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Antibiotics in feed, with special reference to pigs: a veterinary viewpoint

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Abstract

The historical background of the present UK legislation is briefly reviewed, and the current legal situation as it pertains to the UK and European Community is summarised. The reasons for the inclusion of antibiotics in feed are outlined and discussed. In the first case, feedstuffs may have to be medicated for reasons of disease prevention and control. In large herds, especially in loose housing, mass medication by injection is not possible and even minimal disease herds will become infected with airborne pathogens from time to time. In the second case, continuous low-level feeding of antibiotics to growing pigs (growth promoters) suppresses the growth of harmful bacteria and allows healthier pigs to grow faster and more efficiently, thus producing cheaper food at the same time as improving welfare. The legal requirements regarding medicines available only on prescription are outlined and discussed. The fears and worries of the general public are noted and found to be overstated because of misconceptions and misunderstanding. It is concluded that food and milk produced today will remain safe provided the safety rules are adhered to.

Introduction

Antibiotics (substances produced by moulds or synthetically produced which either kill bacteria or stop them from multiplying) have been incorporated in animal feed for almost four decades. Chemotherapeutic agents such as the sulphonamides will be treated as antibiotics for the purpose of this review.

The thalidomide tragedy prompted the UK Government to introduce The Medicines Act 1968, Section 40 of which is the principal enabling legislation relating to all medicated feedingstuffs (as amended by The Animal, Health and Welfare Act 1984). More recently, the legislation was amended by The Medicines (Medicated) Animal Feedingstuffs Regulations 1992 (again under Section 40). Under The Medicines Act, antibiotics have been classified into two groups: feed antibiotics and therapeutic antibiotics. This division was recommended by the Swann report (Anon., 1979), in an attempt to curb the use of sub-therapeutic levels of antibiotics in animal production. Legislation introduced by the Commission of the European Communities allocated antimicrobial agents into one of three categories depending on the proposed
use of the product, the date of introduction of the product and certain safety
criteria. Annex 1 and Annex 2 products refer to antibiotics available under
the Pharmacy Medicine List (PML) category in the UK and are covered by
EEC Directive 70/524. The third category refers to prescription-only medi-
cines (POM), which are controlled under EEC Directive 90/107. The pro-
visions of these directives have been incorporated into the UK legislation.

The general public has become very concerned about food safety, and fears
relating to the use of antibiotics in animal feedstuffs have been widely ex-
pressed. Before addressing the fears of the general public, however, the back-
ground and need to use antibiotics in animal foodstuffs will be discussed.

Alexander (1971) summarised the rapidly changing trends in agriculture
towards larger and more specialised units, towards more effective pig im-
provement and towards more integration and industrialisation. At the same
time, pig keeping in particular has tended to concentrate in certain geograph-
ical areas for reasons that are not relevant to this paper. New hybrids with
greater potential for growth and better food conversion efficiency have been
introduced, thus making the production of food cheaper. This is extremely
laudable when one considers that large numbers of people throughout the
world are either on the poverty line or below it. However, little attention has
been given to the development of genotypes resistant to disease, and at the
same time new diseases have continued to appear, e.g. the porcine respiratory
coronavirus and the virus of Blue Eared Pig Disease (Porcine Respiratory
and Reproductive Syndrome). No matter how high the standard of husban-
dry, large populations of animals are susceptible to outbreaks of disease in the
same way as individuals are.

Reasons for medication

Treatment and control of disease

In the first instance, it is vital that prompt treatment be given so that af-
fected animals can be returned to full health and productivity. Treatment of
both clinical and subclinical disease will reduce the excretion rate of patho-
gen, many of which have the potential for affecting humans. To maintain
high welfare standards, it is imperative that the farmer should be allowed to
use all legitimate means available to reduce the suffering of affected animals.
With regard to bacterial disease, the scientifically applied strategic use of drugs,
such as antibiotics, will ensure that animals will recover quickly and that meat
can be produced at a price which most families can afford.

Animals are now kept in large numbers and often in large groups because
of the high cost of production. It would be unreasonable and counter-productive
to treat individual animals in these cases. The stress of chasing and catching
each pig in turn, or indeed the herding of pigs in a strawed yard into a
catching pen would cause serious welfare problems which could not be justified. Indeed, it would be 'anti-welfare' to wait until an animal was clinically ill before instituting therapy. Because of these constraints, it is usually necessary to treat pigs and poultry by including medication in the diet. Although some therapeutic agents may be included in the water, the water system in most farms is unsuitable for this form of medication. Water should also be regarded as a nutrient (Brooks et al., 1989), so, by definition, water medication is no different from feed medication in that sense. Nevertheless, watersoluble drugs are usually more expensive to buy and also to use because of waste by the animals, e.g. nipple drinkers. There are no vaccines available for many bacterial and viral pathogens, and in other cases, even when vaccines have been produced, they may not be licensed for use in some countries.

Even minimal disease herds and specific pathogen free herds will have to be given antibiotics from time to time; for example, when the virus of Swine Influenza is spread by wind and enters the herd, secondary bacterial infection will have to be controlled by antibiotics as soon as possible. In-feed medication has also been used in a specific way as part of the medicated early weaning system for setting up minimal disease herds.

**Growth promotional effects**

It has been clearly established that germ-free (GF) animals grow faster than conventionally reared (CR) animals (Coates et al., 1963); and that the inhibitory effect on growth in CR animals is due to the toxic effects of particular bacteria in the gut (see Table 1). The growth rate of CR animals can be increased to almost that of the GF animals by feeding low levels of antibiotics continuously. The increase in food conversion efficiency and better growth

| Activity                        | Effect                                      |
|---------------------------------|---------------------------------------------|
| **Effect on gut wall**          | Increased tissue mass                        |
|                                 | Distortion of absorptive surface             |
|                                 | Reduction in nutrient absorption             |
|                                 | Increased metabolic demand                   |
|                                 | Increased cell renewal                       |
| **Effect on protein metabolism**| Increased ammonia                            |
|                                 | Increased toxic amines                       |
| **Effect on carbohydrate metabolism** | Depletion of glucose                      |
|                                 | Increased lactic acid                        |
|                                 | Increased peristalsis                        |

Adapted from McKinnon (1985).
rate allow production of cheaper meat, as the antibiotics in use are comparatively cheap. The animals, of course, are also healthier.

It is suggested that antimicrobial substances have a growth promotional effect through their actions on enteric bacteria by one or more of the following mechanisms (McKinnon, 1985): (1) reduced production of harmful bacterial metabolites; (2) suppression of potentially pathogenic organisms; (3) suppression of competition for nutrients; (4) alteration in metabolic activity; (5) enhanced intestinal absorptive capacity.

Veterinary aspects

When disease outbreaks occur in large intensive units, the veterinary practitioner has to act quickly in the interests of animal welfare. In many instances, he or she will not be able to wait while time-consuming laboratory tests confirm the diagnosis or establish the most suitable antibiotic to use. The choice of drugs will depend on the practitioner's experience of the farm, the nature of the disease, the record of the drug, and its cost and availability. It will first be necessary to establish if the medicament can be legally added. There is now legislation in force which states that 'a medicinal product may only be incorporated into animal feed in accordance with a product licence, an animal test certificate or a veterinary written directive'. In addition, in the UK, those incorporating medicinal products into animal feedstuffs must be registered with the Pharmaceutical Society of Great Britain, and this includes farm mill and mixers as well as compounders. In the UK, the veterinarian has therefore to establish that the drug he or she wishes to use is licensed for use and that the farmer is registered with the Pharmaceutical Society should he or she be a home mixer. The latter ruling may be waived in an emergency, but this would only be regarded as a one-off situation. However, even if these criteria can be fulfilled, the practitioner must ensure that the drug can be administered and deployed in such a way that no residues in meat will occur. Instructions for the use of each licensed drug are given in a data sheet which accompanies the drug. When in-feed use of the drug is intended, the data sheet will provide information on the inclusion rate, e.g. \( x \) g of drug per tonne of finished feed. However, an inclusion rate is not a dose rate (\( x \) mg of drug kg\(^{-1}\) liveweight) and, in many instances, if the directions in the data sheet were adhered to, the animals would be under-dosed. Examples include newly weaned pigs with poor feed intake and pregnant sows on a restricted diet. The practitioner must therefore assess the average food intake of each group of pigs before issuing a veterinary written directive. The practitioner is allowed to alter the official inclusion rate if it is required in the interests of animal welfare, but in this case all responsibility for drug failure, toxic reactions, etc., automatically falls on the practitioner's shoulders. Each licensed drug has a
stated withdrawal period before slaughter and this should ensure that no resi-

dues can occur.

Farmers are now legally required to keep records of animal medicines ad-

ministered to their stock and to keep records of slaughtered stock. The follow-
ing information must be recorded: (1) date of purchase of veterinary medi-
cine; (2) name of veterinary medicine and quantity purchased; (3) supplier
of veterinary medicine; (4) number and identity of animals treated; (5) date

treatment finished; (6) total quantity of veterinary medicine used; (7) name
of person who administered veterinary medicine. There are other regulations
relating to the storage of medicines, storage of medicated feedingstuffs and
mill flushing procedures. The aim of this legislation is to minimise the possi-
bility of drug residues occurring in meat.

Finally, the practitioner must have a sound knowledge of pharmacology
and pharmokinetics if he or she is to prescribe successfully the correct medi-
cation. For example, some penicillins are destroyed by pelleting whereas oth-
ers are destroyed by the acid in the stomach. On the whole, veterinary written
directives are not issued indiscriminately or indeed on request of the farmer.
Medication regimes are never continuous for several reasons. A veterinary
written directive can only be issued to cover a period of 30 days at the most.
The cost of continuous medication would be prohibitive in most cases and it
would not be in the interests of good veterinary practice. Once a disease has
been controlled, other methods of prevention are usually examined, e.g. re-
duction in stocking density or alteration of the management system. On oc-
casions, the veterinarian will be aware that certain diseases are likely to arise
from time to time and it is only by strategic pre-emptive or preventive medi-
cation that these can be controlled. A good example is Porcine Intestinal Ad-
renomatosis, the causal bacterium of which is present in most herds irrespec-
tive whether they are minimal disease or otherwise.

Potential hazards and consumer fears

The report of the joint committee on the use of antibiotics in animal hus-
bandry and veterinary medicine (the Swann report (Anon., 1979)) sug-

gested that growth promoting antibiotics should not be used for the control
of treatment of disease and therapeutic antibiotics should not be used for
growth promotion. One of the reasons for this demarcation was based on the
fallacious misconception that low-level use of antibiotics selected resistant
strains of bacteria which were capable of transferring this resistance to other
bacteria. Transference of resistance does occur. However, to select resistant
strains from a bacterial population, one has to apply some form of inhibitory
pressure, to allow the recognition of resistant variants, and such inhibitory
pressure can only be applied by therapeutic concentrations of antibiotics
(Walton, 1988), i.e. the minimal inhibitory concentration of an antibiotic must be exceeded to select resistant strains.

Shearer (1990), discussing fears related to human health, stated that there were four main areas of concern. First, there was a fear that people might become sensitised to drugs and develop allergies on exposure to drug residues in food. However, whether drugs at typical residue levels (usually sub-parts per million) could cause such an effect is unclear. A second fear related to the possibility of residues of drugs which have carcinogenic properties. These drugs include the stilbenes, such as diethyl stilboestrol, hexoestrol and dien-oestrol, which are now banned substances. Other drugs with carcinogenic properties and still licensed for use in some countries include carbadox and olaquindox (not in the UK). The third area of concern related to the interference in trade between countries in which the laws are different, e.g. the EEC ban on meat from the USA because of the use of hormones in that country. Finally, the most common cause of concern related to the possible emergence of resistant strains of bacteria and the appearance of such strains in the human food chain or the transference of such resistance to bacteria commonly found in humans. This has led to the fear of disease in humans which could not be treated by antibiotics. However, the results of two large studies in the USA, one large study in Europe and another in the UK indicated that, in general, antibiotic resistance was not increasing (Walton, 1988). Indeed, there was no evidence forthcoming to show that there was a linkage between bacterial antibiotic resistance in man and antibiotics commonly used in agriculture. Hindsight suggests that antibiotic resistance problems in man are the direct result of use of antibiotics in man or perhaps even the misuse of antibiotics in man. The question of bacteria in animals, resistant to antibiotics, infecting man and causing untreatable disease is often raised. Fortunately, the majority of animal bacteria are incapable of colonising the tissues of man. Nevertheless, some can and do, e.g. some Campylobacter species and Salmonella species. Certain phage types of Salmonella typhimurium have become selected, not by antibiotic use, but by calf marketing networks, which leads to a mobile population of infected and non-infected susceptible animals which have been moved and mixed on several occasions (Sojka et al., 1986). These salmonellae may transfer genes for multiple resistance and do occasionally infect humans because of errors in food handling, plant failure and personal hygiene. Multiple antibiotic resistance in bacteria can be readily controlled by applying a suitable prescribing policy by which antibiotics are rotated and certain antibiotics are kept for serious systemic bacterial infections (Walton, 1988).

The fear of tissue residues is a real one and must not be glossed over. The indiscriminate use of oestrogens in cattle caused high tissue residues and resulted in the abnormal development of certain tissues in human babies in Italy. However, the likelihood of in-feed therapeutic antibiotics resulting in
tissue residues in the UK is very low. Legislation is now in force which makes it an offence to sell or present for sale animals containing residues of antibiotic above permitted maximum tolerance levels. Testing methodology and techniques have now become so sophisticated that levels of less than 0.1 ppm can be detected. The maximum permitted level of sulphonamide residues is 0.1 ppm and this level is 2000 times the human safety factor. A recent government survey has shown that tissue levels of antibiotic residues have steadily fallen, but there is still a problem with positive sulphonamide residues, which remain around the 5% level in samples examined. This is disappointing, but the fault does not always lie with the farmer or veterinary surgeon. In the first instance, occasional positives may arise as a result of unusual circumstances affecting the individual in a population. For example, a low metabolic rate, or damaged kidneys or liver, or variation in the proportion of different tissues in the same species can occur.

Problems may arise during the manufacture of drugs, and these include the following: (1) isomers which are non-therapeutic but would test positive for residues may be created; (2) the stability of drugs in feed or in the alimentary canal may be affected by drug particle size (e.g. procaine penicillin).

Mill factors include the following: (1) the wrong inclusion rate may be used—this has led to poisoning in some cases; (2) the drug may not be dispersed uniformly throughout the feed; (3) the drug may be altered by the manufacturing process, e.g. conditioning and pelleting; (4) the drug may be altered by certain dietary constituents; (5) cross-contamination may occur in the mill (this is very difficult to avoid in spite of a strict code of conduct adhered to by all compounders and mixers; not only may the medicated feed become stuck temporarily in a nook or crevice but the electrostatic properties of some drug formulations make it extremely difficult to clean the plant).

On-farm factors include the following: (1) medicated feed may be delivered to the wrong bin; (2) the drug may have been added at the wrong inclusion rate; (3) wet mixers are not suitable for high concentrations of insoluble premix; (4) recycling of drugs from pig to pig via common dunging passages can occur; (5) bacteria in dung can convert metabolites of the drug back into its active principle; (6) there may be failure to clean hoppers and pipelines after medicated feed is used; (7) deliberate contamination by an aggrieved worker is also a possibility.

Post-farm factors include the following: (1) contamination may occur in a lorry which has not been washed properly; (2) contamination may occur in the abattoir, e.g. 2 ppm of a sulphonamide in the environment can lead to positive drug residues in meat 7–24 h after consumption (McCaughey et al., 1990).

False positives may recur as a result of the following errors: (1) pigs may be wrongly identified at the abattoir; (2) true false positives may occur as a result of laboratory error; (3) samples may be mixed up after collection.
The use of drugs on the farm is strictly controlled by legislation and it is the duty of the veterinary surgeon to ensure that the farmer observes withdrawal periods. Growth-promoting antibiotics have to be licensed for use and are fed at such low levels that no withdrawal periods are necessary.

Conclusion

The use of antibiotics in food animal husbandry is strictly controlled and monitored by both the Ministry of Agriculture, Fisheries and Food and by British Pharmaceutical Society personnel. All the evidence would suggest that food and milk produced from farm animals is perfectly safe for human consumption and should remain so.

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