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Public Health Impacts of Antibiotic Residues in Foods of Animal Origin: A Review

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Abstract
Residues are defined as all active ingredients or metabolites of those ingredients that remain in meat or other foodstuffs from the animal to which the medicinal product in question has been administered. The presence of antimicrobial residues in foods of animal origin, combined with failure to comply with the instructions for their use (dosage and waiting period) or poor livestock production practices, can have serious consequences for consumer health. Antibiotic residues occur in various types of foods of animal origin including milk, egg and meat due to large-scale application of antibiotics in veterinary practice and creates problems not only in dairy and beef industry but also have immense public health significance. Greater attention from a public health aspect is needed on the safety of drug residues as a result of indiscriminate use of antibiotics and the expanding increase of chemicals and drugs in the food supply. In general, harmful effects of drug and chemical residues may be carcinogenic, teratogenic, reduction in reproductive performance drug allergy and acute toxicity. In accordance with the label directions of the drug product, the safety levels must be strictly observed so that meat, milk or egg products will not contain illegal residues when they are sold for human consumption. Therefore, to prevent residue make individuals and organizations aware of the problem through education about the withdrawal time of the drug and government, producers, veterinarians, teachers and academicians, marketing associations, and other interested parties should work together in order to control and prevent residues in food.
Keywords: Antibiotic, Maximum Residual Limit, Public Health

1. Introduction

Animal production in recent decades has been aided by the use of veterinary medicinal products; in particular, anti-infective drugs in modern livestock production. These medicinal products are used either as a curative treatment, applied individually or collectively to animals with microbial infections, or as a preventive treatment against the onset of certain diseases, or even, in extreme cases, to offset poor animal production hygiene (Sanders, 2005). The use of anti-infective as medicine is a very recent development and is seen as one of the biggest medical breakthroughs because it can dramatically reduce the morbidity and mortality caused by many bacterial infectious diseases (Toutain *et al*., 2011).

Currently, approximately 80% of all food producing animals receives medication for part or most of their lives. The most commonly used antimicrobials in food producing animals are the β-lactams, tetracyclines, aminoglycosides, lincosamides, macrolides, pleuromutilins, and sulfonamides) (Lee *et al*., 2001). After their administration to animals, such treatments leave residues in the tissues of these animals and the foods derived from them (Wassenar, 2005). The presence of antimicrobial residues in foods of animal origin, combined with failure to comply with the instructions for their use (dosage and waiting period) or poor livestock production practices, can have serious consequences for consumer health (Chou *et al*., 2011).

Antibiotic residues in foods of animal origin may be the cause of numerous health problems in humans. These problems include toxic effects, transfer of antibiotic resistant bacteria to humans, immunopathological effects, carcinogenicity (e.g. sulphamethazine, oxytetracycline, and furazolidone), mutagenicity, nephropathy (e.g., gentamicin), hepatotoxicity, reproductive disorders, bone marrow toxicity (e.g., chloramphenicol), and allergy (e.g., penicillin) (Nisha, 2008).

Current developments in the market economy are prompting the liberalization of the veterinary profession. The problem is that, in most African countries, there is no control over the distribution of veterinary pharmaceuticals and products. Worse still, no appropriate legislation yet exists to guarantee the quality of the phytosanitary various products released onto the market. In addition to the health risk to local populations, the presence of residues from veterinary medicinal products in foods of animal origin could jeopardize international trade (Tarawali*et al*., 2011).

Therefore the objectives of this seminar paper are:

- To highlight the public health hazards of antibiotic residue
- To review the control and prevention measures for antibiotic residue

2. Use of Antibiotics in Animal Production

Antibiotics are used largely for three purposes in animals, therapeutic use to treat sick animals, prophylactic use to prevent infection in animals and as growth promoters to improve feed utilization and production for their

growth promoting properties they are routinely used at sub-therapeutic levels as animal feed additives (Debeuckelaere*et al*., 1998). Growth promoters are antimicrobials which, when administered in low doses in animal feed, have a preventive effect against certain bacterial infections and modify the composition of the intestinal micro biota, improving feed assimilation. The impact of these protective effects on animal production is to accelerate livestock growth (Sanders, 2005).

2.1. Concept of Residues

Residues are defined as all active ingredients or metabolites of those ingredients that remain in meat or other foodstuffs from the animal to which the medicinal product in question has been administered (EC, 2002). Regulation No. 470/2009 of the European Parliament and of the Council defines residues as all pharmacologically active substances, whether active ingredients, excipients or degradation products and their metabolites, which remain in animal-derived food. The concept of drug residues in food was developed over the second half of the 20th Century, resulting in the definition of a 'no observed effect' level, an Acceptable daily intake (ADI) and maximum residue limit (MRL) in food (CAC, 2011). This reflected advances in our knowledge of toxicological risk assessment and analytical science in the field of pharmacokinetics. For most antimicrobials and anti- infective, the results of microbiological studies are used to determine the maximum dose that has no observed effect. For a few other substances, there is a toxic risk Studies to compare the absorption, distribution, metabolism and elimination in laboratory and target animals are used as the basis for studying the kinetics of total residues, the extractable fraction compared with the bound fraction, the nature of metabolites and their main effects. These data are used to define the marker residue (parent substance, metabolite or combination of substances) whose depletion from the tissue is correlated with that of total residues. The MRL in various foodstuffs (muscle, liver, kidney, fat, milk and eggs) is determined to minimize the risk of consumer exposure, taking into account dietary intake. Such considerations as food technology, good farming practices and the use of veterinary medicinal products may also be taken into account when setting the MRL (Stolker and Brinkman, 2005).

2.1.1. Occurrence of antibiotic residues in foods

The use of antibiotics in food producing animals may leave residues in foodstuffs of animal origin like meat, milk, and eggs. The occurrence of these residues may be due to any one of the following: a failure to observe the withdrawal periods of each drug, extra-label dosages for animals, contamination of animal feed with the excreta of treated animals, or the use of unlicensed antibiotics (Paige, 1994). The introduction of antibiotics to the veterinary field started soon after the use of antibiotics for the treatment of bacterial diseases in humans. The main use of antibiotics in animal rearing was for the treatment and prevention of diseases. Indeed, antibiotics have been used for the treatment of mastitis, arthritis, respiratory diseases, gastrointestinal infections, and other infectious bacterial diseases (Palleschi*et al*., 2001).

More recently antibiotics have been used for improved growth, especially in broilers and fatteners. Indeed, antibiotics may improve growth rate by the following means: the thinning of mucous membranes in the gut, which facilitates absorption; alteration of gut motility, which enhances assimilation; production of favorable conditions for beneficial gut microbes by destroying harmful bacteria; and partitioning of proteins for muscle growth via cytokine suppression. Antibiotics also favor growth by decreasing the activity of the immune system, reducing the waste of nutrients, and reducing toxin formation. In most cases, however, only young growing animals and poultry are responsive to antibiotic mediated health maintenance (Nisha, 2008). This approach actually is problematic as these feed additives are usually used without prescription and for very long periods, in both large and small doses, which leads to drug residues entering animal-derived food (Mitema*et al*., 2001).

It is a common practice among livestock producers to treat entire groups of livestock, such as birds, fish, or other animals despite there being only a few affected individuals. Such practices unintentionally and unnecessarily expose healthy individuals to antibiotics. Additionally, many livestock producers use sub therapeutic doses of antibiotics to prevent diseases and this of course will lead to antibiotic residues entering the human food chain. Moreover, antibiotics are prescribed inappropriately in cases of viral infection, which do not respond to such drugs. All licensed antibiotics intended for animal use have clear cessation of use periods, pharmacokinetics and pharmacodynamics. Failure to observe the instructions for antibiotic use can lead to antibiotic residues entering animal derived foods. Improper maintenance of treatment records or a failure to identify treated animals adequately may lead to their omission of these animals (Guest and Paige, 1991).

2.1.2. Withdrawal period and maximum residue limit

Use of animal medicines requires observance of the withdrawal period. This is the time between the last doses given to the animal and the time when the level of residues in the tissues (muscle, liver, kidney, skin and fat) and products (milk, eggs, honey) lower than or equal to the MRL. Until the withdrawal period has elapsed, the animal or its products must not be used for human consumption (Jackson, 1990).

The MRL or tolerance is the target concentration in a residue-depletion study. It should be established purely on the basis of safety to the person consuming the product and has no pharmacodynamics reality in the

animal to which the drug has been administered. Tissue tolerances are normally established in fat, milk, muscle, liver, kidney, skin, or sometime meat by-products. The first step in calculating the tolerance is to determine the safe concentration of drug that could be consumed by individuals eating the animal products:

Safe concentration= (ADI) (Body weight) Food consumption factor In this equation, ADI refers to acceptable daily intake which is the maximum amount of chemical (mg/kg) that may be consumed daily over a lifetime without producing an adverse effect. Body weight is the average weight of humans consuming the product (usually assumed to be 60 Kg). The food consumption factor is the amount of edible product estimated to be consumed daily by an individual. The food consumption factor is based upon the average individual's daily intake of different types of foods (Riviere, 1999).

In order to safeguard human health, the World Health Organization (WHO) and the Food Agriculture Organization (FAO) have set standards for acceptable daily intake and maximum residue limits in foods (FAO and WHO, 1995). Regulatory limits for antibiotic residues have been imposed on the dairy industry in many countries (Folly and Machado, 2001).

2.1.3. Antibiotic residue risk factors

The growing use of antimicrobials to prevent and treat diseases, increases the probability of residues of these substances in products obtained from animals (Form, 2003). The factors favoring the presence of antimicrobial residues in foods of animal origin include: failure to comply with the waiting period after the administration of antimicrobials, failure to consult a veterinarian before using antimicrobials and lack of prior training in animal husbandry (Olu-Taiwo*et al*., 2011).

The waiting period is the period after the administration of a treatment, during which any food produced by the treated animal must not be marketed. The defined waiting period takes into account the pharmacokinetic variability between individual animals in the processes of absorption, distribution, metabolism and excretion of residues (active ingredients and metabolites). These processes depend on the physiological condition of the animal and the genetic traits influencing metabolism or excretion. As these differences influence residue kinetics, an adjustment of the waiting period may be required when medicinal products are administered to animals. At this stage of development in veterinary drugs, such variations are not taken into account (EFSA, 2012).

3. Public Health Impacts

The non-restrictive usage of antimicrobials in animals rearing may lead to problems due to the presence of residues in food and raw materials of animal origin. Human health can either be affected through residues of drugs in foods of animal origin, which may cause direct side effects or indirectly through selection of antimicrobial resistance determinant that may spread human pathogen (Peter and John, 2001). Human health problems that may result from intake of sub chronic exposure levels include allergic reactions in sensitive people, toxicity and carcinogenic effect. Penicillin especially, as well as other beta-lactam antibiotics such as cephalosporin could cause allergies if high level of residues persists in milk consumed by penicillin allergic persons. Tetracycline residue also has the potential to stain teeth of young children (Phillips *et al*., 2000).

Development of drug resistance: 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 (Landers *et al*., 2012). The animal fed 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 (NRC, 1991). It has been documented that human develop drug resistant bacteria such as Salmonella, Campylobacter and Staphylococcus from food of animal origin (Landers *et al*., 2012). Examples of drugs that have been shown to cause the growth of resistant bacteria in foods from animals 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 (NRC, 1991).

Hypersensitivity Reaction: It is an immune mediated response to a drug agent in a sensitized patient and drug allergy is restricted to reaction mediated by IgE. Drugs are foreign molecules, but their molecular weight is usually too small to be immunogenic, they act as haptens, which must combine with drug sensitive person to be immunogenic and elicit antibody formation (Riedl and Cassilas, 2003). Allergic reactions to antimicrobials may include anaphylaxis, serum sickness, cutaneous reaction and delayed hypersensitivity reactions. These effects are acquired after human beings consume food of animal origin, which contain drug residue that has allergic effects of the antimicrobials employed as food additives or in chemotherapy. Penicillin and streptomycin appear from clinical use in humans to be more included to produce hypersensitivity or allergy than others in present milking herd use. About 50% of the human population is considered to be hypersensitive to a number of substances including penicillin (McDonald, 1998)

Carcinogenic Effect: Carcinogenic effects refer to an effect produced by a drug having carcinogenic or

cancer producing activity. Among the carcinogenic veterinary drugs in current use in many countries are nitrofurans, nitromidazoles and quinoxaline. These drugs are acquired via food of animal origin as antimicrobial residues. The potential hazards of carcinogenic residue are related to their interaction or covalent binding with various intracellular compounds such as proteins, ribonucleic acid, glycogen,phospholipids and glutathione. This leads to change in cellular components such as DNA (Aiello *et al*., 2005).

Teratogenic Effect: The term teratogen applies to a 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 to hazard that may occur when such agent is administered during pregnancy (Apley, 2003). Tetracycline, the type of antibiotic, can cross the placental membrane and is deposited in the embryo in bones and teeth. Tetracycline exposure can result in yellow staining of the primary or deciduous teeth and diminished growth of the long bones.

Disruption of Normal Intestinal Flora: 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 (Cotter *et al*., 2012).

4. Occurrence of Antibiotic Residue in Ethiopia

Antimicrobials pass into every tissue and fluids of the body before excreted. High levels of antibiotic residues were detected in milk and meat destined for human consumption. In Ethiopia 70.58 % of farms in DebreZeit and 83.33% of the farms in Nazareth the oxytetracycline level; similarly, in 20.58% of the farms found in DebreZeit and 16.16% of the farms found in Nazareth, the penicillin G level were above the maximum residue limit established by FAO. In another study conducted on poultry meat 27.4% of chicken contained oxytetracycline (Myllyniemi *et al*., 2000). Other studies were also conducted in Ethiopia in which oxytetracycline and penicillin G from milk (Desalegne*et al*., 2014) and tetracycline from beef (Addisalem and Bayleyegn, 2012).

5. Prevention and Control of Residue

Self-monitoring and the control of residues are based on standardized laboratory analytical methods; the residue control strategy is based on a two-step approach; namely, the detection of residues using sensitive tests followed by confirmation (Cristofani*et al*., 2009).

The responsibility for residue control and prevention cannot lie solely within a governmental agency; rather the responsibility must be shared by the government, producers, veterinarians, teachers and academicians, marketing associations, and other interested parties, who must strive for both healthy and efficiently grown animals as well as a safe food supply. Several approaches can be taken to achieve this goal: The first step in residue prevention is to make individuals and organizations aware of the problem through education. When the animal is slaughtered or its edible products are collected there should be a legal requirement that drug concentrations in these products are not at levels greater than those established as safe by the relevant regulatory authority in the country of origin (Riviere, 1999).

Hence, the residue Prevention and control strategy is based on preventing entry of residues in meat or milk intended for human consumption by proper drug use guide developed for use by both veterinarians and food animal (dairy and beef) producers include the following (AVMA and NMPF, 1991)

All food animals should be maintained in a clean and healthy environment whenever possible. Drug residues are best avoided by implementing management practice (good nutritional to meet growth, maintenance and lactation needs) and herd health program that keep animals healthy and producing efficiently, dairy and beef producers should not use or store unapproved drugs, special mixes or products within adequate labels as unapproved drugs have no data regarding efficacy, safety or withholding time (Gerald and Joseph, 1991)

The use of prescription drug and a veterinary-client patient relationship, which is established hence a veterinarian is closely with the owner in health management of the herd; Proper drug administration and identification of treated animals before administering or dispensing drugs one has to: know the drugs approved for all classes of cattle on the farm and be familiar with approved dosage, route of administration, and withholding time; Proper maintenance of treatment records and identification of treated animals; institute a workable health record for each animal to record all health related events, including administration of medication (Scippo*et al*., 1994).

6. CONCLUSION AND RECOMMENDATIONS

Once antibiotics are administered to animal body, antibiotic residues are present in high or low concentrations in their products. However, it mainly depends on the duration of the administration of antibiotics. After the

administration of antibiotic, concentration of their residues gradually reduces in the milk or meat. The use of antibiotics as growth promoter and inappropriately for treatment purpose is creating the greatest problem in the health of the public. Generally the public health risks resulting from antibiotics residue are either with short or long term effect and these can be allergic reaction and hypersensitivity, reproductive disorders, carcinogenicity, nephropathy and antibiotic resistance. For the prevention and control of antibiotic residue a shared responsibility among different stockholders including the government is very imperative. Using antibiotics for therapeutic purpose only and in the proper doses and for proper time has great contribution in the prevention and control of antibiotic residue. The availability of sensitive equipment and modern analytical techniques are of paramount importance in the detection, control and prevention approaches. Based on the above conclusion the following recommendations have been forwarded:

- A shared responsibility among government and other stockholders in providing awareness for people about drug residue and withdrawal period should be given due attention.
- Using of antibiotics in the veterinary field should be only through veterinarian's prescription.
- The therapeutic use of antibiotics must be in proper doses and for appropriate time
- Government regulations and control should necessitate more stringent adherence to withdrawal times.

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