

The Role of Antibiotics in Immunosuppressive Diseases

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■ Introduction

During recent years the pig industry has showed a radical change in disease patterns. Veterinarians were familiar mainly with mycoplasmal and bacterial diseases. In the last decade the emergence of immunosuppressive viruses (ISVs) has meant a significant change in the pattern of the diseases seen in pigs. The ISVs cause immunodeficiency that can be defined as a group of diverse conditions caused by one or more immune system components and characterized clinically by increased susceptibility to infections with consequent severe, acute, recurrent, or chronic diseases (Manual Merck, 2005). The most common agents related to ISVs are PRRSV, Swine Influenza virus (SIV), Pseudorabies virus (PRVv - Aujeszky's Disease) and Swine Fever virus (CSVv) (Waddilove, 2005, Thacker, 2002). Another virus that has had high impact in the swine industry is Porcine Circovirus 2 (PCV2), which is related to Post Weaning Multi-systemic Wasting Syndrome (PMWS). The major impact of these viruses has been the ability to allow the growth of other pathogens, mainly bacteria and mycoplasma, and cause new and more severe syndromes. Considering this reality, the presence of multifactorial diseases, known as syndromes or complexes, are the true challenges for practitioners. The goals of veterinarians are to optimize the benefits of using antibiotics, appropriate preventive measures (vaccines), and management to deal with these infections in immunosuppressive diseases. The objective of this review is to return to the basics and have a better understanding of the effect of different antimicrobial drugs on the immune system.

■ Defining Antibiotic Medication Programs

To define a strategic medication program, to be used during a bacterial or mycoplasma challenge, some criteria have been used: efficacy data,

sensitivity tests, regulatory issues, withdrawal time, pathogens involved in the sanitary challenge, pharmacokinetics of the drug and return on investments ratio. These points added to the timing of the intervention, form of medication, frequency and duration of administration have been essential to determine the success or not of the antibiotic program.

When we are faced with ISVs, the rational use of antibiotics continues to be important to avoid or control the impact of secondary bacterial pathogens. However, in this scenario another fundamental criteria needs to be considered: the impact of the antibiotic and how it interacts with the immune response.

Effect of the Antibiotic on the Immune System

Some antibiotics can weaken immunity and others work to strength the response of the animal.

Tetracyclines

According to Challem (1996), researchers at the Baylor School of Medicine in Houston, re-discovered in 1972 that some antibiotics prevented white blood cells from attacking and killing bacteria. This author described that tetracycline-class antibiotics may be the worst offenders in this regard. Other literature reinforces the negative impact of tetracycline on immune response. Banck & Forsgreen (1979) evaluated the effect of antibiotics on suppression of lymphocyte function in vitro. They concluded that doxycycline caused a significant depression of the mitogenic response of both B and T lymphocytes. This effect was not reversible, as the lymphocytes could not be stimulated when washed after 2 days of incubation with 50µg/ml. Antibody production by lymphocytes incubated for 6 days with doxycycline was completely depressed. Tetracyclines acts by inhibition of protein synthesis and according to these researchers this same mechanism justifies the negative effect over antibody production. As indicated by Shils (1963) and Korkelia (1971), the catabolic effects in patients receiving normal doses of tetracycline could completely abolish the effect of parenteral nutrition by inhibiting the utilization of amino acids for protein synthesis. In addition chemotactic response is also inhibited by doxycycline (Banck & Forsgreen, 1979). Consistent with those results Grondel et al. (1985a; 1985b) demonstrated that low concentrations of tetracycline delay leukocytes mitosis, which means that these drugs impact the number of cells available to guarantee the cellular immune response. Stetsenko et al. (1981) evaluated the impact of tetracycline administered orally in daily doses on the immune and hematopoietic systems of rabbits and concluded that this antibiotic causes the depletion of the immune system

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which was intensified if the drug was used for a prolonged period of time and in higher doses. More recently Cranton (2005) expounded that tetracyclines are likely to cause an increase of yeast in the colon after only a few days of treatment in humans. This effect could be justified because some species of bacteria, which normally reside in the intestine, produce protein-like peptides that stimulate the immunity of their animal and human hosts. Broad-spectrum antibiotics such as ampicillin, tetracyclines, and the cephalosporins can destroy both beneficial and disease-causing bacteria and, in doing so, temporarily stop production of these immune-stimulating peptides promoting the yeast overgrowth. Considering these adverse effects in immune system, tetracyclines - including doxycycline - may not be the best choice of medication for immune compromised animals. Another concern is related to the nephro toxicity potential of this drug. The recommendation is to pick another drug in an animal with pre-existing kidney lesion (Shils, 1963). For instance, in PMWS outbreaks it is possible to identify animals presenting necrotizing and fibrinous glomerulonephritis (Morrow & Anderson, 1994). In this case the use of excessive dosages of tetracycline may cause hazard effects.

Penicilins

Penicillin V is commonly recommended by swine practitioners to control and treat encephalitis. The adverse effects of this drug in immune system include hemolytic anemia, leukopenia, or thrombocytopenia (Manual Merck 2005). Chaperon & Sanders (1978) demonstrated that cephalosporins can suppress in vitro lymphocyte responses to the mitogens.

Sulfamethazine

Studies have shown that sulfamethazine depresses the phagocytic ability of the pulmonary alveolar macrophages (PAM). Gardner et al. (1968) related that PAM of sulfamethazine-treated rabbits ingested fewer bacteria than those of untreated animals. According to these authors, this effect was described in human leucocytes also. The fact that sulfonamides affect the process of phagocytosis is not widely known. Some reviews, however, cited reports of increased, decreased and unchanged phagocytosis after sulfonamide administration (Gardner et al., 1968).

Streptomycin / Chloramphenicol / Others

Streptomycin and chloramphenicol reduce neutrophil production causing neutropenia. Chloramphenicol, now banned for use in livestock, can cause two types of bone marrow depression: a reversible dose-related interference with iron metabolism and an irreversible idiosyncratic form of aplastic anemia (Manual Merck, 2005). Antibiotics, such as actinomycin D and doxorubicin, are used as immunosuppressive agents, and some antibiotics used in the treatment of bacterial and fungal infections have also been shown to depress

granulocyte and lymphocyte functions in vitro and the immune response in humans and experimental animals (Banck & Forsgren, 1979).

Macrolides

The macrolide class of antimicrobials is characterized by a multi-membered lactone ring with one or more amino sugars attached. These antibiotics accumulate within leucocytes and can enhance the performance of certain aspects of cellular immune system. These unique contributions to the host defense and immune systems have been reviewed (Shryock et al. 1998) and there were observed positive effects related to attachment, adherence and bacteria-phagocyte. Macrolides are similar in structure and activity but their differences in structure will interfere in their absorption when taken orally and in their broad spectrum. In veterinary medicine the impact of tilmicosin has been extensively studied. More details about this molecule will be described below.

Tilmicosin

There is scientific evidence that tilmicosin interacts with and strengthens the innate immunity in different ways:

- Accumulation of drug in phagocytes
- Chemotaxis (migration) to the site of infection
- Efflux (release) of drug from phagocytes

The ability of an antimicrobial agent to penetrate into phagocytic cells is essential for activity against intracellular organisms (Mandel, 1973; Meyer et al., 1993). Although it has been demonstrated that most antimicrobial agents have limited cellular penetration, only a few are accumulated by phagocytes (Scoreaux et al., 1987; Butts, 1994). Scoreaux & Shryock (1998a) observed a marked accumulation of tilmicosin by chicken heterophils, but also in monocyte-macrophages. Furthermore, they showed that tilmicosin was 61 to 88% localized in chicken lysosomes and 51 to 85% in swine lysosomes (Scoreaux & Shryock, 1998a,b). The rapid concentration of tilmicosin in chicken phagocytes could be due in part to its lipophilic properties, which favor passage through the lipid membranes of the chicken phagocytes. The presence of two basic amine groups in the structure of tilmicosin similar to azithromycin, may have allowed for greater ionization and lysosomal trapping than that which may occur with classical macrolides, such as erythromycin or roxithromycin, which contain only one basic amine group. Like other weak bases, tilmicosin ($pK_a = 7.4$ and 8.5) would be expected to concentrate in the acidic lysosomes. Moreover, the observation that agents which neutralize lysosomal pH or prevent protonation and trapping of weak bases, significantly decreased the uptake of tilmicosin. These observations provide additional evidence on the importance of pH trapping as an explanation of lysosomal

accumulation. In addition it was related that tilmicosin uptake by chicken phagocytes is enhanced by stimulation of the phagocyte's lipid membrane but the exact mechanism remains to be elucidated (Scoreaux & Shryock, 1998a). Tilmicosin not only concentrated in swine phagocytes but was also maintained, for at least 4 hours in neutrophils and in macrophages, even in the absence of extracellular antibiotic. This suggested that, in vivo, phagocytic cells could retain tilmicosin even though levels in serum may be negligible. Furthermore, the rapid release of tilmicosin in the presence of bacteria demonstrated in vitro, may produce locally high concentrations of active drug (Scoreaux & Shryock, 1998b).

Enhanced intracellular killing by phagocytes: Studies using swine phagocytes showed that tilmicosin uptake increased lysosomal enzyme (acid phosphatase, lysozyme and beta-glucuronidas) production (Scoreaux & Shryock, 1998b). These enzymes are specially made for the lysosome by the rough endoplasmic reticulum and work only at low pH levels. The reason for this is that the enzymes are so strong that they could eat the whole cell if the lysosome ever let them out. During the process of phagocytosis the phagosome merges with a lysosome filled with these enzymes that usually destroy the bacteria.

Pathogens adherence: The initial step in the pathogenic process is the attachment of the microorganism to the host cell. The microbe need to encounter mucosal or epithelial cells to which it must adhere, otherwise it will be eliminated. A description of the inhibitory effects of tilmicosin on *M. hyopneumoniae* adhesion to respiratory epithelial cell surfaces is provided. According Thacker et al. (2001) higher concentrations of tilmicosin inhibited the adherence of *M. hyopneumoniae* to ciliated epithelial cells. The mechanism of action was not described.

■ Final Considerations

Effective control of ISVs may require fundamental changes in management, which could include major system changes. The prudent use of antibiotics to control the secondary infections is part of the control program. Aspects related to the impact of these products in immune system and the adverse effects in other organs, as kidneys, for instance, are relevant to choose the ideal drug. In addition biosecurity and an effective disinfection program can play a significant rule in minimizing the problem.

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