What dosing regime is required for intravenous benzylpenicillin sodium in the horse?

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Introduction

Conflicting advice exists on the interval that should be observed between intravenous doses of benzylpenicillin sodium in horses. Guidance provided by the British Equine Veterinary Association is that the dosing interval should be 6 – 8 hours. The Summary of Product Characteristics for the only product authorized for use in horses in the United Kingdom and certain European Union countries recommends that it should be given twice a day.

Pharmacodynamics

Penicillins are time-dependent bactericidal antibiotics. They kill bacteria at a rate which depends mainly upon the duration of exposure of the bacteria to the antibiotic.

At the end of a period of exposure to an antibiotic at a concentration above the minimum inhibitory concentration (MIC), the rate of replication of bacteria is reduced for a period, particularly in Gram-positive species; this phenomenon is known as the post-antibiotic effect. The dose then needs to be repeated to provide a concentration again above the MIC before the reduced bacterial population returns to substantial growth.

Craig (1996) showed that the survival rate in animal models of infection with *Streptococcus pneumoniae* was 100% when treatment with penicillin maintained a concentration in greater than the MIC for the organism for at least 40% of the time. The same study showed that, when a cephalosporin was used, the concentration needed to remain above the MIC for at least 50% of the time for a survival rate of 100%. This may explain why some authors state that the concentration of penicillin should be above the target for 40% of the dosing interval, whilst others state that it should be so for 50% of the dosing interval.

Olsén *et al.* (2013) state that the breakpoint for clinical efficacy for benzylpenicillin is a free-drug concentration exceeding the MIC for 50-80% of the dosing interval, giving Toutain *et al.* (2002) as the reference. What Toutain *et al.* actually wrote was " … it can be recommended that T > MIC should be at least 50% and preferably ≥ 80% of the dosage interval to achieve an optimal bactericidal effect." The optimal bactericidal effect is, obviously, a different concept from an effective dosing regime. However, it may be the one to follow in serious acute conditions. For example, in man, Sandoe *et al.* (2013), found that 4-hourly injections of benzylpenicillin to patients with streptococcal infective endocarditis achieved a higher cure rate than 6-hourly injections, even though a standard guide to antimicrobial therapy recommends a 8- or 12-hour dosing interval.

Minimum inhibitory concentrations

Benzylpenicillin is most commonly used in horses to treat or prevent infections caused by *Streptococcus equi* subsp. *zooepidemicus* (*Str. zooepidemicus*), and *Streptococcus equi* subsp. *equi* (*Str. equi*). When it is used for pre-operative antibiosis, it may be intended that the spectrum of activity should extend to include *Str. dysgalactiae* subsp. *dysgalactiae* and sensitive strains of *Staphylococcus aureus.*

Published data on the actual MIC of benzylpenicillin for isolates of these organisms collected from horses are few. The most recent data are as follows.

For *Str. zooepidemicus*

- 0.012 µg/ml. The organism was isolated from a clinical case of endometritis in the Netherlands (Ensink, 2003).

For *Str. zooepidemicus* and *Str. equi*

- ≤ 0.015 µg/ml. The organisms were isolated from respiratory and genital infections in Germany (Schwarz, 2007).
- ≤ 0.06 µg/ml. This was the lowest concentration tested. There were 264 isolates of *Str. zooepidemicus* and 36 isolates of *Str. equi,* collected in the United States between 2012 and 2016 (Younkin *et al.*, 2019).

For *Str. dysgalactiae* subsp. *dysgalactiae* no data have been found.

For *S. aureus*

- 0.032 – 0.125 µg/ml for sensitive strains (EUCAST, 2011, cited by Olsen, 2013).
- ≤ 0.06 µg/ml; MIC_{50} for 36 isolates collected in the United States between 2012 and 2016 (Younkin *et al.*, 2019). It seems likely that that, as for the MICs for streptococci reported in the same paper, this was the lowest concentration tested, but the authors do not make this clear.

Binding to plasma proteins

Only free benzylpenicillin has an effect on bacteria. A proportion of it is bound to plasma proteins, and this must be taken into account when determining the target concentration to be achieved in plasma to provide the free drug at or above its MIC for a given pathogen.

Olsén *et al.* (2013) found that 62.8% of the dose of benzylpenicillin is bound to plasma proteins in the horse. Durr (1976) had found it to be a lower percentage, 52 – 54%. But previously Keen (1965) had found a figure of 62.1%, lending credibility to Olsén's figure. That implies that a total benzylpenicillin concentration 2.69 times the MIC will provide free benzylpenicillin at the MIC.

Pharmacokinetics

Love *et al.* (1983) investigated the concentration of penicillin in the serum of horses following injection of various salts at various doses. For intravenous injection of

benzylpenicillin sodium they used doses of 10,000, 20,000, and 40,000 i.u. per kg. These doses are equivalent respectively to 6, 12, and 24 mg per kg. Pharmacokinetic data stated herein are taken from this paper of Love *et al.*, read from the graphs in the paper.

Calculation of dosing intervals

In cases other than serious acute conditions, the target is to maintain a concentration of free benzylpenicillin in plasma above the MIC for at least 40% of the dosing interval. In serious acute conditions, maintaining this concentration for at least 80% of the dosing interval, for the optimum bactericidal effect with continuous reduction in the size of the bacterial population, seems preferable.

The concentration of benzylpenicillin required in the plasma to achieve a free-benzylpenicillin concentration equal to the MIC for the organism in question can be calculated by multiplying the total benzylpenicillin concentration by a factor of 2.69, to take account of the binding of 62.8% of the dose to plasma proteins.

Using the pharmacokinetic data of Love *et al.* (1983), the following calculations may be made for a horse of 500 kg given a dose of 6.36 g, equivalent to 12.72 mg/kg or 21,200 i.u./kg.

Infection caused by *Str. zooepidemicus* or *Str. equi*

- MIC of benzylpenicillin ≤ 0.015 µg/ml
- Required minimum concentration (2.69 x MIC) ≤ 0.040 µg/ml
- Time taken to fall to required minimum = 6 hours
- Concentration to be above MIC for 40% of the dosing interval
- Dosing interval = 6/0.4 = 15 hours

Infection caused by *S. aureus*

- MIC of benzylpenicillin ≤ 0.125 µg/ml
- Required minimum concentration (2.69 x MIC) ≤ 0.336 µg/ml
- Time taken to fall to required minimum 2.5 hours
- Concentration to be above MIC for 40% of the dosing interval
- Dosing interval = 2.5/0.4 = 6.25 hours

Serious acute infection caused by *Str. zooepidemicus* or *Str. equi*

- MIC of benzylpenicillin ≤ 0.015 µg/ml
- Required minimum concentration (2.69 x MIC) ≤ 0.040 µg/ml
- Time taken to fall to required minimum = 6 hours
- Concentration to be above MIC for 80% of the dosing interval
- Dosing interval = 6/0.8 = 7.5 hours

Serious acute infection caused by *S. aureus*

Requires continuous intravenous infusion.

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Revised on 13th June 2024

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