Antibiotic Growth-Promoters in Food Animals

Manish Kumar Srivastava*

A.N.D. College of Pharmacy, Gonda, Uttar Pradesh

*There has been a developing controversy surrounding the use of antibiotics as growth promoters for food animals. These drugs are used at low doses in animal feeds and are considered to improve the quality of the product, with a lower percentage of fat and higher protein content in the meat. Other benefits of the use of antibiotic growth-promoters include control of zoonotic pathogens such as **Salmonella, Campylobacter, and Escherichia coli.** Use of any antibiotic is associated with the selection of resistance in pathogenic bacteria and it has been argued that the use of antibiotic growth-promoters imposes a selection pressure for bacteria that are resistant to antibiotics that may be used in clinical or veterinary practice, thus compromising the continued use of antimicrobial chemotherapy. This paper considers the use of antibiotics as growth promoters and then examines some of the alternative methods for achieving meat of high quality*

Introduction

The term **"antibiotic growth promoter"** is used to describe any medicine that destroys or inhibits bacteria and is administered at a low, sub therapeutic dose or in alternative way, **"antimicrobial growth promoters"** (AGPs) are antibiotics added to the feed of food animals to enhance their growth rate and production performance. The use of antibiotics for growth promotion has arisen with the intensification of livestock farming. Infectious agents reduce the yield of farmed food animals and, to control these, the administration of sub-therapeutic antibiotics and antimicrobial agents has been shown to be effective. The use of growth-promoters is largely a problem of intensive farming methods and the problems caused by their use are largely those of developed rather than developing countries .The mechanism by which AGPs work is not clear. AGPs reduce normal intestinal flora (which compete with the host for nutrients) and harmful gut bacteria (which may reduce performance by causing sub clinical disease). The effect on growth may be due to a combination of both fewer normal intestinal flora and fewer harmful bacteria. The class of antimicrobial drugs used and the animal species involved may determine the relative importance of each mechanism. The quantity used in feed varies with each antimicrobial agent.

According to the **National Office of Animal Health (NOAH, 2001),** antibiotic growth promoters are used to "help growing animals digest their food more efficiently, get maximum benefit from it and allow them to develop into strong and healthy individuals". Although the mechanism underpinning their action is unclear, it is believed that the antibiotics suppress sensitive populations of bacteria in the intestine. It has been estimated that as much as 6 per cent of the net energy in the pig diet could be lost due to microbial fermentation in the intestine (Jensen, 1998). If the microbial population could be better controlled, it is possible that the lost energy could be diverted to growth.

The farming industry is the second largest consumer of antibiotics after medical practitioners. About 40 per cent of antibiotics are used as growth promoters although antibiotics are also used therapeutically for animals. To reduce the risk of selecting resistant bacteria, the use of antibiotics must be restricted. The most attractive area for reducing the use of antibiotics is to ban their use as growth promoters in food animals. This review examines the consequences of the use of antibiotics as growth promoters and looks at alternatives aimed at reducing the pressure for the selection of resistance in bacteria that cause disease in both humans and animals

In Denmark, as well as in other countries, only a few glycopeptides have been used; for human's vancomycin and (to a lesser extent) teicoplanin have been used, and for animals avoparcin has been used exclusively as a feed additive for growth promotion. Avoparcin has not been used in animals in Sweden since 1986 because of a national prohibition of AGPs; in the United States, avoparcin was never approved because of its carcinogenic effects.

Table - 1: Trends In The Therapeutic Use Of Antimicrobial Compounds In Food Animals In Denmark (WHO, 2003)

Compound	1994	1996	1998	1999	2000	20012	20022
Penicillins, β-lactamase sensitive	9,400	7,200	14,300	14,700	15,100	16,000	16,900
Other penicillins, sporins	4,400	5,800	6,700	6,600	7,300	8,700	9,800
Sulfonamides and trimethoprim	9,500	4,800	7,700	6,800	7,000	9,400	10,400
Sulfonamides	5,600	2,100	1,000	1,000	1,000	900	850
Macrolides, lincosamides, tiamulin	11,400	7,600	7,100	8,700	15,600	19,900	21,200
Aminoglycosides	8,600	7,100	7,800	7,500	10,400	9,600	9,200
Others	4,400	600	650	350	300	900	1,600
Total	**89,900**	**48,000**	**57,300**	**61,900**	**80,700**	**93,700**	**94,300**

Note :

1) Only veterinary drugs are included, excluding drugs obviously used in pets (kg of active product).
2) Does not include consumption in aquaculture before 2001.

*E-mail:

Current Use Of Antibiotic Growth Promoters

On a world scale, the use of antibiotics as animal growth promoters differs dramatically. Sweden now makes no use of antibiotics for growth promotion purposes; the USA uses a wide range of antibiotics, including some considered to be "medically important". The following information is taken from the Report of the **Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR, 1999)** on the use of antibiotics in food producing animals. Pigs are exposed to the greatest range of growth promoters. In the USA, for example, pigs are exposed to lactam antibiotics, including penicillins, lincosamides and macrolides, including erythromycin and tetracyclines. All these groups have members that are used to treat infections in humans. Pigs in the USA are exposed to a range of other compounds intended for growth promotion. These include bacitracin, flavophospholipol, pleuromutilins, quinoxalines, virginiamycin and arsenical compounds. In the USA, compounds used as growth promoters for cattle include flavophospholipol and virginiamycin, both also used as growth promoters in poultry. Cattle are also exposed to ionophores such as monensin to promote growth.

In Australia a range of growth promoters are employed. Pig farmers use arsenical compounds, flavophospholipol, the macrolides, kitasamycin and tylosin, the quinoxaline olaquindox, and also virginiamycin, a streptogramin. Poultry producers use arsenical compounds, flavophospholipol, bacitracin and virginiamycin. Australian cattle farmers employ a range of ionophores, namely lasalocid, monensin, narasin and salinomycin. They also employ flavophospholipol and the macrolide oleandomycin. The glycopeptides avoparcin was withdrawn from the Australian market in December 1999 and existing stocks were not permitted to be used after 1 July 2000 when the registration lapsed. Use of this compound is discussed more fully below.

The use of growth promoters in the European Community is more limited. The oligosaccharide avilamycin is used in pig and poultry farming, ionophores, namely monensin and salinomycin are used for cattle and pigs and flavophospholipol is used with a range of livestock, including cattle, pigs, poultry and rabbits. In pig production, feed conversion efficiency is improved, along with daily growth rates, by approximately 2.5 per cent. Mortality rates, associated with scouring and proliferative enteritis, are 10-15 per cent lower than in countries, such as Sweden, who do not use antimicrobial growth promoters).

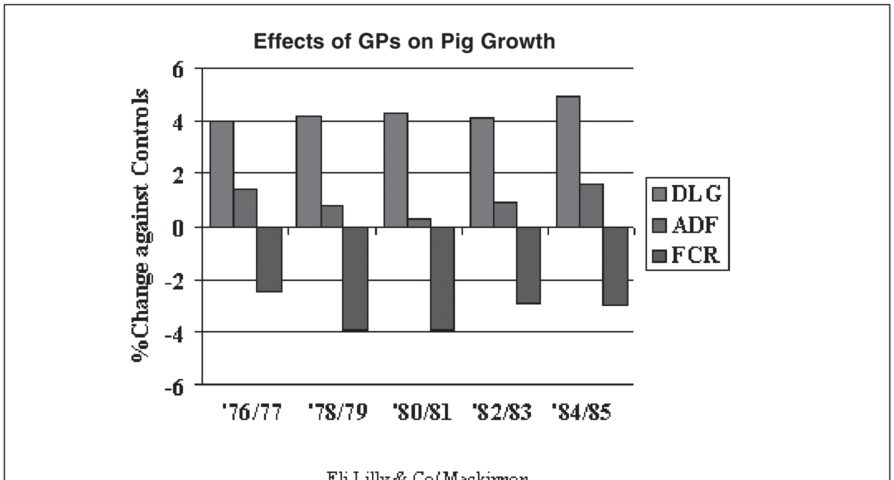
Future Of Antimicrobial Growth Promoters Worldwide

On a global level, a recent joint workshop was held involving the WHO, Food and Agriculture Organization of the United Nations (FAO), and the World

Organization for Animal Health (OIE) on nonhuman antimicrobial usage and antimicrobial resistance (World Health Organization, 2004). The resulting report recommends implementation of the WHO global principles for the containment of antimicrobial resistance in animals intended for food (World Health Organization, 2004). These principles include the withdrawal from food animal production of AGP that are in classes also used to treat human disease unless and until a risk assessment is carried out (World Health Organization, 2000). In addition, the report recommends the implementation on a national level of risk assessment studies and establishment of surveillance programs to monitor AGP use and antimicrobial resistance in bacteria from food animals (World Health Organization, 2004). The use of risk assessment models in evaluating and regulating food animal antibiotics has been reviewed recently (Cox, 2004).The reality that AGP use is being curtailed by market actions, if not legislative, has led to a new urgency in the search for replacements. Among the candidates for replacement, organic acids appear to have the most widespread acceptance at this time (Dibner and Buttin, 2002; Dibner, 2003). Any replacement for AGP would have to provide an improvement in feed efficiency that is economically viable. If the replacement does not have antimicrobial properties, other concerns, such as incidence of enteric diseases and air sacculitis, will have to be addressed with the continued use of ionophores, management changes, or both. A recent review of the major categories of replacement candidates and methods to select among them has been provided by Rosen (2004).The review points out the need for analysis of numerous candidates simultaneously rather than evaluating the accumulating database one study at a time. This would involve the inclusion of all properly controlled test data available using a multifactorial model (Rosen, 2004). The strength of the argument is that the relevant properties of AGP (i.e., improved efficiency, gain, and livability) would be the basis for selection, and that combinations of candidates could be identified. The mode of action of AGP, which is of theoretical interest and the subject of the rest of this report, is in fact incidental to the issue of rapidly identifying replacement combinations.

Human Health And The Consequences Of Using Antibiotic Growth Promoters

Human health can either be affected directly through residues of an antibiotic in meat, which may cause side-effects, or indirectly, through the selection of antibiotic resistance determinants that may spread to a human pathogen. A drug that illustrates both potential problems is chloramphenicol. Gassner & Wuethrich (1994) have demonstrated the presence of chloramphenicol metabolites in meat products and have concluded that a link with the presence of these antibiotic residues in meat and the occurrence of aplastic anaemia in humans cannot be ruled out. Banned for growth promotion use in America over a decade ago and in the EU since 1994, chloramphenicol remains a drug used in treating typhoid fever. Over-use in animal husbandry is believed to have led to an increase in resistance to the drug in bacteria of the genus *Salmonella,* including *Salmonella* typhi, the causative bacterium of typhoid. It should be noted that the link



between the use of antibiotic growth-promoters and increasing resistance remains unproven and that typhoid rates of infection and cure have not changed significantly since the introduction o the ban in 1994.

In general, the effect of antibiotic residues in meat is insignificant when compared with the issue of selection and amplification of antibiotic resistant strains of bacteria. On another level, the resistance determinant may be selected in a bacterium that is a member of the commensal flora of the animal being fed a growth promoter. If such a resistance determinant is mobilisable, it may subsequently transfer to human or animal pathogens. The consequences of selection of resistance can range from prolonged illness and side effects, due to the use of alternative, and possibly more toxic, drugs, to death, following complete treatment failure. Modern medicine has furnished us with a wealth of antibiotics but, as the MRSA example discussed above illustrated, alternatives are starting to run out. The four types of bacteria most commonly associated with resistance due to use are *Salmonella, Campylobacter* and *Escherichia coli;* these bacteria are likely to be transmitted frequently from animals to humans.

Salmonella Sp.

Bacteria of the genus *Salmonella* are responsible for many human diseases. *Salmonella typhi* is the causative agent of the potentially lethal typhoid fever. This infection is exclusively of human origin, spread via human faecal contamination of food or water and has a high mortality rate if left untreated. As it is mainly spread through in sanitary conditions, and from human carriers, it is not within the scope of this review. Other species of *Salmonella* are zoonotic and are usually acquired from contaminated food sources, such as poultry. They commonly cause gastroenteritis. Symptoms can range from mild diarrhoea and nausea to severe vomiting, fever and violent diarrhoea. Most infections are confined to the gut but with people at the extremes of the age range, *Salmonella* may cause invasive disease. Such cases can require hospitalization due to extreme dehydration coupled with endotoxic shock and may even result in death. The most common causative agents of salmonellosis are *Salmonella enterica* var. Enteriditis and *Salmonella enterica* var. Typhimurium can usually be treated with fluoroquinolones, chloramphenicol and ampicillin. Molbak et al. (1999), however, reported that isolates of *Salmonella enterica* var. Typhimurium DT104, which is already resistant to multiple drugs including ampicillin and tetracycline, was showing resistance to quinolones. Consequently, some infections caused by DT104 can be very difficult to treat.

In 1998, Bonner reported that, in 1983, an outbreak of food poisoning caused by a resistant strain of *Salmonella* was linked to hamburgers made from cattle fed with chlortetracycline. Spika et al. (1987) traced a chloramphenicol-resistant strain of *Salmonella enterica var.* Newport from beef burgers to herds that had been dosed with chloramphenicol. Tacket t al. (1985) reported an outbreak of multi-drug resistant *Salmonella enterica* var. Enteriditis following consumption of raw milk. All of these reports originated in North America but this is not just an American problem; bacteria do not respect national boundaries. *Salmonella enterica* var. Typhimurium DT104 was isolated in the UK in 1988 and has subsequently migrated around the world. Using medically important drugs, such as chloramphenicol and tetracycline, as growth promoters would seem to be the most obvious route towards resistant strains that pose a threat to human health, but the selection of resistance is not necessarily that simple.

Some scientists believe that antibiotic growth-promoters may contribute indirectly to the spread of salmonella by allowing animals to be kept in unhygienic conditions. Growth promoters may act as masking agents for proper sanitation by reducing the pathogen load. The fundamentally unhygienic conditions of intensive broiler chicken production have been criticized. Broilers are reared in confined housing: this allows any pathogen to spread through the cohort rapidly.

Campylobacter Sp.

Campylobacter, particularly *Campylobacter jejuni* and *C. coli,* is the most common cause of bacterial food poisoning in developed countries, such as the UK and USA. The Public Health Laboratory Service in the UK reported 53,858 faecal reports of *Campylobacter* in the year 2000, compared with only 14,844 faecal reports of *Salmonella* Public Health Laboratory Service, On-Line). Gastrointestinal disease caused by *Campylobacter* shares many of the clinical symptoms of *Salmonella* infection, including diarrhoea, vomiting and fever. Hospitalization is uncommon, affecting mostly those individuals at the extremes of age; death due to *Campylobacter* infection is even less common.

C. jejuni, the commonest species to cause of human *Campylobacter* infection, is sensitive to a range of agents, including erythromycin, chloramphenicol, tetracyclines, amino glycosides and quinolones. Unusually for a Gram-negative bacterium, the agent of choice in infections requiring therapy is the macrolide erythromycin, which is also used as a growth promoter for pigs in America. This use is not believed to have compromised therapy. Due to the relative unimportance of *Campylobacter* in animal health, however, few studies on the resistance of animal isolates have been completed. The widespread use of macrolides in the food industry is of concern because of the clinical importance of this family of antibiotics. Thus, investigations into the occurrence of antibiotic resistance determinants in animal isolates are required.

If growth-promoting macrolide antibiotics have had little or no effect, then the therapeutic use of fluoroquinolones has had been associated with increased resistance. Fluoroquinolone-resistant strains are emerging around the world. Engberg et al. (2001) reviewed in vitro macrolide and quinolone resistance prevalence and trends in campylobacter isolated from humans, showing a temporal relationship between use of quinolones in food animals and resistant isolates in humans. Endtz et al. (1991) reported that the use of fluoroquinolones to treat respiratory diseases in poultry seems to have led to the development of fluoroquinolone-resistant *Campylobacter* in the gut of treated birds. It is worth noting that the use of therapeutic drugs is often at doses that are orders of magnitude larger than the dose administered for growth promotion purposes. Such a high dose exerts a huge selection pressure and, in the case of *Campylobacter,* has allowed resistant strains to emerge and even dominate.

Escherichia coli

When they are located in the gut, *Escherichia coli* strains are regarded as non-pathogenic, Gram-negative members of the commensal flora of humans and animals. They are, however, the frequent cause of a variety of human infections. Pathogenic strains are most commonly associated with urinary tract infections but strains are also the cause of traveller's diarrhoea. This bacterium is also involved frequently in abdominal infection, such as perforated bowel or appendicitis. It is also one of the most common causes of septicaemia. Rarely, it is the causative agent of neonatal meningitis. In summary, *E. coli* is capable of causing problems at almost any site of the body.

Antibiotic resistance in *E. coli* is widespread globally, with agents such as the penicillin's found to be of decreasing efficacy against it (Heritage et al., 2001). Leclerc (1996) warns about the dangers of complacency by reporting high rates of mutation in *E. coli* O157, following observations that they could acquire resistance determinants easily by horizontal gene transfer. It was noted that this was a possible route via which antibiotic resistance, from a pool of environmental pathogens, could be conferred. Even if antibiotic growth-promoters were not directly targeted against the bacteria, it remains possible that strains of this bacterium may acquire resistance from the gut micro flora of the food animal. For this reason, and for the sheer volume and severity of disease it causes, it would be sensible not to ignore *E. coli* when considering the risks associated with the use of antibiotic growth-promoters.

Infection Control Measures

The use of antimicrobials as growth promoting agents rests on their role in controlling infection in growing animals. Similarly, many of the alternatives are aimed at controlling infection, often indirectly. But what of direct measures used to control infection in farm animals? The Australian Pig Farming Industry pioneered the "all-in-all-out" method of pig production. This is a new system, used to replace the older technique of having a constant stream of pigs moving through the farm. Instead of having a range of ages, all the pigs weaned within a week are designated into a single cohort and are housed together in one shed. They are not allowed to mix with pigs from other cohorts and so cross-infection between groups is prevented. "Segregated early weaning" takes note of the observation that the sow is an important source of pathogens. If piglets are weaned early, they are less likely to come into contact with pathogens from their mothers. Care must be taken not to create welfare problems by weaning animals too early, however.

The "specific pathogen-free" system is used to prevent pigs from acquiring many of the diseases that require antibiotic intervention, especially respiratory disease. To achieve this, they are born by hysterectomy and hand reared. This will only be cost-effective for valuable breeding stock.

Finally, vaccination is used to offer protection against certain pathogens, such as enterotoxigenic *E. coli* and various mycoplasma infections.

The Swedish Model

Sweden posed the question of suitable alternatives to antibiotics in 1985, when its Parliament passed the Feeding stuffs Act and banned the use of antibiotics for growth promotion. Calves, turkeys and fattening pigs did not appear to be affected significantly by the ban: growth rates may have decreased slightly, but there were no major increases in mortality. Efforts were made to establish new feeds and housing for broiler chickens and, after an initial "unsettled" period of outbreaks of necrotic enteritis, were considered successful. Animal Welfare groups were also happy to note that the new conditions were much better for the birds. Weane pigs did not, however, enjoy the same level of success. JETACAR (1999) reported that scouring increased and there was an increase of 1.5 per cent in mortality, roughly fifty thousand pigs. Furthermore, the time taken to reach 25kg increased by 5-6 days. Housing and hygiene were improved, livestock buildings were partitioned to help slow the spread of disease, "all-in-all-out" measures were introduced and the feed was changed. This resulted in a 50 per cent reduction in the use of antibiotics by 1993 and was followed by further reductions each year. In 1995-96, only 11 per cent of weaners were treated with antibiotics in their food.

The ban stimulated new ideas and technologies are successfully achieved its goal of an agricultural industry independent of growth promoting antibiotics. In addition, animal welfare was improved overall. The Swedish experience shows that antibiotics are not necessary to produce healthy animals, provided their living conditions, rearing and foods are improved. This did come at a cost: thousands of pigs and chickens probably died as a direct result of the ban, despite the overall improvement in animal welfare. Swedish produce is more expensive and so less competitive on the market, and the costs of the venture are expensive. It may be argued, however, that the problems encountered by adopting the Swedish model have been justified by the outcome. Sweden has shown the rest of the world that it is possible to have modern farming without the use of antibiotics as growth promoters.

Conclusions

The best alternative to **Antibiotic growth-promoters** is a general improvement of conditions for animals that produce our food, following, for example, the Swedish model. Medically important antibiotics must be prohibited from use in a growth promotional role as a matter of immediacy. Unfortunately, reform can be slow and extremely costly, as Sweden showed. In order to start a reformation of the Industry as a whole, it s essential that attitudes to the use of antibiotic growth promoters be changed. While the greatest threat to the continued use of antibiotics comes from human medicine, selection of resistance is a problem that affects everyone. It matters very little to someone whose antibiotic treatment is failing if selection of the resistant strain resulted from clinical overuse of the antibiotic or from other sources.

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