Introduction to Veterinary drug residues: Hazards and Risks

Hisham Ismail Seri

Department of Animal Health and Surgery, College of Veterinary Medicine, Sudan University of Science and Technology

ABSTRACT

Recently, consumers have expressed concern regarding the presence of chemical adulterants or residues, mainly antimicrobials, hormones and pesticides, in animals meat, poultry, and milk supplies, and the health impact of drug residues in their food. The animal drug approval process worldwide is based upon the premise that the presence of drug residues in meat and poultry above tolerance is a public health hazard. Animal drug residues in animal tissues above the legal tolerance clearly have an impact on human health. Tolerances represent the maximum level of concentration of a drug permitted in animal tissues at the time of slaughter. The tolerances are intended to ensure that residual drugs will have no harmful effects if ingested.

This paper describes the existing evidence for specific health hazards of certain pharmacological classes of drugs and explains the hazardous risks associated with drug residues in milk, meat and poultry above the established tolerance levels. The primary focus is on possible public health consequences that may occur as a result of acute and/or chronic exposure to food of animal origin contaminated with drug residues above tolerance. The impact of food-borne drug residues on public health, residue detection limitations, and the responsibility of the Veterinary Practitioner in ascertaining food safety is discussed.

Although, at present most residues of veterinary drugs occur in food at such low levels that they rarely pose a chronic or long-term health hazard to consumers, the importance of vigilance about food safety through the reduction of residues in food supply cannot be overemphasized. Food safety remains a major concern for society.

In conclusion, based on the thus far available data, possible adversities to human health by consumption of food of animal origin contaminated with above tolerance drug residues can hardly be excluded.

Keywords: *Veterinary drugs, Residues, Hazards, Risks, adverse effects*

INTRODUCTION

The problem of satisfying the dietary requirements of a growing world population is becoming increasingly acute. Drugs that improve the rate of weight gain, improve feed efficiency, or prevent and treat diseases in food-producing animals are critically needed to meet the challenge of providing adequate amounts of food for that population.

But, the benefit of improved production from the use of animal drugs in food producing species is not

obtained without risk — the risk associated with drug residues that remain in the tissues of treated animals at the time of slaughter. If animal drugs were not absorbed or were metabolized to harmless products, there would be no concern. Unfortunately, this is not usually the case. It is therefore necessary to collect data on residues and their safety as a basis for establishing safe residue concentrations and withdrawal periods for food animal drugs. And, it is equally important that slaughtered animals be monitored for possible unsafe residues.

In both human medical and companion-animal veterinary practice, the primary concern in drug selection and use is the therapeutic end point, whether or not the drug is efficacious against the disease being treated. Doses are usually administered at label recommendations, and if greater than label dose is administered, only potential toxicity is of concern. While this line of reasoning is also true to a large degree in food-animal production, veterinarians and producers involved in the treatment of disease in food animals bear the additional concern of the persistence of drug residues in the edible tissues after the disease process has been treated. Adulteration of the food supply with antimicrobial agents, pesticides, environmental contaminants, and other chemicals has been a growing source of concern to the general public and special-interest groups in recent years (Riviere and Sundolf, 2009).

The implementations of WTO regulations demand that veterinarians working in food animal medicine should learn how to avoid drug/chemical residues in food animals and disseminate this information to the farmers to safeguard the health of general public. This issue is also of paramount importance for the veterinarians employed in pharmaceutical and regulatory sectors responsible for assessing the fate of drugs and chemicals that enter the human food chain via the edible products.

The primary parameter used by veterinarians to prevent illegal tissue residues is the length of the withdrawal time (WDT), or the time required for a drug to be depleted from the animal before the animal's meat can be marketed for human consumption. In dairy practice, this is the milk discard time (MDT) (Riviere and Sundolf, 2009).

This article discusses some important issues in this context such as hazards of drug/chemical residues, establishment of maximum residue levels (MRL), withdrawal times (WDT) and limitations in residue analysis.

THE CONCERN OVER RESIDUES IN FOOD

In Sudan, a great deal of concern has been demonstrated over the last two decades about the presence of chemical adulterants or residues, mainly antimicrobials and pesticides, in the meat, poultry, and milk supplies.

By definition, a chemical residue is either the parent compound or metabolite of the parent compound that may accumulate, deposit, or otherwise be stored within the cells, tissues, organs or edible products (e.g. milk, eggs) of an animal following its use to prevent, control or treat animal disease, or to enhance production. Residues can also result from unintentional administration of drugs, or food additives. Finally accidental exposure to chemicals in the environment can also result in tissue residues.

Concerns over food residues are economic as well as public health related. For example, the contamination of milk with antibiotics, most commonly Penicillin, can affect starter cultures used to make fermented milk products such as cheeses, buttermilk, sour cream, etc., which can result in economic losses to those processors.

From public-health viewpoint, both the U.S. government and producers associations have taken active roles in minimizing antibiotic residues in meats and milk. Penicillin for example, is known to induce

allergic reactions in some sensitive people, and therefore, penicillin-tainted milk poses a health risk for these individuals. Similarly, chloramphenicol has been reported to induce blood dyscrasias that may lead to death; hence its use in food-producing animals has been prohibited by the Food and Drug Administration (FDA). The FDA has also prohibited the use of nitrofurans in food-producing animals (excluding the topical routes for administration) because studies have shown them to be carcinogenic.

Not only therapeutic drug but pesticides create residue problems. Most pesticides are administered topically, allowing some amount of percutaneous absorption and sequestration in edible tissues. Lindane has been detected in the fat deposits of sheep dipped in a 0.0125% lindane emulsion 12 weeks after topical exposure (Collet and Harrison, 1963).

The FDA and Environmental Protection Agency (EPA) establish tolerances for a drug, pesticide, or other chemical in the relevant tissues of food-producing animals. The tolerance is the tissue concentration below which a marker residue for the drug or a chemical must fall in the target tissue before that animal's edible tissue (s) (meat, milk, or eggs) are considered safe for human consumption. The marker residue may be the parent compound, or a metabolite, and reflects a known relationship to the total residues of the drug or chemical (parent and all metabolites). The target tissue is an edible tissue, frequently liver or kidney which, when the compound has depleted below the tolerance, assures that all edible tissues are safe for human consumption. Tolerances for different tissues are considered legal end points for which drug withdrawal times are established. Tolerances are established based on assessment of potential hazard of consumption to humans.

Oral toxicity studies are conducted in animals leading to the determination of an acceptable daily intake (ADI) for the compound in the human diet. These studies consider the compound's carcinogenic potential, systemic, reproductive, and developmental toxicity, and incorporate various safety factors. Recently, the potential for an antimicrobial compound to induce resistance in bacteria is also factored in.

Generally, a drug is administered to healthy animals, groups of the animals are slaughtered at sequential time intervals, and their edible tissues are analyzed for drug concentrations. The withdrawal time is the time from cessation of treatment to the time it takes for the residues of the drug to deplete below the safe concentration.

MAXIMUM RESIDUE LIMIT (MRL)

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 pharmacodynamic 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. The Food and Drug Administration (FDA) and other regulatory agencies have tabulated food-specific

consumption factors. Examples (Kg consumed per day) are 0.3 for muscle, 0.1 for liver, 0.05 for kidney, 0.05 for fat, and 1.5 for milk in USA (Riviere, 1999). The milk consumption in children is especially high since the total diet for an infant may entirely be the milk.

Other countries use similar food consumption factors but distribute the ADI based on independent organ consumption data.

HAZARDS OF DRUG RESIDUES

Potentially, there are two types of hazards relating to drug residues i) direct and short term hazards, and ii) indirect and long term hazards.

DIRECT AND SHORT TERM HAZARDS

Drugs used in food animals can affect the public health because of their secretion in edible animal tissues in trace amounts usually called residues. For example, oxytetracycline (Salehzadeh *et al*., 2006) and enrofloxacin residues (Salehzadeh *et al*., 2007) have been found above the maximum residual level in chicken tissues. Similarly, diclofenac residues were reported to be the cause of vulture population decline in Pakistan (Oaks *et al*., 2004). Some drugs have the potential to produce toxic reactions in consumers directly; for example, clenbutarol caused illness in 135 peoples as a result of eating contaminated beef in Spain in 1990. Other types of drugs are able to produce allergic or hypersensitivity reactions. For example, 2-β lactam antibiotics can cause cutaneous eruptions, dermatitis, gastro-intestinal symptoms and anaphylaxis at very low doses. Such drugs include the penicillin and cephalosporin groups of antibiotics (Paige *et al*., 1997).

INDIRECT AND LONG TERM HAZARDS

Indirect and long term hazards include microbiological effects, carcinogenicity, reproductive effects and teratogenicity. Microbiological effects are one of the major health hazards in human beings. Antibiotic residues consumed along with edible tissues like milk, meat and eggs can produce resistance in bacterial populations in the consumers. This is one of the major reasons of therapeutic failures amongst such peoples. Certain drugs like 3-nitrofurans and nitroimidiazoles can cause cancer in human population. Similarly, some drugs can produce reproductive and teratogenic effects at very low doses consumed for a prolonged period of time. One such example is vaginal clear cell adenocarcinoma and benign structural abnormalities of uterus with diethylstilbesterol (Sundlof, 1994).

THE VETERINARIANS AND EXTRALABEL DRUG USE

The FDA approves new animal drugs for specific indications in a particular species or subclass of animals (dairy cattle, weanling pigs, etc.). Occasionally, veterinarians may encounter diseases or conditions in animals for which there are no FDA approved drugs. Under such circumstances, veterinarians often administer drugs that are not approved for use in food animals or they administer approved drugs in non approved ways, practices commonly referred to as "extralabel' usage. Extralabel drug use is defined as the use of a drug in a manner that is inconsistent with its FDA-approved labeling, a practice that, until 1994, was technically illegal.

This act placed Veterinarians in an untenable position of having to choose between providing for relief of animal suffering or complying with the law. Under specific conditions, veterinarians are allowed to prescribe and administer drugs in an extralabel manner.

LIMITATIONS IN RESIDUE ANALYSIS

One basic limitation to conduct residue and risk analysis is the detection of chemical residues in edible animal products. Without accurate detection, exact risk is impossible to assess. This process needs highly qualified expertise, sensitive instruments and modern analytical techniques. High Performance

Liquid Chromatography (HPLC), Gas Chromatography (GC) and Mass Spectrometry (MS) are sensitive instruments while Solid Phase Micro-extraction (SPME) and Microdialysis are modern analytical techniques used for residue analysis.

RESIDUE PREVENTION

Although public awareness of the drug residue problem in food is high and several governmental agencies spend large amounts of time attempting to control this problem, residues in animal tissues are still an important concern today. 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.

HOW THESE ISSUES CAN BE HANDLED?

Such problems can be resolved by taking into consideration three steps i.e. risk assessment, risk management and risk communication. Basically, risk assessment is a systematic scientific characterization of potential adverse health effects following exposure to hazardous agents. Results from the risk assessment are used to inform risk management, who work with factors like social importance of risk, social acceptability of the risk, economic impacts etc. Finally, risk communication involves making the risk assessment and risk management information comprehensible to lawyers, politicians, judges, environmentalists and community groups.

One basic step to build this foundation is the determination of residue levels in our foods. When the animal is slaughtered or its edible products are collected, there is 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. In many countries of the world, this upper level is referred to as the maximum residue level (MRL), while in United States it is termed as tolerance (Riviere, 1999).

MRLs and tolerances are established by regulatory authorities based on many factors primarily relating to the safety of the animal product to the consumer, the usage pattern of the compound (pesticide in the field), and analytical methodology. The major determining factor is food safety. In this context, the focus is the length of time after discontinuation of drug administration or chemical exposure required to allow a tissue to deplete to a concentration below the MRL (Fitzpatrick *et al*., 1995). If the matrix is milk, then the parameter of interest is the milk discard interval (MDI).

CONCLUSION

Veterinarians must be well aware of the importance of drug/chemical residues in the food animals and their possible risk to the general public. They must have updated information about the proper withdrawal times of all the drugs/chemicals used in their areas of practice. They must extend this information to the livestock and poultry farmers for the production of residue free edible animal products like milk, meet and eggs. For residue analysis, trained manpower are needed. In this regard, the availability of sensitive equipment and modern analytical techniques are of paramount importance.

RECOMMENDATIONS

Government regulation and control should necessitate more stringent adherence to withdrawal times

On-site monitoring for many drugs must be instituted

REFERENCES

Collet, J.N., and Harrison, D.L. 1963. Lindane residue in sheep following dipping. NZJ Agricul Res. 6: 39-42.

Fitzpatrick, S. C., S. D. Brynes and G. B. Guest, 1995. Dietary intake estimates as a means to the harmonization of maximum residue levels for veterinary drugs. J. Vet. Pharmacol. Therap., 18: 325-327.

Oaks, J. L., M. Gilbert, M. Z. Virani, R. T. Watson, C. U. Meteyar, B. A. Rideout, H. L. Shivaprasad, S. Ahmed, M. Jamshed, I. Chaudhry, M. Arshad, S. Mahmood, A. Ali and A. A. Khan, 2004. Diclofenac residues as the cause of vulture population decline in Pakistan. Nature, 427: 630- 633.

Paige, J. C., L. Tollefson and M. Miller, 1997. Public health impact on drug residues in animal tissues. Vet. Human Toxicol., 9: 1-27.

Riviere, J.E., Sundlof, S.F. 2009. Chemical residues in tissue of food animals. In: Veterinary Pharmacology and Therapeutics. Jim E. Riviere and Mark G. Papich (eds.). willey-Blackwell. Usa. 1453-1462.

Riviere, J. E., 1991. Pharmacologic principles of residue avoidance for veterinary practioners. JAVMA. 198 (5): 809-815.

Riviere, J. E., 1999. Comparative Pharmacokinetics, Principles, Techniques and Applications. Iowa State Univ. Press, Ames, Iowa, USA.

Salehzadeh, F., R. Madani, A. Salehzadeh, N. Rokni and F. Golchinefar, 2006. Oxytetracycline residue in chicken tissues from Tehran slaughterhouses in Iran. Pakistan J. Nutr., 5(4): 377-381.

Salehzadeh, F., A. Salehzadeh, N. Rokni, R. Madani and F. Golchinefar, 2007. Enrofloxacin residue in chicken tissues from Tehran slaughterhouses in Iran. Pakistan J. Nutr., 6(4): 409-413.

Sundlof, S. F., 1994. Human risks associated with drug residues in animal derived food. J. Agrimedicine, 1: 5-22.

Table 1. Drugs prohibited from extralabel use in food animals

Chloramphenicol
Clenbuterol
Diethylstilbestrol (DES)
Dipyrone *
Gentian violet
Nitromidazoles (including dimetridazole, metronidazole, and ipronidazole)
Nitrofurans (including nitrofurazone and furazolidone; topical use prohibited as well)
Phenylbutazone use in adult dairy cattle
Sulfonamide drug in lactating cows **
Fluoroquinolones*
Glycopeptides

*Prohibition does not apply to approved uses

**Prohibition does not apply to approved uses of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine