dosing frequency is required; however, the same dose of 2.2 mg/kg as horses (Oukessou et al. 1996).

NSAID	Presentation	Route	Dose	Frequency
PBZ	Injectable, or tablets	IV, PO	IV: 4.4 mg/kg q24h PO: Day 1: 4.4 mg/kg q12h Days 2–5: 2.2 mg/kg q12h, Thereafter: 2.2 mg/kg q24h	Donkeys require more frequent dosing than horses; however, more studies are needed for recommended dosing to prevent toxicity Present advice is to give the horse dose and monitor carefully for the need to re-administer sooner
Flunixin meglumine	Injectable, or granules	IV, IM, PO	Anti-inflammatory 1.1 mg/kg. (Toutain et al. 1994) Anti-endotoxic 0.25–0.55 mg/kg. Foal 0.5 mg/kg BID/ SID – avoid if gastric ulceration is suspected (Holcombe 2003) Donkey 1.1 mg/kg (Cheng et al. 1996b) Mule Same dose as horses (Coakley et al. 1999)	SID–BID QID–TID BID/SID Use lowest dose possible Donkey Dose frequency may be increased from that of horses due to faster body clearance (Coakley et al. 1999) Mule The same dose frequency as horses (Coakley et al. 1999)
Dipyrone	Injectable, or tablets	IV, PO	22 mg/kg	Depends on formulation – check before use
Acetylsalicylic acid	Tablets	PO	100 mg/kg (Lees and Higgins1985, Cambridge et al. 1991) Antithrombotic 10 mg/kg	SID
Ketoprofen	Injectable	IV	2.2 mg/kg of 10% solution	q24h for up to 5 days for musculoskeletal pain Single dose for abdominal pain

(IV = intravascular, IM = intramuscular, PO = orally, q = every, SID = once per day, BID = twice per day, TID = three times per day, QID = four times per day)

Table 5.4.1 Reported dose rates, routes of administration and frequency of NSAIDs commonly used in working equids.

Steroidal anti-inflammatory drugs (corticosteroids) 5.5

Corticosteroids can be used to treat a wide range of pathology in equine medicine:

- Topically Eye and skin inflammation
- Intra-articular Chronic joint pain/inflammation
- Systemically Either orally or injected, for chronic inflammatory disease such as recurrent airway obstruction (RAO), allergic dermatitis and many immune-mediated diseases

There are many corticosteroid formulations available for veterinary use, all with varying durations of action and concentration. Examples include prednisolone (short acting) and dexamethasone (long acting > 48h), see Table 5.5.1. Other corticosteroids used in equids are methylprednisolone for treating shock (Muir 1987) and intra-articular inflammation, although there is research showing its deleterious effects on the joint (McIlwraith 2010), and triamcinolone acetonide, commonly used for intra-articular inflammation, has been shown to be chondroprotective (Soma et al. 2011, McIlwraith 2010). See Section 14.7 for further information on treatment of joint disease.

The safe, effective use of corticosteroids in equids requires a good understanding of their mode of action and potential side effects. Equids are very sensitive to suppressive effects on the endocrine system from long-term systemic use, so it is advisable to use short-acting, less potent topical or local applications wherever possible.

Conditions where it is advisable not to use steroids

1. Laminitis
2. Corneal ulceration
3. Wound treatment

In working equids, corticosteroids should be considered in any immune mediated or hypersensitivity reaction (anaphylaxis, sweet itch, recurrent uveitis) or chronic respiratory illness (recurrent airway obstruction – RAO). Assess the local availability of different types of corticosteroid preparations and their recommendations. Always use them judiciously, remembering the adverse effects, especially from systemic use.

Serious potential side effects of corticosteroid use

- Laminitis Cause is unclear
- Iatrogenic Cushing's syndrome Due to adrenal insufficiency occurring with long-term use
- Immunosuppression Lowers the body's ability to fight off infections and may lead to secondary bacterial infection
- Slows wound healing Due to reduced collagen synthesis
- Withdrawal response It is advised that a decreasing dose is administered when

withdrawing treatment. When being treated with corticosteroid the body's endogenous corticosteroid production is lowered. Although in reality this is rare, always aim to taper treatment before stopping.

- Gastric ulceration A very rare complication
- During pregnancy Potential to induce parturition or abortion in third trimester, although single doses have been administered safely. Potentially teratogenic in first trimester. However, corticosteroid may be administered to mares at risk of pre-term delivery to aid maturation of the foal (Ousey et al. 2011). It is important when treating pregnant mares to consider the health of the mare versus that of the foetus.
- Joint injection can lead to damage of cartilage and changes in synovial fluid, post injection flare (non-septic inflammation), septic arthritis, arthropathy (joint enlargement and increased rate of damage) especially with high doses and high frequency of administration (see Sections 4.1 and 14.7).

Drug	Duration of action (hrs)	Presentation	Route	Dose rate (mg/kg)	Frequency
Prednisolone	12–24	Tablet, or injectable	PO, IV	1 mg/kg	SID/BID Taper dose according to effect Use minimal effective dose to reduce side effects
Dexamethasone	> 48	Check formulation before injection to confirm dosing interval and route compatibility	IV, IM	0.1–0.5 mg/kg (lower end of range for anti-inflammatory, higher end of range for shock and hypersensitivity)	Dose frequency depends on preparation – so check this (Cornelisse and Robinson 2011, Ousey et al. 2011)
Methylprednisolone	12–24	Injectable	IV	Shock: 15–30 mg/kg	Administered as soon as possible after the onset of shock (Muir 1987)
Triamcinolone acetonide	Intra-articular (IA), IM: days to weeks IV: 36 hours	Injectable	IA, IM, IV	IA: 6–18 mg per joint; maximum 40 mg total dose per horse (McIlwraith 2010) IM, IV: 0.04–0.2 mg/kg	IA: Detected in synovial fluid for up to 10 days. Larger joints may require larger doses. IM: clinically effective for weeks (Soma et al. 2011)

(PO = orally, IV = intravenous, IM = intramuscular, IA = intra-articular, SID = once per day, BID = twice per day)

Table 5.5.1

5.6 References

Cambridge, H., Lees, P., Hooke, R.E., Russell, C.S. (1991) Antithrombotic actions of aspirin in the horse. Equine Vet. J. 23 (2), 123–127.

Carroll, C.L., Huntington, P.J. (1998) Body Condition scoring and weight estimation in horses. Equine Vet. J. 20 (1), 41–45.

Cheng, Z., McKellar, Q.A., Nolan, A., Lees, P. (1996a) Pharmacokinetics and pharmacodynamics of phenylbutazone and oxyphenbutazone in the donkey. J. vet. Pharmacol. Therap. 19, 149–151.

Cheng, Z., McKellar, Q.A., Nolan, A., Lees, P. (1996b) Preliminary pharmacokinetic and pharmacodynamic studies on flunixin meglumine in donkeys. Vet. Res. Comms. 20, 469–472.

Coakley, M., Peck, K.K., Taylor, T.S., Mathews, N.S., Mealey, K.L. (1999) Pharmacokinetics of flunixin in meglumine donkeys, mules, and horses. Am. J. Vet. Res. 60 (11), 1441–1444.

Cornelisse, C.J., Robinson, N.E. (2011) Glucocorticoid therapy and equine laminitis: fact or fiction? Equine vet. Educ. 16 (2), 90–93.

Daghio, M.M., Fattori, G., Ciardullo, A.V. (2010) Use of pictorial advice to promote compliance to diet and drugs among illiterate and migrant patients. Journal of Diabetology, 3, 3.

Grosenbaugh, D.A., Reinemeyer, C.R., Figueiredo, M.D. (2011) Pharmacology and therapeutics in donkeys. Equine vet. Educ. 23 (10), 523–530.

Hanson, E.C. (1995) Evaluating cognitive services for non-literate and visually impaired patients in community pharmacy rotation sites. Am. J. Pharm. Ed. 59, 48–55.

Holcombe, S.J. (2003) Current therapy in equine medicine. Elsevier.

Hollins, A.R., Wilkins, P.A. (2009) Current controversies in current antimicrobial therapies. Equine vet Educ. 21 (4) 216–224.

Lees.P, Higgins.A. (1985) Clinical pharmacology and therapeutic uses of non-steroidal anti-inflammatory drugs in the horse. Equine Vet. J. 17 (2), 83–96.

Lizarrago, I., Sumano, H., Brumbaugh, G.W. (2004) Pharmacological and pharmacokinetic differences between donkeys and horses. Equine vet. Educ. 16 (2), 102–112.

McIlwraith, C. (2010) The use of intra-articular corticosteroid in the horse: what is known on a scientific basis? Equine Vet. J. 42 (6), 563–571.

Miller, S.M., Mathews, N.S., Mealey, K.L., Taylor, T.S., Brumbaugh, G.W. (1994) Pharmacokinetics in Mammoth asses. J. vet. Pharmacol. Therap. 17, 403–406.

Muhammed, F., Hussain, F., Nawaz, M., Javed, I. (2003) Disposition kinetics in mules. Vet. Arhiv. 73 (4), 221–226.

Muir, W.W. (1987) Equine shock: the need for prospective studies. Equine Vet. J. 19 (1), 1–7.

Oaks, J.L., Gilbert, M., Virani, M.Z., Watson, R.T., Meteyer, C.U., Rideout, B.A., Shivaprasad, H.L., Ahmed, S., Chaudhry, M.J.I., Arshad, M., Mahmood, S., Ali, A., Khan, A.A. (2004) Diclofenac residues as the cause of vulture population decline in Pakistan. Nature. 427, 630–633.

Oukessou, M., Bouljihad, M., Van Gool, F., and Alvinerie, M. (1996) Pharamacokinetics of ketoprofen in the donkey (Equus Asinus). J. Vet. Med. A. 43, 423–426.

Ousey, J, Kolling, M., Kindhal, H., Allen, W. (2011) Maternal dexamethasone treatment in late gestation induces precocious fetal and delivery in healthy thoroughbred mares. Equine Vet. J. 43 (4), 424–429.

Reichmann, P., Lisboa, J.A.N., Araujo, R.G. (2008) Tetanus in equids: a review of 76 cases. J. Equine vet. Sci. 28 (9), 518–523.

Soma, L.R., Uboh, C.E., You, Y., Guan, F., Boston, R.C. (2011) Pharmacokinetics of intra-articular, intravenous and intramuscular administration of triamcinolone acetonide and its effects on endogenous plasma hydrocortisone and cortisone concentrations in horses. Am. J. Vet. Res. 72, 1234–1242.

Stack, A., Schott II, H.C. (2011) Suspect novel adverse drug reactions to trimpethoprim-sulphonamide combinations in horses: A case series. Equine Vet. J. 43 (1), 117–120.

Svendsen, E.D. (2008) The Professional Handbook of the Donkey, 4th Ed. Whittet Books, London, UK.

Toutain, P.L., Autefage, A., Legrand, C., Alvinerie, M. (1994) Plasma concentrations and therapeutic efficacy of phenylbutazone and flunixin meglumine in the horse: pharmokinetic/pharmacodynamic modelling. J. vet. Pharmacol. Therap. 17, 459–469.

Welfare, R.E., Mealey, K.L., Matthews, N.S., Taylor, T.S. (1996) Pharmacokinetics of gentamicin in donkeys. J. vet. Pharmacol. Therap. 19, 167–169.

Widmer, A., Kummer, M., Wehrli Eser, M., Furst, A. (2009) Comparison of the clinical efficacy of cefquinome with the combination of penicillin G and gentamicin in equine patients. Equine vet. Educ. 21 (8), 430–435.

Further Reading

Bertone J.J., Horspool, L.J.I. (2004) Equine Clinical Pharmacology, 1st Ed. Elsevier, Oxford, UK.

Grosenbaugh, D.A., Reinemeyer, C.R., and Figueiredo, M.D. (2011) Pharmacology and therapeutics in donkeys. Equine vet. Educ. 23 (10), 523–530.

Haggett, E.F., Wilson, W.D. (2008) Overview of the use of antimicrobials for the treatment of bacterial infections in horses. Equine vet. Educ. 20 (8), 433–448.

Knottenbelt, D.C. (2006) Equine Formulary. Saunders, Elsevier Ltd. p. 184.