Improving the outcome of antimicrobial treatment for respiratory disease

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.

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Along with the choice of treatment, correct application is of major importance to ensure efficacy.

Prudent use of antimicrobials not only means reducing their use, but also choosing the right product/brand (molecule and formulation) and administering it in an appropriate manner.

The most common and important respiratory causing bacterial pathogens are still Mycoplasma hyopneumoniae, Actinobacillus pleuropneumonia (APP), Pasteurella multocida, Bordetella, Haemophilus parasuis and Streptococcus suis. In most cases animals are affected by a combination of the above mentioned pathogens, and initiated by primary pathogens such as Mycoplasma hyopneumoniae, PRRSv, porcine circovirus (PCV) and swine influenza (SIV).

Often a control or treatment program is required to safeguard the respiratory health of the animals.

The clinical outcome of the treatment however depends on three crucial steps in the decision process of the veterinary surgeon:

- Selecting the correct antimicrobial, considering:
  - Known or suspected antimicrobial susceptibility of the pathogen(s).
  - Ability of the antimicrobial to sufficiently reach the site of infection.
- Correct dosing and administration.
- Product choice, with a bio-available/potent active and an appropriate formulation.

The susceptibility can be based upon testing, 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. Often treatment should not be delayed due to the seriousness of the disease and welfare implications.

Selecting the right antimicrobial

Alongside susceptibility of the targeted pathogen(s), we also want sufficient concentration of the active product in the affected tissues. For example tilmicosin, the active molecule in Tilmovet, is highly concentrated in the nose epithelium and upper respiratory mucosae, in the lung tissue and in the bronchial and tracheal epithelium. This makes this product a good option for the treatment of respiratory disease.

Moreover, tilmicosin is also highly concentrated in the macrophages, an (immune) cell that is strongly present at the site of infection.

Other antibiotics have a rather low lung plasma ratio, meaning they are predominantly concentrated in the plasma (Table 1).

Correct administration

After choosing the antimicrobial based upon susceptibility and pharmacokinetic behaviour, 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, freely available for iPhone, Android and Blackberry mobile devices.

Screen shot of Huvepharma's dose calculator.

The dosage regimen is also of importance. The daily dose can be administered continuously or as a pulse. For concentration-dependent antibiotics, such as apramcyin, 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 tylosin (Pharmasin) and tiamulin (Vetmulin), the efficacy depends on the period during which the bacteria are exposed to the

Continued on page 9

Table 1. Lung concentration, lung/plasma ratio and macrophage concentration ratio of different antimicrobials used for respiratory pathogens. Oral application.

	Dose (mg/kg bw)	Lung level	Lung/Plasma ratio	Macrophage concentration ratio
Tilmicosin (Tilmovet)	20	1.69	43	184
Tiamulin (Vetmulin/Rodotium)	13.2	4.3	18.1	18.2
Lincomycin	5.5	0.66	4.1	-
Enrofloxacin	7.5	0.92	3.1	-
Tetracyline (CTC)	20	0.66	1.9	-
Doxycycline (Hydrodoxx)	13.3	1.7	1.44	-
Tylosin (Pharmasin/Tylovet)	10	0.93	1.79	21
Acetyl isovaleryl tylosin	5.5	0.14	2.29	-

Table 2. Target tissue and defence mechanisms affected by the main pathogens involved in respiratory disease.

Target tissue	Result	Pathogen
Trachea	Epithelial and cilia damage	Bordetella and Mycoplasma hyopneumoniae
Bronchi(oli)	Bronchitis and bronchiolitis	Bordetella, Mycoplasma hyopneumoniae, SIV, PCV
Parenchym	Pneumonia	Bordetella, Mycoplasma hyopneumoniae, APP, SIV, PCV
Alveolar macrophages	Alter immune response	PRRS, PCV
Nose mucosa	Epithelial and cilia damage	Bordetella and PRRSV

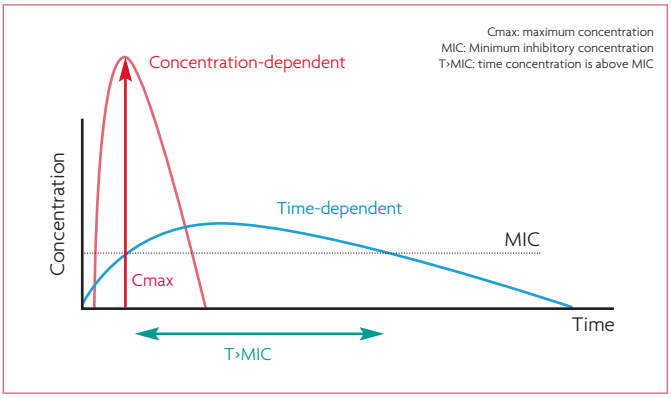

Fig. 1. Three types of antibiotics with an ideal Pk profile with regards to efficacy.

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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.

Product choice

The formulation of the veterinary product will also influence the clinical outcome of an antimicrobial treatment. Stability, solubility and bioavailability of the active can be optimised by the choice of product (brand).

The absorption and distribution rate of a product in the body has a direct and critical impact on the clinical outcome of the treatment.

Often veterinary products containing the same amount of active substance are considered equivalent. This is clearly not the case and is illustrated later.

The behaviour of a pharmaceutical product depends on several product features such as:

- The quality of the active (crystal form and size, impurities, presence of undesired substances such as heavy metals).
- Choice and the quality of the salt (for example: tartrate, phosphate or hyclate).
- Formulation: used excipients and type of formulation (simple mixture, carrier or granulated).

Next to the visible differences, such as in use stability and water-solubility, these product features will also determine the pharmacokinetic behaviour of the active ingredient.

Pharmacokinetic models are typically divided into an A(bsorption), D(istribution), M(etabolisation), E(xcretion) scheme (see Fig. 2).

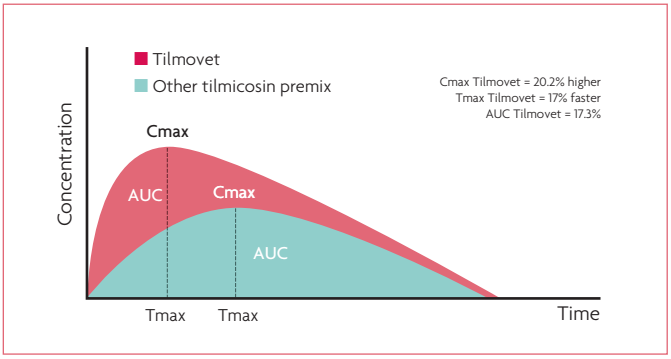
Product features will mainly have an influence on absorption and distribution, although metabolisation and excretion may also differ depending on the quality of the active.

Huvepharma products are developed and tested to optimise clinical results. To test and evaluate our products, pharmacokinetic trials are required. In these experiments, the following parameters are typically evaluated:

- Cmax = maximum concentration reached in a specified compartment of the body. Typically plasma, but also major target organs can be relevant.
- Tmax = is the time at which C max is observed.
- AUCt = Area Under the Curve and represents the total drug exposure over time.

The trial shown in Fig. 3 perfectly illustrates that major differences exist between two products with the same percentage of active

Fig. 3. Pharmacokinetic behaviour of two tilmicosin 20% formulations.



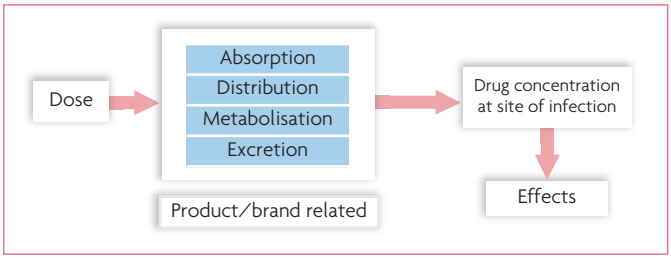


Fig. 2. Absorption, Distribution, Metabolisation, Excretion scheme of a pharmacokinetic model.

ingredient and consequently differ in the clinical outcome of the treatment.

In November 2016, a GLP study was performed at an independent research institute in France to compare the pharmacokinetic behaviour (total absorption and speed of absorption) of Tilmovet 20% with another EU registered 20% tilmicosin containing veterinary premix.

Some 22 pigs were orally administered 16mg tilmicosin/kg bodyweight as a single dose in a cross-over design. Plasma concentrations of tilmicosin were measured in each animal at 12 time points starting from time of administration (0 hours).

Quantification of tilmicosin in the plasma was performed with Liquid Chromatography tandem mass spectrometry (LC-MS/MS), compliant with principles of GLP and validated. The pharmacokinetic parameters under consideration (AUCt, Cmax and Tmax) were statically analysed using ANOVA.

The following results were obtained respectively for Tilmovet 20% premix vs the other premix:

- AUCt: Tilmovet 20%; 249,197µg min/L; other tilmicosin 20% premix; 222,579µg min/L.
- Cmax: Tilmovet 20%; 756.7µg/L; other tilmicosin 20% premix 629.6µg/L.
- Tmax: Tilmovet 20%; 169.4 minutes; other tilmicosin 20% premix; 213.4 min.

This trial clearly shows differences exist between products containing the same amount of active and clinical outcome of treatment is product (brand) related. Optimal absorption leads to higher plasma and tissue concentration and consequently better efficacy.

Conclusion

In conclusion, several aspects should be taken into consideration to improve the clinical outcome of the treatment. On the one hand, choosing the appropriate antimicrobial, correctly dosed and administered is of major importance.

On the other hand, product (brand) choice is also critical to ensure optimal absorption. ■

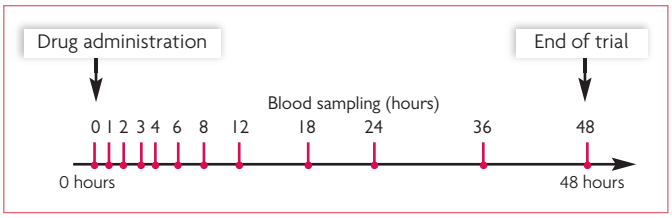


Fig. 4. Set-up of pharmacokinetic trial comparing two tilmicosin 20% premix formulations.

Fig. 5. Results of pharmacokinetic trial, comparing two veterinary products containing EU tilmicosin 20%.