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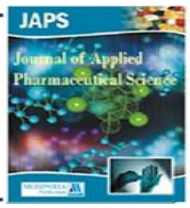

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Growth promoting use of antimicrobial agents in animals

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ABSTRACT

The antimicrobial growth promoter includes varieties of chemotherapeutics agent to be used for improving feed conversion efficiency, body weight gain and overall health. Now a day due to increased pressure of augmenting productivity, the animal husbandry industry is favorably inclined to professional use of antimicrobial growth promoters. AGP are administered at very low dose and they modify the bacterial quality and quantity in animal body towards favorable outcome with respect to reduced incidence of some diseases and infections. Today, non inophore group of compounds are being used widely for the purpose. These compounds alter the cell membrane permeability and causes death of bacterial cells. Wide varieties of compounds are available with specific purpose. The most ideal characteristic of AGP desired is minimum tissue residue and no cross resistance with human pathogens. The total amount of AGP used is difficult to estimate. The present review discusses the detail aspect of AGP at length.

Key words: Antimicrobial, AGP, chemotherapeutic agents.

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INTRODUCTION

The term “antimicrobial growth promoter (AGP)” is used to describe any medicine that destroys or inhibit bacteria and is administered at a low, sub therapeutic dose for the purpose of performance enhancement. The use of antimicrobials for growth promotion has arisen with the intensification of livestock farming. Antimicrobial growth promoters are used to “help the animals to digest their food more efficiently, get maximum benefit from it and allow them to develop in to strong and healthy individuals”. As prevention of diseases, enhancement of growth and feed efficacy are crucial to vital animal husbandry business, the use of AGP is increasing day-by-day. (Ellin Doyle, 2001). The growth promoting effect of antibiotics was discovered in the 1940s, when it was observed that animals fed dried mycelia of *Streptomyces aureofaciens* containing chlortetracycline residues improved their growth. The mechanism of action of antimicrobial agent as growth promoters is related to interactions with intestinal microbial population (Dibner and Richards, 2005; Niewold, 2007). The United States Food and Drug Administration approved the use of antibiotics as animal additives without veterinary prescription in 1951 (Jones and Ricke, 2003). Also in the 1950s and 1960s, each European state approved its own national regulations about the use of antibiotics in animal feeds.

CLASSIFICATION

Antimicrobial agent used for growth promoter purposes include wide varieties of chemical substances having diversified chemical structure and properties. Broadly, they are

classified as under:

1. **Antimicrobials:** e.g., non- ionophore antibiotics and synthetic antibacterial
2. **Ionophore antibiotics:** Monensin, Lasalocid, Narancin.
3. **Quioxalines:** e.g., Carbodox, olaquaidox.

IONOPHORE ANTIMICROBIALS

Inophores are extracted from various actinomycetes (usually Streptomyces spp.). They interfere with the transport of ions through membrane causing an influx of positively charged ions. Ionophores are polyether compounds added to diets of growing and finishing cattle to improve feed efficiency and animal health. The mechanisms of action are initiated by channeling ions through cell membranes and they have marked effect on microbial cells (Bergen and Bates, 1984). Inophores increase propionic acid production in rumen and decrease acetic acid. (Van Maanen *et al.*, 1978). There is also reduction in peptidolysis due to the inhibitory effects of ionophores on certain proteolytic bacteria. As a result, there is an increased post-ruminal flow of dietary amino acids. In this way they increase nutrition efficiency.

NON-IONOPHORE ANTIMICROBIALS

Non ionophore antimicrobials include bleomycin, tetracycline, and chlotetrecycline. All are approved for use in food animals. Bleomycin produces similar effects like ionophores and also exert similar effect on animal. Oxytetracycline and chlortetracycline causes increased rate of gain, and reduction of liver abscess in growing cattle. In addition, chlortetracycline is approved for control of anaplasmosis. Published research quantified that the improvement in feed efficiency and increased gain in grazing animals is not in many numbers. However, It is assumed that improvement of average daily gain is similar to that found with ionophore antibiotics i.e. 15% (Range = 8-45%). Details of antimicrobial growth promoters are given as under in table.

USAGE PATTERNS AND STASTICS

Precise figures on the relative amounts of antibiotics used in humans and animal agriculture are impossible to obtain. The antimicrobial agents currently used to treat or prevent bacterial infections in animals are essentially the same classes of compounds that are used in human medicine. Various estimates have been calculated by the institute of medicine (CDUA, 1999). The Animal Health Institute, a trade organization (Carnevale, 2001), and the Union of Concerned Scientists (Mellon *et al.,* 2001) has proposed the human use of antibiotics as estimated quantity of 1.36-14.64 million kg/yr. while estimated antibiotic use in animal and agriculture is 7.36-11.18 million kg/yr.

Data on the consumption of antimicrobial agents in the EU member states (including Switzerland) have been published by the FEDESA/FEFANA for the year 1997 (http://www.fedesa.be/eng/PublicSite/xtra/dossiers/doss9/). Reportedly, 3494 tonnes (t) of antimicrobial agents have been used, with tetracyclines (2294 t) accounting for almost two-thirds of all antimicrobials used as therapeutic regimes in veterinary medicine. Other frequently-used classes of antimicrobials includes macrolides (424 t), penicillins (322 t), aminoglycosides (154 t), the combination of sulphonamides and trimethoprim (75 t), and fluoroquinolones (43 t). The remaining 182 t of substances includes cephalosporins, amphenicols, lincosamides, polypeptides, nitrofurans, steroid antibiotics, polyene antibiotics and pleuromutilins. Interestingly, certain substances, such as nitrofurans and chloramphenicol, have been banned from use in food-producing animals, but are still allowed for use in pets and companion animals. In 1997, another 1599 t of substances with antimicrobial activity were used for growth enhancement in food-producing animals. These substances also included members of antibiotic classes used as therapeutic agents in human medicine, such as macrolides, streptogramins and polypeptides (Schwarz *et al.*, 2001).

With the ban of most of the growth promoters, antibiotics used in such circumstances represent compounds that are not used in human or veterinary medicine. In addition, antimicrobials that are considered as reserve antibiotics in human medicine, such as streptogramins or glycopeptides, are not licensed for use in animals. New classes of antimicrobials, such as ketolides, glycylcyclines, or oxazolidinones, which are currently under development or in clinical trials, will be exclusively reserved for human therapy.

As per Australian statistics, 55.8 % of antibiotics were used as stock feeds. Larger proportion (40 %) of antibiotic produced in USA was for use in stock feeds including 55-60 % of penicillin and tetracycline production. In Europe, it is 15 % of total antibiotic used. (Prescott and Baggot, 1993)

DESIRABLE CHARACTERISTICS OF AGP

1. Improve growth or production quantitatively and qualitatively.
2. Improve feed conversion efficiency and promote better use of expensive nutrients, such as proteins.
3. Have general, nonspecific action on metabolism in addition to preventing disease associated with the early phases of life.
4. Eliminate *Enterobacteriaceae* carrying R plasmids or at least not induce such plasmids.
5. Minimum residue effect for foods of animal origin. Shorter withdrawal period.
6. Environment friendly when excreted in feaces, it should not alter microbial growth of soils.
7. Free from cross resistance.
8. Should not cross-react with substance used as therapeutics. *e.g.*, growth promotional levels of salinomycin with therapeutic levels of tiamulin.
9. Nontoxic to the animals, to non target species, and to worker of feed plants.
10. Stable after pelleting with a long shelf life and with a readily reproducible method of assay. (Thomas, 1994).

MECHANISM OF ACTION

Antimicrobial growth promoters produce beneficial effects like increase growth, feed efficiency and animal health by acting on gastrointestinal bacteria. Agent causes a range of beneficial changes like: causing lethal or sub lethal damage to pathogens; causing a reduction in the production of bacterial toxins; reducing bacterial utilization of essential nutrients; allowing increased synthesis of vitamins and other growth factors; improving the absorption of nutrients by reducing the thickness of the intestinal epithelium; reducing intestinal mucosal epithelial cell turnover and reducing intestinal motility (Prescott and Baggot, 1993).

Stimulation of intestinal synthesis of vitamins by bacteria; inhibition of bacterial urease; inhibition of bacterial cholyltaurine hydrolase activity and improved energy efficiency of the gut (Prescott and Baggot, 1993) are several important mechanisms in monogastric animals (Pig, poultry and calves). Addition of growth promoter to feed rations alters intestinal characteristics leading to beneficial effects as mentioned here (Commission on Antimicrobial Feed Additives, 1997).

Among the hypotheses already proposed and tested in monogastric species (poultry, pigs and calves) are the following:

- A gram positive bacterium causes hydrolysis of conjugated bile acids and reduces the physiological functions like emulsification and absorption of fats and fat soluble compound. The hydrolyzed product of conjugated bile acids is lithocholic acid, which is hepatotoxic and causes inflammatory reaction in intestine. Antimicrobial growth promoters decrease the hydrolysis of conjugated bile acids. The supplementation with avilamycin and salinomycin reduced the number of *C. perfringens*, enzyme activity and concentration of conjugated bile acids. It also improves ideal absorption of fatty acids in broiler (Knarreborg *et al*., 2004).
- Antimocrobial growth promoters cause shortening and thinning of the intestinal wall. Such morphological change causes improvement of absorptive function by intestine.
- Antimocrobial growth promoters also influence many enzymatic activity and availability of nutrition.
- Feeding of antimicrobial growth promoter results in decreased immune reactivity of animals and this reduced immune reaction helps to conserve metabolic energy and improves absorption of nutrients.

Although it was thought in the 1950s that oral antibiotic administration was detrimental to ruminants, when dose rates were lowered and when novel agents such as the ionophores were introduced in the 1970s significant benefits in performance were realized.

BENEFITS OF USE

Now a day animal husbandry practices all over the world is undergoing rapid transformation. There is shift in strategy from small scale to large scale beef and milk farming involving large scale farm operatrions. There is intense pressure to raise animal productivity, reproductivity and economic output. At this time, the antimicrobial growth promoter is one of inevitable tool for animal husbandry farmers/producers to tune up with the current situation demanding heavy rise in productivity. The use of antimicrobial growth promoters has got the first hand preference and many strategies for its use and application have been developed enabling us to select appropriate antimicrobial growth promoter based on age group of animal, duration of medication and utilization of professional consultation (Dewey *et al.*, 1997).

Ionophore supplementation is effective for the prevention of acute bovine pulmonary emphysema, edema (ABPEE) and bloat when cattle graze lush pasture (Wikse *et al.*, 1991). If the ionophore is hand-fed (rather than fed free-choice), it will help prevent and control coccidiosis. Ionophores also produce impact of mineral utilization. In general, Ionophores enhance absorption of nitrogen, magnesium, phosphorus, zinc and selenium with inconsistent effects on calcium, potassium and sodium (Spears, 1990).

The several important benefits involved in use of antimicrobial are listed and discussed below:

1. Enhances the efficiency of nutrient utilization.
2. Less feed intake.
3. Provides stable fermentation process.
4. Reduces bacterial load and hence immune reactivity.
5. Reduces variation in size of carcasses, and helps to achieve quality standard in slaughter process and product.
6. Suppresses pathogenic bacteria and there by reduction in incidences of enteric disease.

Enhancement of feed efficiency increase weight gain and reduces feed consumption. This saves resources like land, water and man power. Reduction in feed intake reduces fecal discharge of nitrogen and phosphorus and protects environmental balance. Stability of fermentation process in rumen and small intestine decreases incidence of metabolic disease, such as severe ketosis, milk fever and lactation tetany. It will also help to cut down emission of methane from rumen; an important green house gas. By reducing bacterial load the immune reactivity will reduce and conserve metabolic energy. This helps to make animals more healthier.

In four European countries, an annual reduction of approximately 140-190 million cubic meter of methane from cattle was ascribed to the use of monensin (CEAS, 1991). In cattle, the use of inophores in particulars reduces ketosis and bloat. Viagiamycin reduces the risk of lactic acidosis in sheep and cattle. The uses of antimicrobial as a feed additive also suppress several bacteria and protozoa. The antimicrobial at initial stage prevents colonization of pathogen in gastro intestinal tract. Several diseases like necrotic enteritis in poultry, ileitis or *Clostridial* enteritis in poultry and swine; liver abscess and coccidiosis in cattle are reported to be suppressed. Sub therapeutic concentration of antimicrobial reduces incidence of swine dysentery, porcine

hemorrhagic enteropathy and *Clostridium perfringens* infection (Corpet, 2000).

Additional benefits like improvement of heat tolerance, increase mineral absorption and enhanced immune function are also observed in animal (Page, 2003). It also increase digestibility of proteins by reducing proteolytic enzyme secretion by bacteria. Experimentally, pig receiving chlortetracycline, penicillin and sulfamethazine produced higher serum level of insulin like growth factor-1. (Committee on drug use in animals, 1999)

Antimicrobial growth promoters also improve reproductive efficiency in domestic animal by increasing more number of heifers at puberty, decreasing age at puberty, increasing corpora luteal weight and increasing the amount of progesterone secretion. This may be due to increased propionic acid production leading to endocrine response which influences the reproductive efficiency (Moseley *et al.*, 1982).

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