

Review Article

Review on Rational Use of Veterinary Antimicrobials and Anthelmintics

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A systematic review was conducted to assess the rational use of veterinary antimicrobials and anthelmintics. Veterinary drugs are used as therapeutic, prophylactic and growth promotion, and can be used in either rational or irrational way. Rational use of drugs means the sick animals receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community. Irrational drug uses are characterized by over-prescription, inappropriate dosage, incorrect duration and unnecessary risk. This irrational activity of antimicrobial use results antimicrobial resistance which is the current global health threat. The review shows problems in generic prescribing, incorrect diagnosis, and non-availability of standard veterinary treatment guideline and drug formulary especially in developing countries. Therefore, veterinary drugs, especially, antimicrobial agents should be judiciously used; and a wide scale study to safeguard the public from drug residual effects and antimicrobial resistance development is recommended.

Keywords: Anthelmintics; Antimicrobials; Review; Rational use; Veterinary**Introduction**

Veterinary drugs are used as therapeutic, prophylactic and growth promotion, and can be used in either rational or irrational way. Rational use of drugs is based on the use of right drug, right dosage and right cost which is well reflected in the world health organization (WHO) definition: "Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, at the lowest cost to them and their community" [1]. The irrational use of drugs is a problem, and to manage it the World Health Organization (WHO) convened an international conference in Nairobi, Kenya, in 1985 to develop useful guidelines [1,2].

Now, in the clinical practice of human and veterinary medicine throughout the world large amount of antibiotics are used. Equally, many scientists intensively work on discovery and synthesis of new drugs with broader antimicrobial spectrum, stronger action and more satisfactory safety profile. Most failures during antimicrobial therapy may occur when the pathogenic microorganism is unknown and combination of two or more drugs administered empirically. To avoid these mistakes, clinically confirmed, effective antimicrobial combinations should be used [3]. Globally, more than half of all medicines are prescribed, dispensed or sold improperly, and 50% of human patients fail to take them correctly. This is more wasteful, expensive and dangerous, both to the health of the individual patient and to the population as a whole that magnifies the problem of misuse of antimicrobial agents [4].

Improper use of drugs may cause ineffective treatment, unnecessary wastage of resources, and may harm the patient [5]. Irrational use of drugs in veterinary medicine as well as the need for control of their use becomes even bigger problem when used on food

producing animals. In this case, there is the possibility that minimal quantities of drugs and their metabolites (residues) which remain in edible tissues or in animal products (meat, milk, eggs, honey) induce certain harmful effects in humans as potential consumers of such food [6]. When drugs are used to improve the productivity of food animals that are intended for human consumption, then there is possibility for producing adverse effects on humans. To prevent this risk, it is necessary to use drugs rationally, i.e., to use them only when they are really indicated, in the right way, at the right time, in the right dose and respecting withdrawal period. Also, it is necessary to regularly control sensitivity to antimicrobial agents and regulate residue of antimicrobial agents commonly used in veterinary practice [3,7].

Rational approach to therapeutics requires careful evaluation of the health problem in each species of animals and selecting appropriate therapeutic strategies [8,9]. Selection of treatment requires cost/benefit analysis particularly in food animals. Its efficacy, safety with minimal adverse effects and minimal residues in food animals should be also given due attention. Drug choice depends on individual patient and prescription; whenever written it should indicate species of animal, the age, sometimes breed, the dose of the drug in the formulations available locally and the duration of treatment [5,8]. Advice on nutritional support and nursing care are also very important to ensure rational therapeutics [8].

Over use of antimicrobials [10] and anthelmintics [11] in veterinary practice, for both food producing and companion animals, favors the development of both intrinsic or acquired antimicrobial and anthelmintic resistance. Acquired resistance develops due to widespread and irrational use of drugs while intrinsic resistance is a result of inherent structural or functional characteristics, which allows tolerance of a particular drug or antimicrobial class. Antimicrobial/anthelmintic drug resistance is a growing problem; and indeed

developing new drugs may not be the solution for this problem. Some of the common causes that contribute to the development of antimicrobial resistance are unnecessary use of antimicrobial drugs, inappropriate dose, inadequate duration of therapy, use of irrational antimicrobial fixed dose drug combinations [12].

In humans, assessments of drug use patterns with the WHO drug use indicators are becoming increasingly necessary to promote rational drug use. These indicators are now widely accepted as a global standard for problem identification and have been used in developing countries [13,14]. In Ethiopia, a survey conducted on human subjects at hospitals located in different regions of the country revealed the presence of irrational drug use [15-17]. Similarly, in veterinary medicine, a study conducted on rational use of veterinary drugs at veterinary teaching hospital of the college of veterinary medicine and agriculture, and Ada district veterinary clinic showed irrational drug use [18].

- Therefore, the objectives of this study to review rational and irrational use of veterinary antimicrobials.
- To outline magnitudes of different drugs commonly used for the treatment of animal diseases in different parts of the world.

Literature Review

Uses of veterinary drugs

Drugs in animals can be used as in therapeutic, prophylactic, growth promotion and other uses. Therapeutic use refers to the treatment of established infections whereas prophylaxis is the use of drugs in either individual or groups to prevent the development of infections. Both therapeutic and prophylactic uses involve administrations of drugs by different routes at therapeutic levels for short period of time [19]. The use of antimicrobials as feed supplements can promote the growth of food animals and also enhance feed efficiency [20-22].

Therapeutic and prophylactic: Most drugs, around 60%, are used for therapeutic purposes in humans, although an increasing amount is administered as prophylaxis to prevent infection, the farming industry is the second largest consumers of antimicrobials after humans. Depending on action, prophylactic and therapeutic drugs may be divided into different groups. The most widely distributed drugs are antimicrobials, antiparasitic and antimycotic preparations and their use in prevention and treatment of animal diseases [23]. Veterinary drug products licensed for use throughout the world do not vary greatly from country to country, although the level of use, withdrawal times accepted safe level in food do change from country to country in almost all cases. Depending on the requirements in different countries, feedstuffs containing veterinary drugs may be available only on the prescription of a veterinarian or they may be freely available. In most circumstances, if recommended withdrawal periods are observed, the presence of unacceptable residues is not expected [24].

The choice of antimicrobial drugs to use for the treatment of animal diseases caused by an infectious agent should be in line with the guidelines as it aids in decision making process. The gold standard for this determination is the result of microbiological culture. However, strict application of this standard is unrealistic because

the decision to use antimicrobial drugs is made several days before culture data are available. Therefore, as an aid in determining that a particular process has infectious component, certain clues are used. The infectious control committee at veterinary medical teaching hospital, university of California has drawn up guidelines for rational use of antimicrobial drugs which are: demonstrations of an infectious agent; clinical data (at least two of the following): fever; leukocytosis; localized inflammation and radiographic evidence. The whole purpose of the exercise is to know whether there is an infectious agent present or the best antimicrobial drugs to be used [19].

Growth promoters (GPs): Growth promoters are any antimicrobial agents administered at low or sub therapeutic dose and destroys or inhibits growth of microbes as infectious agents reduce the yields of food animals [25]. Antibiotic GPs are used to help growing animals by increasing the rate of weight gain and to improve feed conversion efficiency, and get maximum benefit from it and allow them to develop into strong and healthy individual [22,26].

Although the mechanism underlining their action is unclear, it is believed that the antibiotic suppresses sensitive populations of bacteria in the intestines. It has been estimated that as much as 6% of the net energy in the pig diet could be lost due to microbial fermentation in the intestine. If the microbial population could be controlled, it is possible that the lost energy could be diverted to growth [26]. It is also hypothesized that cytokines released during immune response as a result of bacterial infection may stimulate the response of catabolic hormones, which could reduce muscle mass. Therefore, a reduction in gastro intestinal tract (GIT) infections would result in the subsequent increase in muscle weight. Whatever the mechanism of action, the result of the use of GPs are resulting in meat of better quality, with less fat and increased protein content [25]. There can be no doubt that GPs are effective; however, the effects of GPs are more noticeable in sick animals and those housed and confined, and unhygienic conditions [27]. The use of GP is largely a problem of intensive farming methods and the problems caused by their use are largely those of developed rather than developing countries [25].

Preservation and processing of food: In preservation and processing, food additives are added to prevent the onset of spoilage, to promote the binding properties and to enhance flavor and nutritive value. These additives include antioxidants, sequestrants, coloring agents, stabilizers, sweeteners, tenderizers, etc. At both production and processing stages, residues or contaminants may enter the food chain from intentional exposure to these chemicals [28].

Pre slaughter control of stress in abattoir: Certain neuroleptic drugs (tranquilizers) are administered to avoid excitement of animal or to curb aggressive behavior. The misuse of such drugs and some beta-adrenergic blocking are used to reduce the stress of transportations to the slaughter house raises concern from the view point of consumer protection. Residues of drugs given for these purpose will remain at a high level in edible tissues, since animals are slaughtered shortly after the drug is administered and while the concentration of the drug remains at therapeutically effective levels [29].

Control of reproduction: Prostaglandins and their analogs and sex steroids are used to regulate fertility and breeding programmes. Glucocorticoids and prostaglandins are used as abortifacients or to

control timing of parturition. Animals would not be slaughtered shortly after the treatment and residue problem in meat could only occur in the event of causality meat slaughter [29].

Ways of veterinary drug use

Rational veterinary drug use: Rational use of medicines in veterinary science is defined as that sick animal should receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them [30]. These requirements will be fulfilled if the process of prescribing is appropriately followed. This includes: steps in defining patients problems (or diagnosis); in defining effective and safe treatments (drugs and non-drugs); in selecting appropriate drugs, dosage and duration; in writing a prescription; in giving patients adequate information; in planning to evaluate treatment responses [31].

Irrational veterinary drug use: Irrational drug use or inappropriate drug uses are characterized by over-prescription (prescribing drug when none are needed clinically), omission (when required drugs for conditions are not prescribed), the use of inappropriate dosage (too high or too low), incorrect duration (too short or too long), incorrect selection (mismatch between organism) and unnecessary risk (use of injection or intravenous antibiotic when oral forms would be suitable) [32]. The irrational drug use causes a particular concern for the development of resistance. Antimicrobial drug is now becoming a major problem both in veterinary and human medicine as consequence of the intensive use and misuse of antimicrobial drugs [33]. There is a wide spread misuse of permitted drugs which result in unwanted residues in foods of animal origin. Also, there has been wide spread failure to observe the recommended withdrawal and withholding period for antimicrobial agents [34].

Reason for irrational use of drugs: There are several reasons which may contribute to irrational use of drugs. These are: lack of information; faulty and inadequate training and education of medical and/or veterinary graduates; poor communication between health professional and animal owner; lack of diagnostic facilities/uncertainty of diagnosis; demand from the owner (to satisfy the patient expectations and demand of quick relief, clinicians prescribe drugs for every single complaint). Also, there is a belief that 'every ill has a pill'. All these increase the tendency of poly-pharmacy, defective drug supply system and ineffective drug regulation (absence of well-organized drug regulatory authority and presence of large numbers of drugs in the market leads to irrational use of drugs) and promotional activities of pharmaceutical industries (the lucrative promotional programmes of the various pharmaceutical industries influence the drug prescribing) [32,35].

Impacts of irrational use of drugs: Irrational use of drugs can have a negative impact on the public health, some of them are as follows: reduction in the quality of drug therapy (limited efficacy) leading to increased morbidity and mortality; increase risk of unwanted effects such as adverse drug reactions and the emergence of drug resistance due to widespread overuse of antibiotics as well as their use in under-therapeutic dosage; waste of resources leads to reduced availability of other vital drugs and increased costs and adverse, possibly lethal effects, for example due to antibiotic misuse or inappropriate use of drugs in self-medication [32]; psychosocial

impact, such as when patients come to believe that there is 'a pill for every ill', which may cause an apparent increased demand for drugs [36].

Significance of rational veterinary drug use

Rational use of drugs in veterinary medicine has both public health [37] and economic significances [23].

Public health significance: No significant reported episodes of adverse human health effects occurring in food when the veterinary drugs were used at the correct dosages and at the levels permitted [37].

Improve food safety concern: When drugs indicated rationally, the potential adverse effects of their use as a result of consumption of animal products are reduced and their efficacy increased. However, in non-rational use of drugs in veterinary medicine, mainly when used on food producing animals, there is the possibility that minimal quantities of drugs and their metabolites (residues) which remain in animal products (meat, milk, eggs and honey) and induce certain harmful effects in people as potential consumers of such food [3].

Reduce the development of drug resistance: Human health can be affected by a widespread of antibiotic resistance pathogens, as it is occurring due to extensive overuse of antibiotics, as well as their use in under-therapeutic dosage [32]. Resistant microorganism can get access to human either through direct contact or indirectly via meat, milk, egg. As the bacteria, the endogenous flora of food animal, contaminate food of animal origin, might either colonize human or transfer resistant gene to humans endogenous flora or super impose an additional load to the reservoir of resistant genes already present in man [38].

The use of antibiotics in food animal can result in antibiotic resistance bacteria reaching the human population through variety of routes. Antimicrobial resistant bacteria such as *Escherichia coli* can colonize intestines of heavily exposed humans (farmers, who used food containing antibiotics, slaughter house workers, cooks and other food handlers) often have a higher incidence of resistant *E.coli* in their feces than the general population. Contaminated meat by intestinal bacteria at slaughter is extensive and an important route by which resistant bacteria reaches people. While many bacteria are nonpathogenic, some pathogenic bacteria species from the intestines of animals causes zoonotic infection to humans such as *Salmonella* species, *Campylobacter jejuni* and this infection may be harder to treat because it is acquired by humans and are a potential source of resistance plasmids for human pathogenic bacteria other than zoonotic infection [19]. Rational use of drugs can also significantly minimize the risk of microorganisms' resistance development (in case of antimicrobials). Hence, no significant reported episodes of adverse human health effects occurring in food when the veterinary drugs were used at the correct dosages and at the levels [37].

Reduce the development of drug residue: Veterinary drug residues are one of the major problems for food contamination. Human health can be affected through residues of drugs in food of animal origin, which may cause direct side effects. In general, the effect of antibiotic residue in food of animal origin is significant when compared with the antibiotic misuse or selection and amplification of antibiotics resistant strain of bacteria [25].

Food animal origin such as meat, milk and eggs intended for human consumption, may have some residual amounts of veterinary drugs which remains in edible tissues after harvest. In some countries where legislative directions are followed by the farmer/producer, drug residue level will be within safe limits. In a relatively few cases, however, levels of residue exceed permitted maximum limits. This is attributed to the improper/irrational drug use and as such, it is not legally allowed into the food system [39]. Generally, there are no significant reported episodes of adverse human health effects occurring in food when the veterinary drugs were used at the correct dosages and at the levels permitted [37].

Economic significance: A wide spread availability and use of antimicrobials have several negative implications on global health care: among these developments of drug resistance is one. The primary economic implications of resistance on the diminishing efficacy of antibiotic treatment includes the need to rely on more expensive drugs that may be practically unaffordable for most primary health care programs [23]. Antimicrobial residue remains very significant from the prospective of international trade and consumer confidence, because it results in international trade barrier. As tariffs are removed and goods flow freely between countries, importing countries must be in confident that goods available for purchase are safe, and in addition to this, from time to time, there is pressure to use antimicrobial residues on non-tariffs barrier to importation [20]. Major economic loses and animal welfare problems could arise in veterinary medicine, because antimicrobial resistance has been found to cause therapy failure and higher mortality and morbidity rate [40,41].

Measures to promote the rational veterinary drug use

To avoid entering a post antibiotic era, agents around the world are determining the use and abuse of antimicrobials. To reduce the risk of selecting resistant bacteria, the use of antibiotics must be restricted. Thus, the most attractive area for reducing the use of antibiotics is to ban their use as growth promoters. Some of the measures that reduce the irrational (promote rational) drug use are as follows [23].

Herd health management: All food animals should be maintained in a clean healthy environment whenever possible. A nutritional program should in effect meet growth, maintenance and lactation needs. The veterinarian should implement a health program that encompasses preventive medical procedures. Drug misuse or irrationality are best avoided by implementing management practices and health programs that keeps animals healthy and producing efficiently [42,43].

Alternatives for antimicrobials growth promoters: Essentially, there are many ways by which we can reduce our dependence on antibiotic use in animals. Developing an alternative to antibiotics that work via similar mechanisms, promoting growth whilst enhancing the feed conversion efficiency, is the best option. A more difficult route would be to improve animal health. Growth promoters have been shown to perform best when the condition is worst, that is when animal is in poor health and the living conditions are unhygienic; if their local environment is improved with overcrowded reduced and injection control technic is introduced, then the actual need for growth promoter may be removed [27].

Competitive exclusion products: These are in feed microbes

consisting of a variety of species of bacteria that are marketed as being friendly. The mechanism of action is believed to be that, by allowing bacteria to colonize the GIT, potential pathogens are prevented from colonizing the gut and thus causing infection. These products are often administered to new born animals, especially poultry, to colonize the GIT and prevent *Salmonella* and *Campylobacter* infections. It is not known how the treatment is but it is believed to reduce diarrhea and level of mortality. These products are also given to animals that have been treated with therapeutic antibiotics, to recolonize a gut that may be depopulated by antimicrobial action of the drug [25].

Probiotics: Probiotics are a term used for products containing 'beneficial' microorganism. Most contain either *Lactobacillus* species (primarily *L. acidophilus*) or *Streptococcus faecium*. Additionally, they may contain vitamins, trace minerals and various growth factors [44].

Probiotics are similar to exclusion products. They are believed to improve the overall health of an animal by improving the microbial balance in its gut. It has been hypothesized that their action can be summarized in three ways. The first is reiteration of competitive exclusion principle by colonizing the gut in large number; the probiotic bacteria exclude pathogens and thus prevent them from causing infection. The second possibility is that they act as a stimulus for the immune system. As the immune system is engaged following exposure to probiotic bacteria; any hostile bacteria are also noticed. Following increased surveillance by leukocytes and thus potential pathogens are eliminated. The third suggestion proposes that probiotics have strong, positive influence on intestinal metabolic activities, such as increased production of vitamin B12, bacteriocins and propionic acid [25].

Prebiotics: Prebiotics are defined as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon [45]. In other words, prebiotics are meant to provide a substrate for beneficial GIT microbes. Large amounts of bacteria present in the mono-gastric small intestine and are potentially capable of utilizing these indigestible carbohydrate sources for energy. Some researches [46,47] have been conducted to manipulate beneficial bacteria in GIT. The use of prebiotics is promising approach for enhancing the role of endogenous beneficial organisms in the gut [48]. They can be used as potential alternatives to growth promoting antibiotics [49]. The use of prebiotics or fermentable sugars instead of antibiotics is going to be popular in birds in order to improve the useful microbial population of the GIT [50].

In feed enzymes: Enzymes are routinely added to animal feeds and work by helping to break down certain components of the feed that the animal may have problems in digesting. They are produced by fermentation processes from fungi and bacteria and seen to only have a positive effect on the animal. The scientific committee for animal nutrition concludes that conditions of use evaluated so far are acceptable as respected to consumers, users and animals [25].

Infectious control mechanism: The use of antimicrobial as growth promoting agent rests on their role in controlling infection in growing animals. Similarly, many of the alternatives are aimed at controlling infection, often indirectly. For instance, the Australian pig farming pioneered the 'all in-all out' method of pig production.

This is a new system used to replace the older technique of having constant system of pig 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 cohort and so cross infection between groups are prevented. The 'Specific Pathogen Free' system is used to prevent pigs from acquiring many of the disease that require antibiotic intervention. 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 [25].

Adhering to withdrawal period: Depending on the drug product, dosage form, and route of administration, the withdrawal time may vary from a few hours to several days or weeks. It is the interval necessary between the last administration to the animals of the drug under normal condition of use and the time when treated animal can be slaughtered or the production of safe foodstuffs [20]. To ensure that drug residues have declined to a safe concentration following the use of drugs in animals, a specified period of drug withdrawal must be observed prior to providing any products for human consumption. Drug withdrawal time is the time required for drug residues to reach a safe concentration for human or animal consumption, and defined as maximum residual limit (MRL). Failure to follow recommended withdrawal time is often implicated in residual problems [51]. It is advisable to follow recommended withdrawal time to avoid residual effects of drugs in the food of animal origin; that is, we have to check and observe the withdrawal period laid down for the particular medicine and food animals should not be sold for slaughter, or slaughtered before the end of withdrawal period [28].

Minimizing misuse of antimicrobial: This is achieved by different strategies. These are: educations of prescribers and dispensers (including drug sellers); education of the farmers to create awareness; limiting the availability of antimicrobials to prescription; ensuring that only antimicrobials meeting international standards of quality, safety and efficiency are granted marketing authorization; establishing and maintaining updated national standard treatment guidelines; developing guidelines for veterinarians to reduce overuse and misuse of antimicrobial in food animals and enhancing immunization coverage and other preventive measures, thereby reducing the need for antimicrobial [28]. WHO came out with twelve core interventions to promote more rational use of drugs. Some of them are: public education about medicines; clinical guidelines; appropriate and enforced regulations; supervision, audit and feedback; independent information on medicines and problem based pharmacotherapy training in undergraduate curriculum [52].

Conclusion

Veterinary drugs are used as therapeutic, prophylactic and growth promotion, and can be used in either rational or irrational way. Rational use of drugs in veterinary medicine has numerous benefits, such as increasing efficacy, decreasing the potential adverse effects, reducing risk of drug residue and combating development of microorganism's drug resistance. According to the review, things which aggravates irrational veterinary drug use are: incorrect diagnosis and drug administration of diseases, lack of laboratory

tests, low prescribers, educational status, lack of standard veterinary treatment guide lines, presence of few essential drugs and absence of standard case paper which has to contain all necessary information of routine clinical examination and treatments.

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