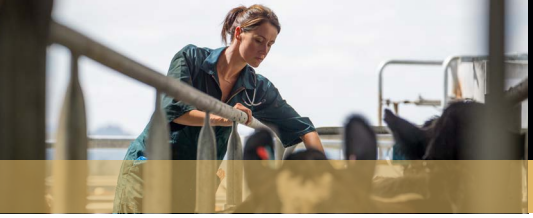

PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

Pharmacokinetics can be described as the body's effect on a drug (e.g. absorption, metabolism and excretion, including the speed and efficacy of these processes).

In contrast, pharmacodynamics can be thought of as the drug's effect on the body (and mechanism of action in the target species).

When choosing antibiotics consideration should be given to the drug's pharmacokinetics and pharmacodynamics. As well as considering the correct dose, how and when the antibiotic is administered will be an important determinant to its efficacy.

When considering dosing pattern it is important to remember the differences between concentration-dependent and time-dependent antibiotics.

Concentration-dependent antibiotics

- The most important parameter is C_{max} > MIC (maximum concentration above MIC)
- If the concentration is increased, the rate and extent of bacterial mortality is also increased
- Increasing drug concentrations will result in greater bacteriocidal activity compared to giving the same total daily dose, administered over several doses
- Concentration dependent antibiotics commonly exhibit a prolonged post-antibiotic effect
- Pulse medication works very effectively for this group, rather than administering multiple dosages over a 24 hour period
- Examples of concentration-dependent antibiotics are aminoglycosides and polymyxins

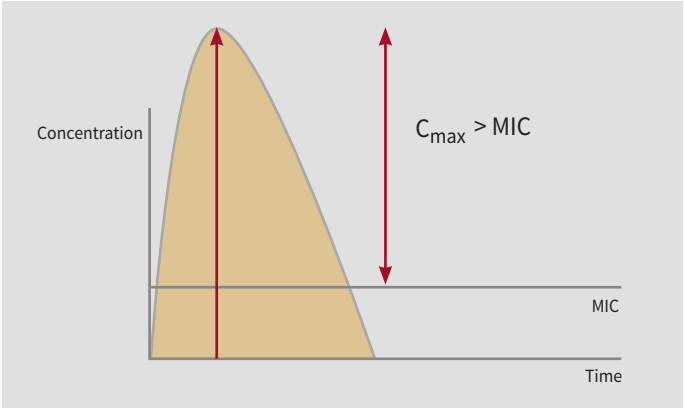

Figure 1: Optimal profile of antibiotic concentration in the blood over time for a concentration-dependent antibiotic

Time-dependent antibiotics

- The most important parameter is T > MIC (time above MIC)
- The goal is to maintain serum concentrations above the MIC as long as possible during dosing intervals
- Kill bacteria effectively once a threshold concentration is reached
- Have a very short, or no post-antibiotic effect
- Time-dependent antibiotics are typically administered in several dosages to maintain time above the MIC for as long as possible
- There are no benefits in increased dosing to reach tissue concentration several times above the MIC
- Macrolides (such as tylosin and tilmicosin), pleuromutilins, florfenicol, lincosamides, ß-lactams and sulfonamides are examples of time-dependent antibiotics
- Advice: Keep the plasma and tissue concentrations above the MIC as long as possible, which often means repeat dosing

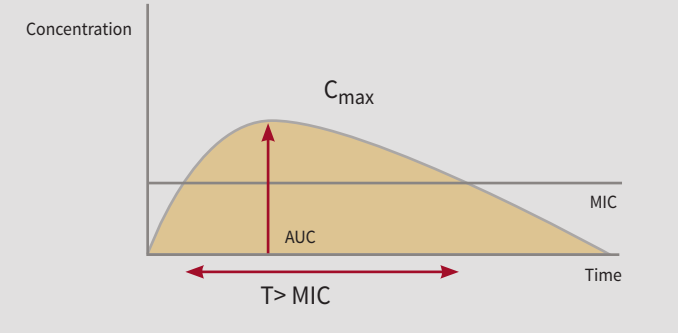

Figure 2: Optimal profile of antibiotic concentration in the blood over time for a time-dependent antibiotic

Definitions

- MIC is the lowest concentration of antibiotic that completely inhibits the growth of a microorganism in vitro
- The area under the curve (AUC) is a pharmacokinetic parameter which is a measure of both the extent of the drug absorbed and its persistence in the body
- The C_{max} (maximum concentration) is the highest concentration of drug in the blood that is measured after a dose
- T > MIC is defined as the percentage of time over a 24 h period that the drug concentration exceeds the MIC

Tylosin Pharmacokinetics

Tylosin is lipid soluble and a weak base. Milk has a high fat content and a pH of 6.7. This means that tylosin easily moves from the capillaries across the lipophilic environment of the milk ducts (where the bacteria causing mastitis are located). In this acidic environment the tylosin becomes ionised (carries a charge). This ionisation traps tylosin within the milk, such that tylosin concentrations in milk can be up to 20 times plasma concentration (Gringerich, et al).

As a weak base, tylosin also becomes "ion-trapped" within macrophage cells. The inside of macrophage cells are acidic so tylosin within these cells becomes charged, and is then trapped within the cells. This means that tylosin is in high concentrations at the site of the highest concentration of bacteria in mastitis, within the macrophages. These white blood cells are key players in the immune response to foreign invaders of the body, such as infectious micro-organisms. Hence, macrophage cells containing a high concentration of tylosin are found in high numbers at the site of infection.

Tylosin tartrate is water soluble so tends to be absorbed from the site of injection, metabolised and excreted from the body more rapidly than tylosin base. Generally injections containing tylosin tartrate require repeat treatments within a 24 hour period to ensure this time-dependent antibiotic remains at sufficient blood levels above MIC for the appropriate period of time to ensure efficacy. Consequently tylosin tartrate is typically used for in-water medication of pigs and poultry as this allows continuous administration to achieve optimal levels over the required time period.

The degree of lipid solubility of injectable mastitis treatments is important in the ability of an active ingredient to cross the blood-milk barrier. Lipophilic drugs such as tylosin base cross easily, whereas water soluble drugs do not move so freely.

Tylosin pharmacodynamics

Tylosin is a macrolide antibiotic that is active against most aerobic and anaerobic gram-positive bacteria. The action of tylosin is via inhibition of protein synthesis by binding the 50S ribosome subunit of the bacterial cell wall. Tylosin is bacteriostatic but becomes bacteriocidal over treatment time, especially against Streptococcus spp (i.e. the bacteriocidal action of tylosin is time-dependent).

Tylosin has a wide spectrum of antibiotic activity, and is effective against gram positive bacteria including Staphylococci, Streptococci, Corynebacteria and *Erysipelothrix rhusiopathiae*. It is effective against some gram negative bacteria, such as *Campylobacter coli* and some spirochaetes. Tylosin is extremely effective against Mycoplasma species isolated from both avian and mammalian hosts.

New Zealand trial work demonstrated bacteriological cure rates of 83.8% for tylosin base injection when used in early season clinical mastitis cases in dairy cattle (McDougall et al, 2007). This cure rate is similar to that reported for other mastitis treatment regimes, so tylosin is an antibiotic of choice for the treatment of mastitis in NZ.

Multi-quarter mastitis infections

In New Zealand dairy cows, it is common for more than one quarter to be infected when a cow has mastitis. McDougall (1998) reported in one NZ study that in cows identified by farmers as having a quarter with clinical mastitis, over 85% of these cows had one or more additional quarters infected (clinical or subclinical), and 23.2% of these cows had at least one additional quarter with clinical mastitis. Using tylosin injection to treat mastitis means all quarters of the udder will be targeted.

Summary

TyloVet injection is ideally suited to treat mastitis in dairy cows.

- The pharmacokinetics of tylosin mean that it is concentrated at the site of infection (in the milk of the cow)
- Tylosin is active against the spectrum of organisms which are the most common bacteria causing mastitis in NZ dairy cows
- Tylosin base is the most suitable form of tylosin to use in injectable mastitis products due to lipophilicity and duration of effect
- It is extremely common for more than one quarter to be infected when a cow has clinical mastitis hence tylosin is an appropriate veterinary medicine to recommend for the treatment of mastitis in NZ dairy cows.

TyloVet injection is manufactured in Europe with high potency, containing quality tylosin base. TyloVet is suitable for up to five x 24 hourly treatment of streptococcal and staphylococcal mastitis infections in NZ dairy cows.

Restricted Veterinary Medicine, ACVM Registration Number: A10807. Only available only under veterinary authorisation.

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