Journal of Veterinary Science & Medical Diagnosis

Review Article A SCITECHNOL JOURNAL

Review on Effect of Antimicrobial Residual on Human

Debeb Dessie *

Department of Veterinary Medicine, Addis Ababa University, Addis Ababa, Ethiopia

***Corresponding author:** Debeb Dessie, Department of Veterinary Medicine, Addis Ababa University, Addis Ababa, Ethiopia,E-mail: dessievet@gmail.com

Received date: October 21, 2021; **Accepted date:** November 05, 2021; **Published date:** November 12, 2021

Abstract

Human beings consume protein-rich foods, mainly of animal origin (milk, meat, and eggs), to fulfill their nutritional requirements, and their health has been associated with the nature and quality of the food consumed. Nevertheless, the quality of animal-based products is of great concern with regard to consumer health globally. Veterinary drug" means any substance or mixture of substances are essential for treatment of diseases (therapeutic), prevention of diseases (prophylaxis), modification of physiological functions (such as tranquilizers, anesthetic drugs), improvement of growth and productivity (growth promoters) as well as for ensuring food safety or restoring, correcting or modifying any physical, mental or organic function in an animal. However, the benefits of drug administration to farm animals used for food production are also accompanied by the risks associated with drug residues in the edible parts of treated animals. Residues are defined as chemical substances or metabolites of medicinal products that may accumulate within the tissues or edible parts of treated animals. These residues may result from failure to observe the proper withholding period following treatment, failure to maintain treatment records, overdose, or using prohibited drugs for economic animal treatment. Contaminated animal feedstuffs also act as an important source of drug residues. Age of animal, disease statuse, Extra-label drug use and Improper Withdrawal Time are the major risk factor for drug residues. The major potential effect of veterinary drug residues on public health are development of drug resistance, hypersensitive reaction, mutagenicity, tratogencity, carcinogrnic disruputioe of intstinal micro flora and microbial drug resistance.

Keywords: Antimicrobial; Risk on public health; Residue

Introduction

Human beings consume protein-rich foods, mainly of animal origin (milk, meat, and eggs), to fulfill their nutritional requirements, and their health has been associated with the nature and quality of the food consumed. Nevertheless, the quality of animal-based products is of great concern with regard to consumer health globally. "Veterinary drug" means any substance or mixture of substances are essential for treatment of diseases (therapeutic), prevention of diseases (prophylaxis), modification of physiological functions (such as tranquilizers, anesthetic drugs), improvement of growth and productivity (growth promoters) as well as for ensuring food safety or restoring, correcting or modifying any physical, mental or organic function in an animal [1] . However, the benefits of drug administration to farm animals used for food production are also accompanied by the risks associated with drug residues in the edible parts of treated animals. The veterinary drugs are used throughout the world and they comprise a broad variety of classes of chemical compounds including vaccines, antimicrobials, antiparasitics and β-agonists.

From which Antimicrobials are the most important and most frequently used group of veterinary drugs. Antimicrobials are medicine (natural, synthetic or semi-synthetic origin) that inhibits the growth of or destroys microorganisms when applied at low concentrations without causing host damage. Among the antimicrobials that are commonly used in livestock production are tetracyclines, amprolium, penicillin, streptomycin, sulphonamides, tylosin, aminoglycosides, β-lactams, macrolides and lincosamides, quinolones and sulfonamides. While that of antiparasitic agents include anthelmintics or coccidiostats, stilbenes, amphenicols, nitrofurans, nitroimidazoles, carbamates, pyrethroids and sedatives. Therefore, veterinary drug residues have been considered as a global food contamination challenge. Residues are defined as chemical substances or metabolites of medicinal products that may accumulate within the tissues or edible parts of treated animals. These residues may result from inappropriate or extra-label drug usage, failure to maintain drug withdrawal periods, or poor livestock production practices.

The treated animals may rapidly and efficiently metabolize some drugs while slowly and poorly metabolizing others; thus, the residues accumulate in the edible portion of the animals. Subsequently, consumers are exposed to these residues, resulting in health hazards. Many livestock producers treat their animals by themselves. Even if they use the same drugs as veterinarians, they have little understanding of the conditions and quantities to administer or the waiting periods. The uncontrolled use of anti-infectious agents can lead to residues in animal products, especially when users fail to respect waiting periods. The risks of residues in foodstuffs of animal origin could be reflected into several forms. The immediate effect of antimicrobial residue is allergenicity and toxicity in human through the food chain.

The long-term health adverse effects such as increased likelihood include disruption of normal human flora in the intestine (microbiological effects), carcinogenicity, and teratogenicity. Other drug residue problems are the development of antibiotic-resistant microbes and drug misuse. Different cooking procedures, temperatures, and storage times, as well as the fermentation processes, have the potential to reduce veterinary drug residues. Hence the objective of this paper is to review the potential sources of veterinary drug residues and their effects on the health of the public and highlight prevention, control, and reduction measures of drug residues in food producing animals.

Literature Review

Sources of veterinary drug residues

Veterinary drugs are generally used in farm animals for therapeutic and prophylactic purposes and they include a large number of different types of compounds which can be administered in the feed or in the

drinking water [2]. The great majority of residues found in edible tissues of animals have their source at the farm of origin. In some cases, the residues may proceed from contaminated animal feedstuffs. By far the most common cause of residues is the failure to observe the proper withholding period following treatment, failure to maintain treatment records, overdose, or using prohibited drugs for economic animal treatment. Contaminated animal feedstuffs also act as an important source of drug residues.

Risk factors for drug residue occurrence

Veterinary drug residues are one of the major problems for food contamination. VMPs and agricultural chemicals used according to label directions should not result in residues at slaughter. However, possible reasons for such residues include: Not following recommended label directions or dosage (extra-label usage); not adhering to recommended withdrawal times; administering too large a volume at a single injection site; use of drug-contaminated equipment, or failure to properly clean equipment used to mix or administer drugs; dosing, measuring, or mixing errors; allowing animals access to spilled chemicals or medicated feeds; Congenital, illness, allergies; chemical interactions between drugs; variations in water temperature for fish species; environmental contamination; and improper use of agricultural chemicals such as pesticides .

Veterinary drugs or VMPs residues usually accumulate in the liver or kidney rather than other tissues. It has been noted that different residue levels can be found in different tissue positions such as site and route of administration [3]. He most likely reason for drug residues may result from human management, such as improper usage, including extra-label or illegal drug applications. However, the most obvious reason for unacceptable residues might be due to failure to keep to the withdrawal period including using overdose and long acting drugs. Inadequate good sanitary care during animal or product transportation, including the cross contamination of animal feeding status with inadvertently applied drugs, environmental and animal to animal transfer of drugs may also cause residues.

Age of animal

Weaning status and, to a lesser extent, the age of the animal drug disposition. For instance, the study conducted on comparisons of the pharmacodynamics of norfloxacin nicotinate between weaning and unweaned calves revealed that the distribution of the drug did not differ between the two groups of calves, but the total body clearance time was increased in weaned calves, possibly due to increased weight from the presence of rumen fluid. Calves fed grain had shorter clearance times (approximately four days) for sulfamethazine than unweaned calves. He elimination half-life of tindazole is shorter in unweaned calves than in adult cows, while the elimination half-life of apramycin is longer in calves than in adult cattle, possibly due to the immaturity of the drug clearance system.

Disease status

The disease status of an animal can affect the pharmacokinetics of drugs administered, which can influence the potential for residues. This can occur either when the disease affects the metabolic system (and consequently drug metabolism), or when the presence of infection and/or inflammation causes the drug to accumulate in affected tissues. For example, cattle with acutely inflamed mastitis quarters, apramycin penetrates these areas of the body, and concentrations of the drug have been observed at ten times over the level recorded from cows without mastitis.

Extra-label drug use

Extra-Label Drug Use (ELDU) refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. It occurs when a drug only approved for human use is used in animals, when a drug approved for one species of animal is used in another, when a drug is used to treat a condition for which it was not approved, or the use of drugs at levels in excess of recommended dosages [4]. For instances, the use of enrofloxacin solution as a topical ear medication (Only approved for use as an injection) are the common ELDU in veterinary medicine.

Improper withdrawal time

Improper withdrawal time is another risk factor; the withdrawal time (also known as the depletion or clearance period) is the time required for the residue of toxicological concern to reach a safe concentration as defined by the tolerance. 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 used and the time when treated animal can be slaughtered for the production of safe food status.

Acceptable Daily Intake (ADI) is the amount of substance that can be ingested daily over a lifetime without appreciable health risk. The evaluation of the safety of residues is based on the determination of the ADI on which in turn maximum residues limits (MRL) is based. The ADI is determined by consecutive estimate of a safe ingestion level by the human population on the lowest no effect level of toxicological safety studies. If the drug is not a carcinogen, the no observed effect level (NOEL) of the most sensitive effect in the most sensitive species divided by a safety factor is used to determine an ADI for drug residues. The FDA will calculate the safe concentration for each edible tissue using the ADI, the weight in kg of an average adult (60 kg), and the amount of the product eaten per day in grams as follows; Safe concentration = [ADI (μg/kg/day) × 60 kg]/[Grams consumed/ day].

Maximum residue level: A tolerance level (or maximum residue levels, MRLs) is the maximum allowable level or concentration of a chemical in feed or food at a specified time of slaughter or harvesting, processing, storage and marketing up to the time of consumption by animal or human. The MRL in various foodstuffs (muscle, liver, kidney, fat, milk and eggs) is determined to minimize the risk of consumer exposure, considering dietary intake. Such considerations as food technology, good farming practices and the use of veterinary medicinal products may also be considered when setting the MRL.

Calculating withdrawal period

The withdrawal period is determined when the tolerance limit on the residue concentration is at or below the permissible concentration. Withdrawal times are determined in edible, target tissues [5]. Most commonly, they are liver or kidneys as they are primary organs of elimination and typically display a residue for the longest time. During withdrawal studies, the target organ is determined and animals are sampled at various times after drug administration is stopped. For those drugs for which only a kidney or liver tolerances has been established, if a violative residue is found in the target organ, the whole carcass

would need to be discarded. On the other hand, for the drugs for which a muscle tolerance has been established, even if a violative residue is found in the kidney or liver a violative residue is not found in the muscle, the carcass would not need to be discarded.

Detection methods

Screening of food products from animal origin for the presence of antimicrobial residues started soon after the introduction of antibacterial therapy in veterinary medicine. Initially it mainly concerned process monitoring in the dairy industry to prevent problems in fermentative dairy production, but from the early 1970s regulatory residue screening in slaughter animals also became more commonly introduced. An efficient screening method needs to be low-cost and high-throughput, able to effectively identify potential noncompliant samples from a large set of negative samples. Advantage of these methods is that they have a wide detection spectrum; they are simple to carry out and cheap; and can be used for the screening of a large number of samples; Possibility of automatization; Reduced time to obtain the result; Good sensitivity and specificity and Detection capability with an error probability (b) <5% . This method includes a large variety of detection methods, ranging from physico-chemical analysis or immunological detection to microbiological method.

Immunological Detection

The immunological methods are based on the interaction of antigen-antibody which is very specific for a particular residue. The most usual technique consists in the Enzyme Linked immunosorbent Assay (ELISA) and the detection system is usually based on enzyme-labeled reagents. There are different formats for antigen quantification like the double antibody or sandwich ELISA tests and direct competitive ELISA tests. ELISA kits are allowing the analysis of a large number of samples per kit, do not require sophisticated instrumentation, the results are available in a few hours and are quite specific and sensitive. It has good performance for the analysis of antibiotic residues in meat like tylosin and tetracycline, chloramphenicol, nitroimidazoles and sulphonamides and also for sedatives.

Microbiological detection

Microbial inhibitions assays are very cost-effective and they have the potential to cover the entire antibiotic spectrum within one test. There are two main test formats: the tube test and the (multi-) plate test. A tube (or vial, or ampoule) test consists of a growth medium inoculated with (spores of) a sensitive test bacterium, supplemented with a pH or redox indicator. At the appropriate temperature, the bacteria start to grow and produce acid, which will cause a color change. The presence of antimicrobial residues will prevent or delay bacterial growth, and thus is indicated by the absence or delay of the color change. This format is commonly applied in routine screening of milk, but it is also increasingly used for analysis of other matrices. A plate test consists of a layer of inoculated nutrient agar, with samples applied on top of the layer, or in wells in the agar. Bacterial growth will turn the agar into an opaque layer, which yields a clear growth-inhibited area around the sample if it contains antimicrobial substances.

Biosensors

Different types of biosensors have been developed in recent years as an alternative approach to screen veterinary drugs in meat. In general, these sensors usually contain an antibody as a recognition element that interacts with the analyte. The resulting biochemical signal is measured optically or converted into an electronic signal that is further processed in appropriate equipment's. Biosensors can be able to detect simultaneously multiple veterinary drugs residues in a sample at a time. In general, these sensors are valid for control laboratories because they can detect multiple residues in one sample and can thus allow the analysis of a large number of residues and samples.

Discussion

Identification and confirmation

The next step after initial screening consists in the unambiguous identification and confirmation of the veterinary drug residues in foods of animal origin. The full procedure and the methodologies for confirmatory analysis are costly in time, equipment's and chemicals. In addition, they require trained personnel with high expertise. Different analytical techniques are available for such purpose. When the target analyte is clearly identified and quantified above the decision limit for a forbidden substance or exceeding the Maximum Residue Limit (MRL) in the case of substances having an MRL, the sample is considered as noncompliant (unfit for human consumption). Identification is easier for a limited number of target analytes and matrices of constant composition. Some examples of the available confirmatory methodologies are as follows: The use of HPLC-Electrospray Ionization (ESI) tandem mass spectrometry or liquid chromatography-mass spectrometry with Atmospheric Pressure Chemical Ionization (APCI). ESI technique facilitates the analysis of small to relatively large and hydrophobic to hydrophilic molecules and is thus very adequate for the analysis of veterinary drug residues. Even though it is more sensible to matrix effects than APCI ionization. ESI and APCI interfaces are the sources of choice to promote the ionization of antibiotics and both complement each other well with regards to polarity and molecular mass of analytes.

Potential effect of veterinary drug residues on public health

Residual amounts of antimicrobials, antibiotics or their toxic metabolites found in meat, organs or other products such as milk and egg of food producing animals after slaughtering is called veterinary drug residues. Consumption of such food products poses a major health risk due to the failure of treatment following the development of resistant microorganisms. Various impacts of antimicrobial residues on human health are reported below.

Development of drug resistance

Human health can either effect through residues of drugs in food of animal origin, which may cause direct side effect or indirectly, through selection of antibiotic resistance determinants that may spread human pathogen. Resistant microorganism can get access to human, either through direct contact or indirectly via milk, meat, and or egg. As the bacteria of animal origin, they may either colonize human endogenous flora or superimpose and additional load to the reservoir of resistance genes already present in man. The potential for animal to human transfer of resistance is existed. Clearly, the use of antibiotic in

livestock production has been associated with the development of human antibiotic resistance. The animal feed with the low prophylactic level of antibiotic may develop bacteria evolving resistance to this antibiotic during the preparation or consumption of food of animal origin. It has been documented that human develop drug resistant bacteria such as Salmonella, Campylobacter, and Staphylococcus from food of animal origin. Examples of drugs that have been shown to cause the growth of resistant bacteria in food of animal are fluoroquinolones and avaoparin. The resistance of microorganisms, arising from subtherapeutic uses of penicillin, tetracyclines, and sulfa drugs; in agriculture is suggested by the WHO to be a high priority issue (National Research Council.

Drug hypersensitivity reaction

Drug hypersensitivity is defined as an immune mediated response to a drug agent in a sensitized patient, and drug allergy is restricted to a reaction mediated by Ig E. An allergic or hypersensitive effect following administration of a drug (i.e., drug allergy is quite similar to that typified by allergic response to protein, carbohydrate, and lipid macromolecules. Allergic reactions to drugs may include anaphylaxis, serum sickness, cutaneous reaction, a delayed hypersensitivity response to drugs appear to be more commonly associated with the antibiotics, especially of penicillin. About 10% of the human population is considered hypersensitive to an amount of a substance, including penicillin, but in animals, the extent of hypersensitive to, the drug is not well known. Certain macrolides may also in exceptional be responsible for liver injuries, caused by a specific allergic response to macrolide modified hepatic cells.

Carcinogenic effect

The term carcinogen refers to an effect produced by a substance having carcinogenic activity, considerable confusion has existed because a carcinogen applies to substances that are so varied in their qualitative and quantitative characteristics. The potential hazard of carcinogenic residues is related to their interaction or covalently binding to various intracellular components such as proteins, Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA), glycogen, phospholipids, and glutathione.

Mutagenic effect

The term mutagen is used to describe chemical or physical agents that can cause a mutation in a DNA molecule or damage the genetic component of a cell or organisms. Several chemicals, including alkalizing agents and analogous of DNA bases, have been shown to elicit mutagenic activity. There has been increasing concern that drugs as well as environmental chemicals may pose a potential hazard to the human population by production of gene mutagen or chromosome breakage that may have adversely affects human fertility.

Teratogenic effect

The term teratogen applies to drug or chemical agent that produces a toxic effect on the embryo or fetus during a critical phase of gestation. Consequently, a congenital malformation that affects the structural and functional integrity of the organism is produced. The well-known thalidomide incident involving a number of children in Europe was a direct testimony to the hazard that may occur when such agent is administered during pregnancy. Of the anthelmintic, benzimidazole is embryo toxic and teratogenic when given during early stage of pregnancy because of the anthelminthic activity of the drug. In addition to embryo toxicity including teratogenicity, the benzimidazole drug of oxfendazole, has also exhibited a mutagenic effect.

Conclusion

The bacteria that usually live in the intestine acts as a barrier to prevent incoming pathogen from being established and causing diseases. Antibiotics may reduce the total number of the bacteria or selectively kill some important species. The broad-spectrum antimicrobials may adversely affect a wide range of intestinal flora and consequently cause gastrointestinal disturbance. For example, use of drugs like, flunixin, streptomycin, and tylosin in animals, and also use of vancomycin, nitroimidazole, and metronidazole in humans are known for this effect.

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