# Factors influencing antimicrobial treatment outcome

***by Wouter Depondt, global product manager veterinary products, Huvepharma.***

As pig practitioners, we constantly aim to improve and safeguard the health status of our farms through good management and biosecurity. Despite these preventive measures, curative intervention with antimicrobials is still required.

The educational background and professional experience of the veterinarian allows them to choose the right antimicrobial for the diagnosed causative pathogen. Along with the choice of treatment, a correct application is of major importance to ensure efficacy. Prudent use of antimicrobials does not only mean reducing their use, but also choosing the right product and administering it in an appropriate manner.

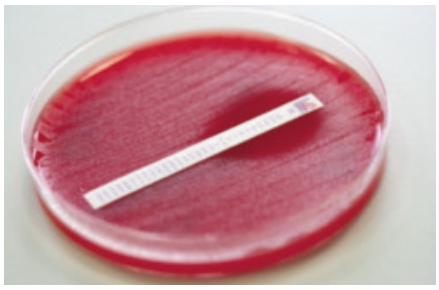
## Making the right choice

The choice of the right antimicrobial depends on the known or suspected sensitivity of the infectious agent. The suspected sensitivity can be based upon the experience of the veterinarian, farm history and surveys of the antimicrobial sensitivity against pathogens in certain areas.

This might help to start-up an empiric treatment before laboratory microbiological reports are available, because often treatment should not be delayed due to the seriousness of the disease and welfare implications.

Often, antimicrobial susceptibility testing is carried out to determine to which antibiotic the suspected causative pathogen is sensitive.

***MIC value can easily be determined with Huvepharma's MIC test-strips.***



Testing for antibiotic sensitivity is often done by the Kirby-Bauer method, or a so-called antibiogram. With this method, small discs containing antibiotics are placed onto a plate upon which bacteria are growing. If the bacteria are sensitive to the antibiotic, a clear ring, or zone of inhibition, is seen around the disc indicating poor growth of the pathogen.

Other methods to test antimicrobial susceptibility include, for example, MIC test strips, agar and broth dilution methods for Minimum Inhibitory Concentration (MIC) determination.

Crucial, but difficult for all susceptibility testing is the isolation (sampling and culturing) of the relevant bacteria. This difficulty, and the lack of clinical breakpoints in animal health explain why susceptibility testing can only give an indication of what the clinical outcome will be.

As well as the susceptibility of the pathogen, the antimicrobial should also reach the site of infection. This is determined by the pharmacokinetic characteristics of the product.

Tilmovet, for example, is lipophilic and consequently easily passes cell membranes and other lipid barriers throughout the body. Once a barrier is passed and Tilmovet enters an environment with a lower pH than its pKa value (7.4), Tilmovet is ionised.

Ionised molecules cannot pass lipid barriers anymore and consequently, the molecule is trapped. This phenomenom is called ion-trapping and explains the high concentrations and accumulation of Tilmovet in phagocytes (acidic lysosomes) and in tissue compartments with a low pH such as the lung.

Other antimicrobials, such as paromomycin (Parofor, an aminoglycoside recently registered by Huvepharma) are hydrophilic, meaning they dissolve well in water. They cannot pass lipid barriers and consequently their uptake by the intestine is very limited.

*Continued on page 11*

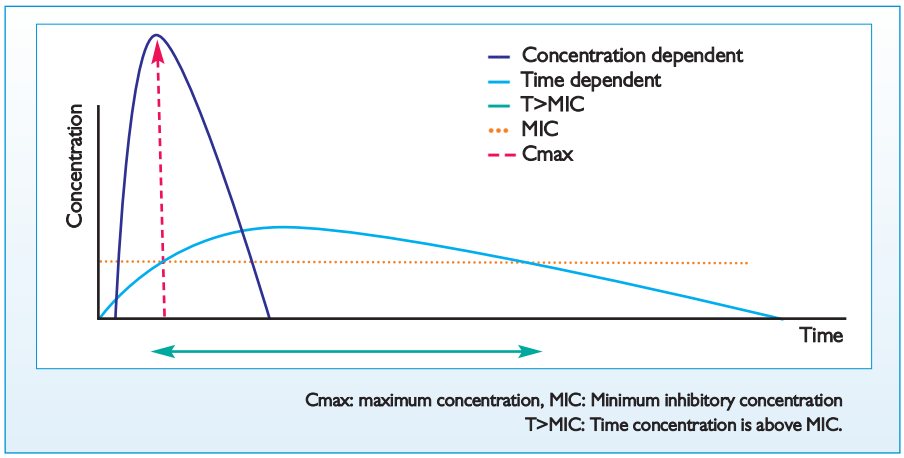
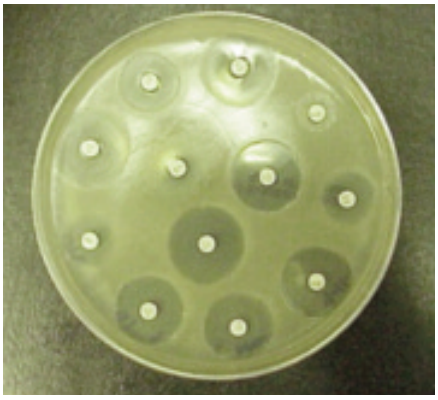



***Fig. 1. Two types of antibiotics with an ideal Pk profile in regards to efficacy.***

***Antibiogram: agar plate with antibiotic discs. Bacteria are not able to grow around antibiotics to which they are sensitive.***



| | Tilmicosin concentrations | | |
|---|---|---|---|
| | Plasma (µg/mL) | Lung (µg/g) | Lung/plasma ratio |
| Day 5 | 0.077 | 2.302 | 30 |

***Table. 1. Concentration of tilmicosin in lung and plasma after five days of treatment with Tilmovet at 16mg/kg bodyweight (Karanikolova et al., 2014).***

| | MIC Tiamulin | MIC Tiamulin + 4 µg/ml Apramycin |
|---|---|---|
| No. of strains tested | 30 | 30 |
| MIC50 | >16 | 0.06 |
| MIC < 1 (No.) | 6 | 15 |
| MIC < 1 (%) | 20 | 50 |

***Table. 2. Susceptibility of Brachyspirae hyodysenteriae against a combination of Vetmulin (tiamulin) and Apravet (apramycin) (Vyt et al., 2014).***

| Classification | Antibiotics | Goal of therapy | PK/PD Parameter |
|---|---|---|---|
| Concentration dependent | Apramycin (Apravet), Paromomycin (Parofor), Polymyxines | Maximise concentrations | C max/MIC |
| Time dependent | Tylosin (Pharmasin), Tilmicosin (Tilmovet), Tiamulin (Vetmulin), Penicillins, Cephalosporins | Maximise duration of exposure | T>MIC |
| Mixed properties | Doxycycline (Doxx-sol), Quinolones, Florfenicol (Amphen) | Maximise amount of drug | 24h-AUC/ MIC |

***Table. 3. Classification of antibiotics based upon their ideal dosing regimen.***

*Continued from page 9*

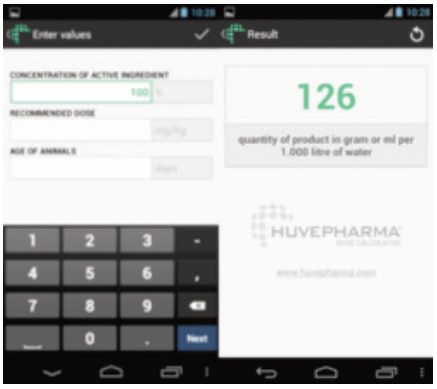
Most hydrophilic antimicrobials are therefore unsuitable for systemic treatment via oral administration. However after single oral administration of 50mg paromomycin per kg bodyweight, concentrations of >5000µg/g were found in the intestinal lumen (internal data). The fact that Parofor intensively concentrates in the intestinal lumen, makes it a good option for the treatment of enteritis caused pathogens sensitive to paromomycin.

Sometimes, the use of more than one antibiotic may be justified, based upon a synergistic effect in vitro. The combination of Vetmulin and Apravet might be justified to treat and eradicate Brachyspira hyodysenteriae. Adding 4µg/ml apramycin (Apravet) to tiamulin (Vetmulin) increased the number of susceptible strains in vitro. The synergistic effect of Apravet and Vetmulin has also been observed in the field.

After choosing the antimicrobial, correct administration is also of importance. Dosing should be done in grams per kilogram live body weight, independently of the application form.

By doing so, underdosing will be avoided by taking account of changing ratio bodyweight/water intake. This can easily be done with Huvepharma's dose calculator,

***Huvepharma's dose calculator.***




***Precipitation: an example of a water soluble veterinary medicine unsuitable for use with a proportioner.***

freely available for iPhone, Android and Blackberry mobile devices. The dosage regimen is also of importance. The daily dose can be administered continuously or as a pulse. For concentration dependent antibiotics, such as aminoglycosides, a high concentration (Cmax) several times higher than the MIC of the targeted pathogen at the site of infection, will result in a faster and better effect. The most important parameter for these antimicrobials is the Cmax/MIC.

Consequently pulse medication will work better for these types of antimicrobials.

For time-dependent antimicrobials, such as the macrolides, the efficacy depends on the period during which the bacteria are exposed to the antimicrobial at a concentration just above the MIC (T>MIC).

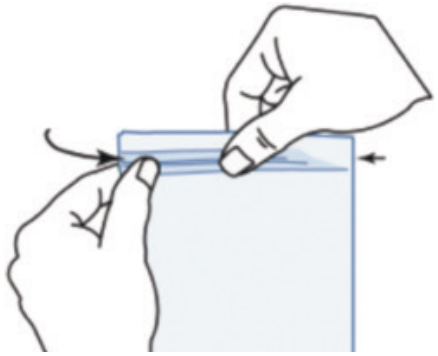
The most important parameter is the time period in which the concentration is higher than the MIC (T>MIC) at the site of infection. Better efficacy can be expected if these antimicrobials are provided continuously.

Other antibiotics, such as tetracylines, have mixed properties: they are time-dependent and concentration dependent. The ideal dosing regimen for these antibiotics maximises the amount of drug received.

Therefore, the 24 hour Area Under the Curve (AUC/MIC) ratio is the parameter that correlates with efficacy.

The formulation of the veterinary medicine can also influence the clinical outcome of an antimicrobial treatment. Stability, solubility and bioavailibility of the active can be optimised by the choice of excipients and the manufacturing method. For water-soluble veterinary medicines for example, there may be a loss of activity and precipitation of the active after dissolving in the drinking water. This will logically affect the effectiveness of the therapy.

Loss of activity can also occur during storage after opening the primary packaging, because of the contact with oxygen, temperature and moisture. Proper storage conditions and re-closable packaging will preserve the active for a longer time.



***Huvepharma zipper bags are resealable to preserve the product.***

Huvepharma keeps investing in new and better formulation techniques for optimal use and results. A good example is Pharmasin, a stable and highly water soluble tylosin with a high bioavailability.

In conclusion, we need a holistic approach to medicine use and by that we mean responsible promotion, responsible prescribing and responsible use of all medicines including antimicrobials.

The prescribers and users of veterinary medicines should operate to the principle of 'as little as possible but as much as necessary'. ■

✉ Wouter.depondt@huvepharma.com