Optimal use of drugs informed by pharmacokinetics, pharmacodynamics and the situation

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My contention is that a drug will be used more effectively, perhaps optimally, when the veterinarian (and the farmer) has some understanding of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of that drug, and the PK-PD relationship.

In an ideal world, the veterinarian would have available all the information and resources necessary to make rational decisions on the choice (or not) of drug and how best to use that drug. In reality, all information will not be available; and what is rational scientifically may not be rational economically. Thus, rationality is limited or bounded and decisions may have to be made which are satisfactory rather than optimal. This has been called *satisficing* (satisfy + suffice). The aim of this presentation is, by way of example, to demonstrate how knowledge of PK-PD can inform thinking on the scientifically rational use of drugs and help in deciding what factors can be neglected in satisficing.

The example I will use is the parenteral use of an antibiotic for treatment of clinical mastitis in a dairy cow. I had planned to use tylosin since the information I needed for my case is available in literature; however, tylosin is classified by WHO as a *Critically Important Antibiotic* and as a *Red* antibiotic by the NZVA *Traffic Light* system (NZVA 2024). Thus, I have chosen penethamate, classified as *Highly Important* by MPI (2019) and as *Green* by NZVA. This means that PNT should be used prudently:

- against susceptible bacterial infections,
- at an appropriate dose,
- treatment interval, and
- for an appropriate duration of treatment.

Product information should advise on the duration of treatment and when to cease therapy in favour of additional diagnostic testing and/or a different antibiotic. Supporting my choice of penethamate is a field study that showed that intramuscular tylosin and penethamate were equally efficacious in treating cows with clinical mastitis (McDougall *et al.* 2007); however, there is a complication which I will leave until the end.

An understanding of PK-PD should support dosing decisions.

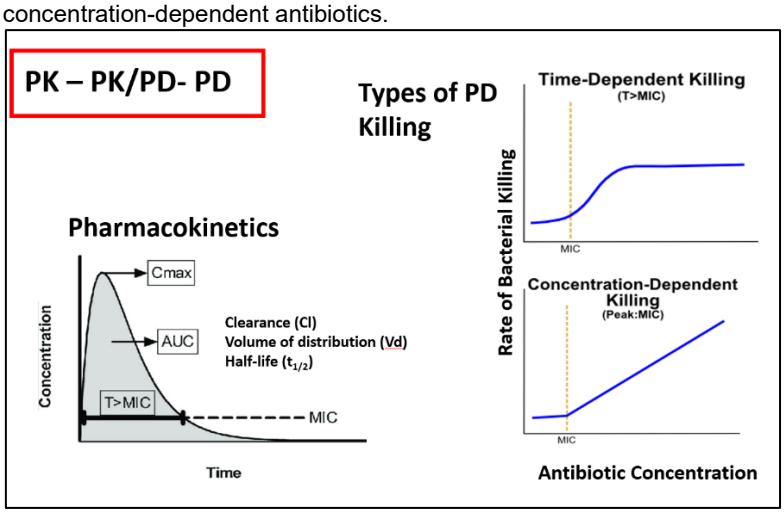
- Pharmacodynamics (PD) is the relationship between drug concentration at the effect site and the observed effect (i.e. antimicrobial response).
- Pharmacokinetic-Pharmacodynamics (PKPD): is the time dependent relationship between drug concentration in plasma/blood and that at the effect site.
- Pharmacokinetics (PK): is the time-relationship between drug dose and drug concentration in plasma/blood.

Pharmacodynamics: In terms of PD, antibiotics have been classified as *time-dependent* antibiotics (e.g. penethamate) and *concentration-dependent* (e.g. fluoroquinolones). The relevant PD killing curves are shown on the rights side of the Figure 1. These curves show the *Rate of Bacterial Killing*, the effect, versus the *Antibiotic concentration* (x-axis) at the effect

site, that is the site of infection. The site could be the milk, mammary parenchyma or within the cells of the alveolae (intracellular). We will assume the causative bacteria is *Streptococcus uberis* in the milk. For penethamate, a time dependent antibiotic, the predictor of successful treatment is the time above the minimum inhibitory concentration (MIC). There are some nuances such as the effects of protein binding on the free antibiotic concentration and the pH at the effect site which could influence the PD response. We will neglect these – satisficing.

It is preferable to maximise the time the concentration at the effect site is above the MIC (T>MIC); however, the literature indicates that it is not essential to exceed the MIC continuously. For example, survival of mice infected with *Strep pneumoniae* treated with penicillins was 100% even when the free drug concentration at the effect site was >MIC for only 50% of the time (Craig 2014).

Figure 1. The relationships between pharmacokinetics and pharmacodynamics for time-dependent and concentration-dependent antibiotics.



Pharmacokinetics: a typical relationship between drug concentration in plasma (y-axis) and time (x-axis) for an IM injection is shown in Figure 1. The T>MIC is marked, but note this graph is showing the concentration in plasma, not the concentration at the effect site. The concentration of interest is the concentration at the effect site so what we need to know is the relationship between the concentration in plasma and the concentration in milk. That is the PK-PD relationship.

Pharmacokinetics-Pharmacodynamics: We assume the PK-PD relationship is fairly straightforward for penethamate and because we are using multiple doses – but see later. Penethamate, a prodrug of benzylpenicillin, penetrates into milk easily and the milk concentration, which is in equilibrium with the plasma concentration, is about two-fold higher (based on AUC) than the plasma concentration (Friton *et al.* 2003).

What is now required is a value for the MIC. The Mastatest® for *Strep uberis* indicates an MIC in the range 0.1-0.5µg/ml (= 100-500ng/ml) (AgriHealth 2024) and this is supported by another New Zealand assessment which found 250 ng/ml (McDougall *et al.* 2014). To labour the point, when the concentration in milk is equal to the MIC, the concentration is plasma will be approximately ½ * 250 = 125ng/ml. From the Friton et al concentration profiles it appears that the milk concentrations are >MIC for 2-3 times longer than the plasma concentrations are >MIC (i.e. milk/plasma (M/P) ratio ≈ 2).

Important PK Parameters: The three important PK parameters are:

- Plasma Clearance(Cl) – it determines the maintenance dose rate.
- Volume of distribution (Vd) – used to estimate the loading dose if required.
- Elimination half-life ($t_{1/2}$) – used to estimate the dosing interval (τ) and the time to reach steady state concentration ($\approx 4 \times t_{1/2}$).

Using the data from (Friton *et al.* 2003), the estimates of these parameters are:

- Cl = Dose/AUC = 3.2L/h/kg (3200ml/h/kg) (note it is assumed 100% bioavailability)
- Vd = Cl x $t_{1/2}$ / 0.693 = 20L/kg (about the same if estimated from the extrapolated concentration at t=0).
- $t_{1/2}$ calculated from the terminal slope of the PK curve = 4.3h.

These parameter values and the M/P ratio can be used to estimate the appropriate **dose rate** to achieve the target milk concentration:

- **Dose rate = Dose/ τ = Cl x Cpss** (Cpss average concentration in plasma a steady state).
- **Cmilkss = M/P x Cpss**

Choice of dose interval (τ) is guided by the $t_{1/2}$ and also convenience of dosing. Given $t_{1/2} \approx$ 4h, a dosing interval of 12 (3 x $t_{1/2}$) to 24h (6 x $t_{1/2}$) is reasonable. Turning these equations around, the milk concentration for a dose of 10mg/kg (10×10^6ng) every τ=24h is:

$Cmilk_{ss}$ = M/P x Cp_{ss} = M/P x Dose/ τ ÷ Cl = 2 x 10×10^6 ÷ 24 ÷ 3200 = 260ng/ml which happens to be the MIC in this case.

These equations are easily used in an Excel spreadsheet and with a little extra effort, some other equations can be entered to calculate plasma and milk versus time profiles as shown in Figure 2. But with 24h dosing and 12h milking things get more complicated (Figure 2).

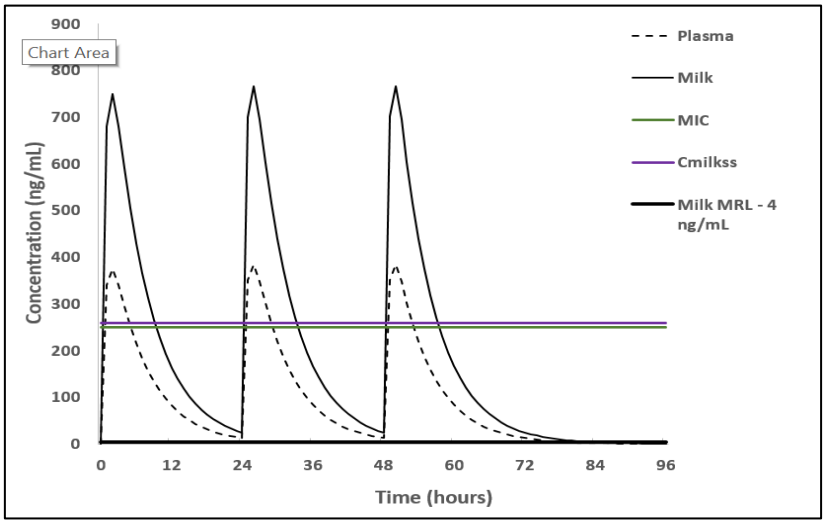
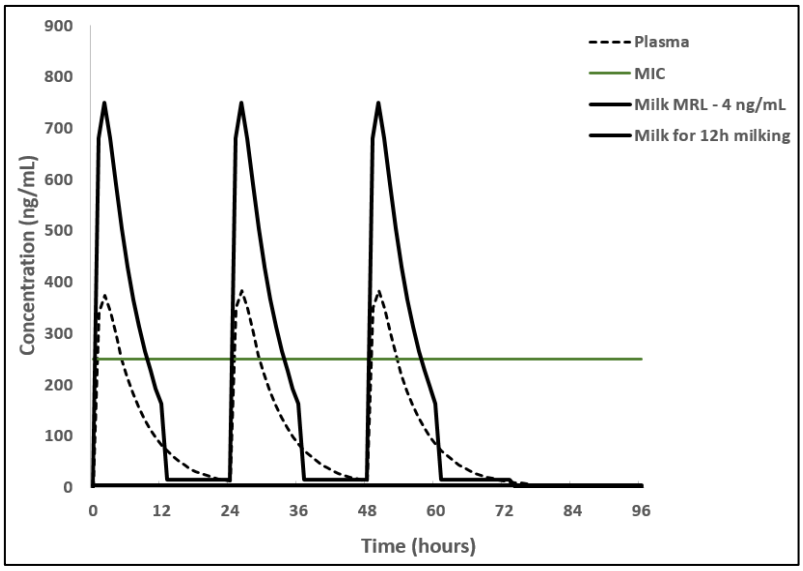


Figure 2. Profiles for milk and plasma concentrations for 3x10mg/kg IM doses of penethamate every 24h and with 24h (left) and 12h (right) milking.



References

AgriHealth. New trends from analysis of nz mastitis milk samples, *Technical Bulletin* MS10.3 Retrieved from: https://agrihealth.co.nz/uploads/ e4c645f8808b9e40362cf5d03f70ae30.pdf. Accessed May 11 2024

Craig WA. Introduction to pharmacodynamics. F*undamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics.* AA Vinks, H Derendorf, JW Mouton (Eds). Springer; New York, pp3-22, 2014

Friton GM, van Hattum JCC, Horstermann D. Pharmacokinetics in plasma and milk of benzylpenicillin following repeated intramuscular administration of Mamyzin (penethamate hydriodide) in lactating cows. *Journal of Veterinary Pharmacology* and Therapeutics. 26 (A-23): 100-101, 2003

McDougall S, Agnew KE, Cursons R, Hou XX, Compton CRW. Parenteral treatment of clinical mastitis with tylosin base or penethamate hydriodide in dairy cattle. *Journal of Dairy Science.* 90(2): 779-789, 2007

McDougall S, Hussein H, Petrovski K. Antimicrobial resistance in Staphylococcus aureus, Streptococcus uberis and Streptococcus dysgalactiae from dairy cows with mastitis. *NZVJ.* 62(2): 68-76, 2014

MPI. *Antimicrobial Resistance Reassessment Review: Macrolides, Later-Generation Cephalosporins, and Penicillins.* New Zealand Food Safety, Ministry for Primary Industries; New Zealand, 2019

NZVA. Antimicrobial Resistance (AMR. Retrieved from: https://nzva.org.nz/clinical-resources/general/amr/. Accessed 10 May 2004