Use of antibiotic in animal feed

Atef M. Shibl,
Dept. of Microbiology,
College of Pharmacy,
King Saud University,
P.O. Box 2457, Riyadh 11451,
Saudi Arabia

Abstract

Antibiotics are used in veterinary medicine for either therapy, prophylaxis or nutrition. One of the major public health problem is that selective pressure of antibiotic use may lead to an increase in resistance. The therapeutic and prophylactic use of antibiotics has sometimes led to the emergence of resistant bacteria. The nutritional use has been regulated by several authorities in different countries which demands special investigations into the potential of antibiotics to increase rates of drug resistance. It should be recognized that antibiotics are not suitable as a compensation for poor hygiene standards or for the eradication of a pathogen from a certain environment. As the prudent use of antibiotics by clinicians is effective in lowering the emergence of resistant isolates in humans, animal husbandries and poultry farms should be discouraged to use antibiotics as feed supplement in order to minimize acquisition of resistant flora.

Extensive and sometimes careless usage of antibiotics in medicine, dentistry and agriculture is rendering these drugs reliable for treating important infections. Among these uses, the subthrapeutic application of antibiotics in animal feeds was instituted during the 1950's to promote faster growth and improve the efficiency of feed conversion into meat. During this period, transferable multiple drug resistance traits in enteric bacteria were detected for the first time in Japanese hospitals. By 1962, the phenomenon was also being detected in British hospitals and soon elsewhere as well. Since then, the practice of adding antibiotics to animal feeds has continued.

In contrast to human medicine, veterinary medicine uses antimicrobial agents for these purposes,: therapy, prophylaxis and nutrition. In all instances, a selective pressure is imposed on bacterial populations and antibiotic resistance emerges. The major public health risks factors arising from the use of antimicrobial agents in veterinary medicine are: emergence of antibiotic resistant bacteria, emergence of factors (transfer factor), increase in the pool of resistance genes, increased shedding of enteric pathogens, conversion of a subclinical infection into a clinical episode and non-microbiological risks.

The therapeutic and prophylactic uses of these drugs are not well regulated as far as the emergence of resistance is concerned. In Germany, Salmonella-contaminated Turkeys were an increasing source of food borne infections. For prevention of further cases, the Turkey producer decided to dip hatching eggs into gentamicin solution and to inject 1 day old chickens with the drug. Because of this practice, the emergence and selection gentamicin resistant Salmonella were expected. A similar situation of increasing resistance rates among Salmonella isolates was observed after the licensing of the therapeutic use of quinolones in calves. The predominating clone also showed resistance to tetracycline, ampicillin, chloramphenicol, kanamycin and Thorimetheprim. Most of these strains showed complete resistance between enrofloxacin, nalidixic acid, ofloxacin, norfloxacin and flumequine.

The nutritional use of antimicrobial agent is based on a wide variety of substances. Most of these substances are active against gram-positive organisms and only a few have a wide-spectrum of activity. In 1984, more than one and half million meteric tons of active ingredient, were used within Europe. The nutritional use of these substances led to a public and scientific discussion about their influence on public health. As a consequence the nutritional use of antimicrobials has been regulated. It demands microbiological testing of all antimicrobials and special investigations on their potential for increasing rates of drug resistance. The Microbiological investigations required for licensing of feed additives according to the guidelines for the assessment of additive in animal nutrition are; a) investigation of the microbiological spectrum of action of the additive by determination of the minimal inhibitory concentration (MIC) for various pathogenic and non-pathogenic gram-negative and gram-positive bacterial species, 2) investigation into cross resistance to therapeutic antibiotics by determination of the MIC for mutants produced *in vitro* that exhibit chromosomal resistance to the additive, 3) testing of whether the additive has selective effect on resistance factors, these tests are to be performed under field conditions in the animal species for whom the additive is primary intended. 4) tests for determining the effect of the additive on the normal intestinal flora, the colonization of the intestinal tract and the excretion of pathogenic organisms and 5) Field studies for determining the percentage of bacteria resistant to the additive. These investigations are to be carried out at major intervals before and during the use of the additive.

The magnitude of human antibiotic misuse is out weighed by antibiotic use in veterinary medicine. Not only are antibiotic used therapeutically for pets and given parenterally or orally in controlled doses to individual livestock animals, antibiotics are added to the feed or drinking water given to livestock and in fish-farming for prophylactic purposes or to enhance yield.

The administration of antibiotics to livestock destined for human consumption must be studied at two levels, one, the selective pressure on the animals own bacteria and two, the elimination of antibiotics in milk, meat and excreta. The focus of concern has not been antimicrobial residues in food products but rather the selection of bacteria that are resistant to antibiotics in these animals and the possibility that such resistance can be transmitted to bacterial pathogen that affect human beings. Antibiotic resistance of non-pathogenic bacteria from the intestine of animals or in the environment (e.g. water of the fish-farming) as a result of antibiotic excretion, may constitute a source of transmittable resistance determinants for other pathogen. Of the many ways in which antibiotics are administrater to animals, those that produce most concern are mass antibiotic applications to large numbers of animals for prophylactic purposes, followed by antibiotics administered for the purpose of enhancing yields. This theoretically clear differentiation between therapeutic indications and additive use for increasing yield in practice is less clear. For instance, antibiotics used for prophylactic purpose and dosed in large quantities may have beneficial effects on growth.

About a million kilograms of antimicrobials per year in U.S.A. was destined for supplementing animal feed. Then and now approximately half of the production of antimicrobial agents in USA was used to supplement livestock feed. In Norway, antibiotic consumption by human is relatively low compared with that of other European countries, but the amount of antibiotics used in veterinary practice in the nineties was about double that used in human medicine. In European countries only a few medications are licensed for veterinary use to enhance yield and prophylactic use is strictly regulated and theoretically supervised by veterinarians. Most of the authorized antibiotics for growth promotion purposes are of little or no use in human therapeutics and the authorized dosage for animals is low (in the order of grams/ton of feed). The antimicrobials (substances or residues) for which minimum residue level in feed have been established include, all sulphonamide, Nitrofurans (Furazolidone), all tetracyclines, Nitroimidazales (Dimetridazole), Aminoglycosides (spectinomycin), Macrolides (tylosin, spiramycin, tilmicosin), chloramphenicol derivatives (thiamphenicol, Fluorphenicol), penicillins (Benzylpenicilin, Ampicillin, Amoxycillin, oxacillin, Cloxacillins, Dicloxacillin), Cephalosporin (Ceftiofur, cefquinone), Quinolones (Enrofloxacin, ciprofloxacin) and Miscellanous agents (trimethoprim). Antimicrobial not authorized for use in livestock include chloramphenicol, Ronidazole, Dapsone and Nitrofurans other than Furazolidone. Antimicrobials authorized as feed additives include Bacitracin zinc, spiramycin, virginiamycin, · Flavophospholipid, tylosin phosphate, Monensin, Salinomycin, Avoparcin, Avilamycin and Erotomycin.

In the USA, however, the number of authorized antimicrobials is larger and some of these agents are used in human clinical practice. Among the more than 20 compounds approved by the FDA for feed supplementation in the US are penicillin, erythromycin, Lincomycin, Sulphonamides, Tetracyclines and other antimicrobial agents used in human clinical practice; worse, the use of such agents does not seem to require even veterinary prescription.

It has long been suspected that animals were the source of certain antibiotic resistance genes that have been found in human beings. In strains of *E. coli* showing resistance to trimethoprim that were isolated from swine reared on large farms in Sweden, they report the same isolates of an *E. coli* in the urinary tract infected persons. Another example is apramycin; Following the introduction of this drug, high level resistance to apramycin was reported to occur is *E. coli* from calves after treatment. This high level resistance subsequently was found to be plasmid-encoded and now detected in humans.

The idea that animals and humans exchange antibiotic resistance genes is now less speculative. There is evidence of a natural horizontal transfer of genes conferring resistance to certain antibiotics between bacteria that normally colonize humans and bacteria that normally colonize livestock. In strains of *Campylobacter jejuni* isolated from raw chickens, the percentage of stains resistant to enrofloxacin (a fluoroquinolone that is used in animals and its principle metabolite is ciprofloxaxin, an quinolone use extensively for human therapy), exceeds that of sensitive stains. Recently the selective pressure of its use in veterinary practice is the only explanation for the increase in Campylobacter resistance to fluoroquinolone observed in humans.

Avoparcin, a glucopeptide antibiotic used in chickens exerts selection pressure for cross-resistance or partial cross resistance to vancomycin and similar antibiotics in human associated bacteria. Vancomycin resistant *Enterococcus faecium* are not present on farms not using avoparcin. Animals act as reservoirs for vancomycin resistant Enterococci that enter the human food chain.

Recent meetings under the auspices of the WHO last autumn, 1997 recommended that, because of the importance of antibiotics in human medicine, there use as food supplements and therapeutic in food animals should be reduced. There was wide agreement on several important principles; First, there is agreement that use of antibiotics in animals represent a risk to human health, second use of antibiotics as food supplements for animals should progressively be eliminated. In Sweden, antibiotics are no longer being used as growth promoters and they are being used only sparingly for therapeutic purpose in farm animals.

Concerns in UK about the potential contribution of the veterinary use of antibiotics to this public health risk led to a formal government inquiry and the appointment of the Swann committee. The committee recommended limiting the non-therapeutic use of antibiotics in feeds.

Consensus is emerging that antibiotic resistant pathogens are increasing in prevalence and that the controlled and uncontrolled used of antibiotics in veterinary medicine favours the selection of a pool bacteria resistant to antimicrobial agents. In human medicine and veterinary medicine, the danger of increasing antibiotic consumption has been indicated repeatedly. To prevent the spread of resistant organisms from farm animals to the environment or human, the prudent use of therapeutic antimicrobials is recommended. Antibiotics are not suitable as a compensation for poor hygiene standards or for the eradication of a pathogen from a certain environment. They should be used only by doctors or veterinarians. All the persons involved-physicians., veterinarians, representatives of pharmaceutical industry and health authorities should make a concerted effort to contained the potentially very serious public health problem of microbial resistance to antibiotics.

Suggested reading

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