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Antimicrobial dosing for common equine drugs: a content review and practical advice for veterinarians in Australia

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Background Appropriate dosing with antimicrobial agents is critical for effective treatment and to prevent the development of antimicrobial resistance.

Methods A review was undertaken of equine journal articles (*Equine Veterinary Journal*, *Equine Veterinary Education*, *Australian Veterinary Journal*, *Australian Equine Veterinarian*, *Journal of Veterinary Internal Medicine* and *Journal of Equine Veterinary Science*) between January 2015 and August 2018. Those with dosing regimens for procaine penicillin G, gentamicin or trimethoprim-sulfonamide in adult horses were examined and evaluated. Pharmacokinetics and dynamics of these drugs were also reviewed.

Results & Conclusion The most frequently reported doses for penicillin, gentamicin and trimethoprim-sulfonamide were 20–25,000 IU/kg, 6.6 mg/kg and 30 mg/kg, respectively. Veterinarians treating equine patients in Australia should be aware of the current recommended doses and inter-dosing intervals to ensure efficacy in therapy and to preserve the usefulness of these antimicrobials for the future.

Keywords antimicrobial resistance; dosing regimens; horses

Abbreviations AMR, antimicrobial resistance; $C_{max,}$ peak plasma concentration; MIC, minimum inhibitory concentration; PPG, procaine penicillin G; TMS, trimethoprim-sulfonamide

Antimicrobial resistance (AMR) is a global health emergency. Anecdotally, AMR is a rapidly emerging threat in equine practice in Australia, with resistance in isolates from the general equine population now being reported, in addition to resistance in isolates from specialty hospitals.[1–4] Treatment failure, increased costs of therapy and pan-drug-resistant organisms are being reported by equine veterinarians in Australia[1,2] and may become more frequent if measures are not taken to reduce inappropriate antimicrobial use. Inappropriate use of antimicrobials includes the use of antimicrobials when not required (e.g. viral infections, nasal discharge and cough caused by equine asthma, prophylaxis for placentitis), the wrong choice of antimicrobial agent or the use of antimicrobials at inappropriate doses, duration or frequency of treatment.[5]

A recent paper in the *Australian Veterinary Journal* highlighted the varied, and often inappropriately low, dosing of common equine antimicrobials.[6] Appropriate dosing with antimicrobial agents is critical for effective treatment and in the fight against AMR. All antimicrobial use can select for AMR, but exposure to subtherapeutic levels of antimicrobial agents may increase the rate of development of AMR, particularly when exposure is prolonged or recurrent.[7–9] Here, we provide evidence for doses in adult horses higher than those on the label of common antimicrobials in equine practice in Australia (procaine penicillin G (PPG), gentamicin and

trimethoprim-sulfonamide (TMS)) and practical advice to aid the general equine and mixed practice veterinarian in the selection and dosing of these antimicrobials for horses.

Materials and methods

A review was undertaken of articles published in the *Equine Veterinary Journal*, *Equine Veterinary Education*, *Australian Veterinary Journal*, *Australian Equine Veterinarian*, *Journal of Veterinary Internal Medicine* and *Journal of Equine Veterinary Science* between January 2015 and August 2018. The abstracts of articles were reviewed, with abstracts containing mention of antimicrobials, or scenarios where antimicrobials may have been administered, downloaded for full-text evaluation. Dosing regimens in adult horses for PPG, gentamicin and TMS were documented, together with the country of origin and frequency of administration.

Results and Discussion

A total of 91 papers containing references to antimicrobial doses for PPG, gentamicin or TMS were found in the literature in the six journals between 2015 and 2018. Most papers were from hospitals or research institutes in the USA (23/63), followed by the UK (11/63) and Australia (5/63). These papers included 61 case reports, 18 case series, 10 retrospective studies and 2 experimental studies.

PPG

Procaine penicillin G is a first-generation beta-lactam antimicrobial with excellent activity against many gram-positive bacteria. Most notably, ² -haemolytic streptococci in equine practice still have predictable susceptibility to penicillin, making this the most appropriate choice for infections with these pathogens.[10–12] PPG also has excellent activity against anaerobic organisms, with the exception of *Bacteroides fragilis*, which is a relatively common isolate in anaerobic infections in horses (e.g. pleuropneumonia). Some gram-negative bacteria, such as *Actinobacillus* spp. and many *Pasteurella* spp., are also susceptible to PPG, although *Pseudomonas* spp., *Nocardia* spp. and *Enterobacteriaceae* (*Escherichia coli*, *Salmonella* spp.) are intrinsically resistant.[13,14]

Penicillin G should only be administered systemically to horses and PPG should only be administered intramuscularly. Oral administration is likely to lead to antimicrobial-induced colitis,[15] which can be fatal.

Penicillins are time-dependent antimicrobial agents, so concentrations should exceed the minimum inhibitory concentration (MIC) for as long as possible throughout the dosing interval (time > MIC) for the optimal bactericidal effect (Figure 1). In horses, this typically requires an inter-dosing interval of 12 h for PPG.[16] Long-acting preparations are not considered appropriate for use in horses.[17] Studies of the pharmacokinetics and pharmacodynamics of PPG in horses have resulted in a recommended dose of 22,000 IU/kg.[16,18]

Of the reviewed papers, 64 contained dosing regimens for PPG (Supplementary Table 1). The most frequently reported dose was 20–25,000 IU/kg (53/64) administered every 12 h. All papers with dose rates less than this came from the UK[19–25] (range 12,000–18,000 IU/kg), with the exception of one from Australia[26] (17,000 IU/kg). Of the papers from the UK and Australia, 55% (6/11) and 20% (1/5), respectively, used doses of PPG below the most commonly reported dose of 20–25,000 IU/kg. Only one paper used a dosing interval less than 12 h.[27]

The dosing regimen of 22,000 IU/kg of PPG is now widely accepted as the most appropriate dose, consistent with the above findings. For PPG and benzyl penicillin, 22,000 IU/kg is equivalent to 22 mg/kg. It should be noted that the conversion of international units to milligrams is not consistent for all penicillins. This dose rate is currently being taught in all Australian veterinary schools.[6] However, this dose was only used by 35% of respondents to a recent Australian survey on antimicrobial use in horses.[28] This may be a result of the labelling of PPG in Australia, but there is likely to be other contributing cultural aspects within the Australian equine veterinary profession, such as the hierarchical structure of veterinary practice, which has previously been identified as a barrier to antimicrobial stewardship.[29] Subtherapeutic antimicrobial dosing regimens are not only more likely to result in poor clinical outcomes, but are also more likely to select for AMR. Although lower doses of penicillin may be effective against some pathogens, determination of which cases can be effectively treated with a lower dose will be problematic unless the MIC is determined for the aetiological organisms, so case-by-case dose alterations are not recommended. Table 1 shows the recommended volumes of PPG for the formulations found in Australia (with a concentration of 300 mg/mL) for a range of horse weights. Dosing every 12 h is recommended in all instances.

Some practitioners have expressed concern about the large volumes required to meet the appropriate dosing regimen. However, as can be seen from the content analysis performed here, these doses can and are being administered around the world. Tolerance of this dosing regimen can be improved by alternating injection sites (i.e. neck, pectoral, gluteal muscles) and good injection technique. In addition, the duration of antimicrobial therapy should also be reviewed and may improve compliance with appropriate dosing. The historical use of a

5- or 7-day course of antimicrobials has recently been challenged, with short-duration therapy shown to be as effective as long-duration therapy in several scenarios in human[30,31] and veterinary[32,33] medicine. This is likely to be applicable in equine general practice. For example, routine clean surgeries can probably be performed without prophylactic antimicrobials or, if these are deemed necessary, a single preoperative injection should be adequate.[34–36] Similarly, uncomplicated wounds affecting the distal limbs can typically be managed without systemic antimicrobial therapy. However, if treatment is deemed necessary, 2–3 days of therapy is likely to be as effective as 5–7 days. The recommended courses of therapy for many other syndromes have also been truncated and practitioners should consult with antimicrobial use guidelines to keep abreast of changes (www.fvas.unimelb.edu.au/vetantibiotics, AVA prescribing guidelines also being developed).

Gentamicin

Gentamicin is a bactericidal aminoglycoside antimicrobial with activity against most gram-negative aerobic bacteria, some gram-positive bacteria and mycoplasmas.[37] This includes many *Pseudomonas aeruginosa* and *Staphylococcus aureus* isolates. Gentamicin has no activity against anaerobic bacteria or against facultative aerobic bacteria[37] and limited activity against intracellular pathogens.[38] Gentamicin is a concentration-dependent antimicrobial, so the peak plasma concentration (C_{max}), rather than the time the plasma concentration is over the MIC (Figure 1), is the key determinant of effective antibacterial activity. In fact, a prolonged period of higher plasma concentration is associated with the toxicity of many aminoglycosides, including gentamicin. Gentamicin is most effective when the ratio of C_{max} to MIC is 8–12 : 1.[39] Studies investigating the pharmacokinetics and pharmacodynamics of gentamicin in horses have recommended doses of 6.6 mg/kg every 24 h,[40,41] although a recent study suggests 7.7 mg/kg every 24 h may be more appropriate in adults.[39] Many authors advocate higher doses for foals (8–14 mg/kg[42–45]). An inter-dosing interval of 36 h is generally recommended when higher doses are administered to foals (12–14 mg/kg[42,43]). Most susceptible pathogens, and those of intermediate susceptibility, have a MIC < 4 µg/mL, so the C_{max} should reach 32–48 µg/mL.[39] There is no consensus on the minimum effective concentration, but the medical and veterinary literature suggests a range of < 0.5–2 µg/mL.[39,46] Peak and trough concentrations of gentamicin can be measured, but cost and the time taken to obtain these results limit this to referral hospitals that have in-house laboratories. Nephrotoxicity is the most common side-effect of gentamicin use in horses and is associated with increased dosing frequency, dehydration or other causes of reduced renal perfusion.[37]

Of the reviewed papers, 72 contained dosing regimens for gentamicin (Supplementary Table 2). The most frequently reported dose was 6.6 mg/kg (67/72). Two papers used dose rates of 4–4.4 mg/kg [47,48] (Switzerland and USA) and three papers used dose rates of 7.7–9.7 mg/kg[39,49,50] (Switzerland and USA). All papers reported a dosing frequency of 24 h.

The dosing regimen of 6.6 mg/kg every 24 h for adult horses is therefore widely reported and used. A 6.6 mg/kg dose is widely used by Australian equine veterinarians.[28] However, the dosing regimen for neonatal foals (< 14 days of age) should be increased to 8.8 mg/kg. An increased dose is needed in neonatal foals to account for increased body water content, allowing the post-antimicrobial effect to be maintained in the inter-dosing interval (Figure 1). The recommended volumes of gentamicin for the formulations found in Australia (with a concentration of 100 mg/mL) for a range of horse weights are presented in Table 2. Practitioners should be aware that these doses of gentamicin are off-label in Australia and products often carry a 'do not use' clause that restricts use to cases for which results from culture and susceptibility testing are available. Increasing concerns about antimicrobial use in veterinary medicine may result in more scrutiny and veterinarians should be aware of their legal responsibilities. In the absence of therapeutic drug monitoring, an inter-dosing interval of 24 h is recommended for both adults and neonatal foals. Gentamicin can be administered either intramuscularly or intravenously, although intramuscular administration results in a significantly lower peak concentration.[40]

Trimethoprim-sulfonamide combinations

TMS combinations have a generally broad and bactericidal action against many gram-positive and gram-negative bacteria. They are inactivated by necrotic tissue, so are not effective in closed, non-draining infections where there is significant tissue debris (e.g. abscesses).[51] Susceptibility is often good among *S. aureus*, *Dermatophilus congolensis*, *E. coli* and *Salmonella* spp., but *P. aeruginosa* is intrinsically resistant.[52] TMS has poor ability to clear streptococcal infections because of the tissue debris present in lesions, so therapy with PPG is preferable.[53] Drainage of abscesses is desirable (regardless of the aetiology) to reduce the bacterial load, as penetration of antimicrobials is generally suboptimal and prolonged therapy is required for clinical cure. Penetration is good and TMS remains an excellent choice for infections within the central nervous system,[54]

urinary tract and uterus/placenta. TMS combinations are time-dependent antimicrobials and twice daily dosing is required to maintain serum and tissue concentrations above the MIC for most equine pathogens.[55] Studies investigating the pharmacokinetics and pharmacodynamics of TMS in horses have recommended a dose of 30 mg/kg.[55] TMS combinations are popular with equine veterinarians because oral formulations registered for use in horses are available and these are relatively safe. TMS can also be administered intravenously but should not be administered intramuscularly, because of local inflammatory responses.

Of the reviewed papers, 25 contained dosing regimens for TMS (Supplementary Table 3). The most frequently reported dose was 30 mg/kg (16/25), but 9 papers used dose rates of 20–25 mg/kg. All reported a dosing frequency of 12 h.

The dosing regimen of 30 mg/kg every 12 h is widely accepted and consistent with the above findings. The majority of Australian equine veterinarians are using a much lower dose, with a dose of 15 mg/kg reported by more than half of respondents to a recent survey.[6] According to the Australian Pesticides and Veterinary Medicines Authority, the labelled dose of many TMS products in Australia suggests a dose regimen of 15 mg/kg (Sulprim oral powder, Airway TMPS, Trimidine powder, Tribactral S), although three registered products recommend 30 mg/kg (Bromo Tmps, Bromotrimidine powder, Illium Sulprim oral antibiotic paste for horses).

The dose of TMS combination products can be calculated by combining the concentration of active trimethoprim and sulfonamide together. The concentration of common registered products, and the volume needed for appropriate dosing, is presented in Table 3.

Summary

Many antimicrobials used commonly in equine practice have labels that were licensed many years ago and there is now a disparity between the labelled (registered) dose and current recommendations based on advances in knowledge of drug pharmacokinetics, pharmacodynamics and target plasma antimicrobial concentrations. Veterinarians treating equine patients in Australia should be aware of the current recommended dose rates and inter-dosing intervals to ensure efficacy in therapy and to preserve the usefulness of these antimicrobials for the future. Procaine penicillin G should be administered at 22,000 IU/kg every 12 h. Gentamicin should be administered at 6.6 mg/kg every 24 h in adults and 8.8 mg/kg every 24 h in neonates. Therapeutic drug monitoring for gentamicin should be considered, where possible, to aid in decisions on both dose and inter-dosing interval. Trimethoprim-sulfonamide should be administered at 30 mg/kg every 12 h.

Conflicts of interest and sources of funding

The authors declare no conflicts of interest for the work presented here.

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Supporting information

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Figure 1. Principal pharmacokinetic–pharmacodynamic (PK-PD) characteristics of antimicrobial drugs. For time-dependent antimicrobials the time that the concentration of a drug remains above the minimum inhibitory concentration (MIC) (T > MIC) is the PK-PD index correlated with efficacy. The post-antibiotic effect can be absent (macrolides), minimal (beta-lactams, including penicillins) or moderate (glycopeptides, linezolid). For concentration-dependent antimicrobials (aminoglycosides, fluoroquinolones) the C_{max}/MIC ratio and/or the area under the concentration–time curve at 24 h/MIC ($AUC_{0–24}$/MIC) ratio are the best correlates with efficacy. There is a prolonged post-antibiotic effect with the concentration-dependent antimicrobials.

Table 1. Recommended doses of procaine penicillin G (PPG) for horses in Australia using the most common formulation (300 mg/mL) and the appropriate dose rate of 22,000 IU/kg (22 mg/kg) every 12 h

Horse size (kg)	**PPG dose (mL)**
Small neonatal foal (40)	3
Average neonatal foal (50)	4
Average 1-month-old thoroughbred (TB) foal (80)	6
Weanling TB (150)	11
Yearling TB (300)	22
Adult TB (450–550)	33–40

PPG should be administered IM.

Table 2. Recommended doses of gentamicin for horses in Australia using the most common formulation (100 mg/mL) and the appropriate dose rates of 6.6 mg/kg for adults and 8.8 mg/kg for foals every 24 h

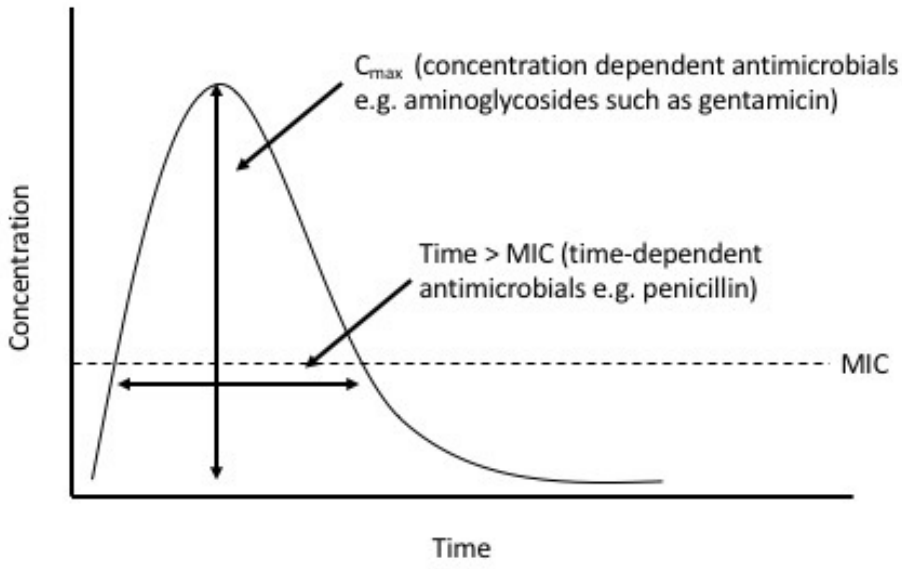
Horse size (kg)	**Gentamicin dose (mL)**
Small neonatal foal (40)	3.5
Average neonatal foal (50)	4.5
Average 1-month-old thoroughbred (TB) foal (80)	5.5
Weanling TB (150)	10
Yearling TB (300)	20
Adult TB (450–550)	30–36

Gentamicin should be given IV or IM.

Table 3. Recommended dosages of trimethoprim-sulfonamide for horses in Australia using the common registered formulations and the appropriate dose rate of 30 mg/kg every 12 h

Registered product	Concentration of combined active ingredients (mg/g)	Weight of 1 scoop (g)	Dosage	Route
Bromo TMPS	516	12	1 scoop/200 kg	PO
Bromotrimidine paste	540	NA	20 mL/450 kg	PO
Bromotrimidine powder	516	6	2 scoops/200 kg	PO
Sulprim oral antibiotic paste for horses	378	NA	16 mL/200 kg	PO
Sulprim oral powder	516	6[a]	2 scoops/200 kg	PO
Airway TMPS oral powder	402	9	2 scoops/250 kg	PO
Trimidine powder	516	6*	2 scoops/200 kg	PO
Tribactril S injection	240	NA	25 mL/200 kg	IV

[a]Weight of 1 large scoop. NA, not applicable.



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