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Antibiotic residues in food animals: Causes and health effects

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Abstract
Administration of antimicrobials to food animals for treatment, prophylaxis and as growth promotors results in deposition of their residues in various organs and tissues. Consumption of these residues through meat and meat products may cause direct and/or indirect toxicity in consumers and results in failure of treatment due to development of resistant microorganisms. Withdrawal periods should be strictly followed and rules pertaining to antimicrobial residues should be rigorously enforced to make the meat safe for human consumption.

Keywords: Antibiotic residues, food animals, resistant microorganisms

Introduction
Antimicrobials are naturally occurring, synthetic or semisynthetic compounds with antimicrobial activity. These agents could be administered orally, parenterally or topically and used in human and veterinary medicine to treat and prevent diseases, and for other purposes including growth promotion in food animals (Barton, 2000) [2]. Consciousness about propagation of resistant bacteria through food chain from treated animals did not draw much consideration until the recognition of avoparcin fed animals developing vancomycin resistance to *Enterococci* (Swann, 1969) [23]. Incidence of antimicrobial residues in meat, meat products, fish and aquaculture products has been impacting their international trade for the last few years (Kaneene and Miller, 1997) [14].

Uses of antimicrobials in food animals and poultry
Antimicrobials in food animals are used for three main purposes they are,

Therapy or treatment: Administration of a course of antimicrobial drug for treatment of clinically evident diseases. It is also practiced to control morbidity/mortality in animals which usually involves high doses of the drug for a relatively short period of time (NCCLS, 2002) [19].

Prevention/prophylaxis: Administration at sub-therapeutic dose of antimicrobial drug to healthy animals considered to be at risk, but before the expected onset of disease.

Growth promotion: Administration at very low doses of antimicrobials usually as a feed additive, over a lifetime, to growing animals that results in improved physiological performance by suppressing the gut bacteria leaving more nutrients for animals or birds to be absorbed (Dennis *et al.,* 1981; Nagaraja *et al.,* 1987) [7, 18]. Antimicrobial agents enhance absorption of available nutrients in intestinal epithelium, promote the synthesis of growth factors and vitamins and destroy pathogens which effectively reduce the release of toxins (Prescott and Baggot, 1993) [21]. Antimicrobial growth promoters are administered mainly to improve productivity (Taylor, 1999) [24]. Generally, administration of growth promoters in pig and poultry helps in improving the growth rate and feed conversion efficiency. It is recognized that growth promoters also play a beneficial role in controlling some chronic conditions and also has role in ensuring animal welfare. Withdrawal of growth promoters would lead to reduced profitability of farming enterprises through increased capital and operational costs (Lawrence, 1997; McOrist, 1997) [15, 16].
Commonly used antimicrobials for treatment, prophylaxis and for growth promotion in food animals are streptopenicillin, benzyl penicillin, enroflaxocin, amoxicillin, ampicillin, sulfa-

trimethoprim, tylosin, sulfamethoxazole and oxytetracycline. As growth promoters in poultry, doxycycline, colistin sulfate, neomycin, tetracycline, tylosin, enrofloxacin, ciprofloxacin, amikacin and tilmicosin are used.

Causes for occurrence of antimicrobial residues

Poor treatment records, poor management, difficulty to identify treated animals, lack of guidance on withdrawal periods, off-label use of antimicrobial, failure to notice drug withdrawal period, accessibility of antimicrobials to laymen, extended usage or unnecessary dosages of antimicrobials, absence or lack of enforcement of restrictive legislation to use antimicrobials, lack of consumer awareness about the magnitude of human health hazards associated with antimicrobial residues consumption through meat and meat products are some of the primary reasons for incidence of antimicrobial residues in meat and meat products (Muhammad *et al.*, 1997; Kaneene and Miller, 1997; CAC, 2001) [17, 14, 6].

Impact of antimicrobial residues on human health

Incidence of antimicrobials residues in foods creates a significant health risk because of the augmented microbial resistance noticed in recent years (Butaye *et al.*, 2001) [4]. Drug low-level contamination normally may not create a ruin problem on public health. However, widespread use of drugs might upsurge the risk of an adverse effect of residues on the customer including the occurrence of antibiotic resistance and hypersensitivity reaction. Therefore, judicious use of drugs in the manner of preventing feed contamination is necessary.

Drug resistance

Progress of drug resistance on human health, can either affect through residues of drugs in food of animal origin, which might cause direct side effects, or indirectly, through selection of antibiotic resistance determinants that may spread to human pathogen. Resistant microorganism can get entrance 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 supplement load to the reservoir of resistance genes already present in man. The potential for animal to human transfer of resistance is existed (Beyene, 2016) [3].

Evidently, the use of antibiotic in livestock production has been associated with the development of human antibiotic resistance. The animal fed with the low prophylactic level of antibiotic might develop bacteria budding resistance to those antibiotic during the preparation or consumption of food of animal origin. It has been recognised 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 sub therapeutic uses of penicillin, tetracyclines, and sulfa drugs in agriculture is suggested by the World Health Organisation (WHO) to be a high priority issue (Beyene, 2016) [3].

Apramycin is not used in human medicine, but development of apramycin resistance human strains of *Salmonella* and *E. coli.* Substantiate the transfer of resistant organisms or resistance genes from animal to human isolates (Barton, 2000) [2]. Resistant strains can cause failure of antimicrobial therapy in clinical situations in future (Nisha, 2008) [20].

Consumption of foods of animal origin containing antimicrobial residues might cause development of direct and indirect toxicity, side effects such as hypersensitivity, injury to liver, discolouration of teeth and gastrointestinal disorders in human beings (FAO, 2002; Jing *et al.*, 2009) [10, 13]. Low levels of antimicrobial exposure results in alteration of microflora, and there is concern about transfer of antimicrobial resistant pathogens through the food chain.

Drug hypersensitivity

Drug hypersensitivity was defined as an immune arbitrated response to a drug agent in a sensitized patient and drug allergy is constrained to a reaction mediated by IgE. Allergic reactions to drugs may include anaphylaxis, serum sickness, cutaneous reaction, a delayed hypersensitivity response to drugs seem to be more frequently linked with the antibiotics, especially of Penicillin. Penicillin residues in milk could provoke allergic reactions in sensitized individuals (Swann, 1969; Dewdney *et al.*, 1991; Demoly and Romano, 2005) [23, 8]. About 10 per cent of the human population was considered hypersensitive to an amount of a substance, including penicillin, but in animals, the extent of hypersensitive to the drug was not well known. Certain macrolides might also in exceptional be responsible for liver injuries, triggered by a specific allergic response to macrolide modified hepatic cells. Acquaintance to chloramphenicol residues in foods can seldom cause a fatal blood dyscrasia in individuals (Settepani, 1984) [22].

Carcinogenic effect

The term carcinogen refers to an effect produced by a substance having carcinogenic activity. The latent hazard of carcinogenic residues was related to their collaboration or covalently binding to various intracellular components such as proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), glycogen, phospholipids, and glutathione (Beyene, 2016) [3]. Chloramphenicol causes cancer (Demoly and Romano, 2005; Nisha, 2008) [20]. The Joint FAO/WHO Expert Committee on Food Additives determined that chloramphenicol was genotoxic and may cause cancer (Anon, 2002) [1].

Disruption of normal intestinal flora

The bacteria that usually live in the intestine acts as a blockade to avert incoming pathogen and causing diseases. Antibiotics might reduce the total number of the bacteria or selectively kill some important species. The broad-spectrum antimicrobials might adversely affect a wide range of intestinal flora and subsequently cause gastrointestinal disturbance. Use of drugs like, flunixin, streptomycin and tylosin in animals and also use of vancomycin, nitroimidazole and metronidazole in humans are known for this e***ff***ect (Beyene, 2016) [3]. There was little scientific information on the effect of antimicrobial residues on the bacterial flora of the human intestinal tract, because human studies have mainly been carried out at therapeutic dose levels and not at the residue range concentrations (Gorbach, 1993) [12].

Mutagenic effect

The term mutagen was 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 growing concern that drugs as well as environmental chemicals may pretence a probable threat to the human population by making of gene mutagen or chromosome breakage that might have adversely affects human fertility (Beyene, 2016) [3].

Teratogenic effect

The term teratogen applies to drug or chemical agent that produces a toxic effect on the embryo or foetus during a critical phase of gestation. Consequently, a congenital malformation, which affects the structural and functional integrity of the organism, was produced (Beyene, 2016) [3]. Among the anthelmintics, benzimidazole, was embryo toxic and teratogenic when given during early stage of pregnancy. In addition to embryo toxicity including teratogenicity, the benzimidazole drug of oxfendazole, has also unveiled a mutagenic effect.

Other affects

Some of the pathological effects caused by antimicrobial residues in human beings through meat and meat products include immune-pathological effects, hypersensitivity reactions, cancer (sulphamethazine, oxytetracycline, furazolidone), mutagenicity, nephropathy (Gentamicin), exposure to chloramphenicol residues in foods can rarely cause a fatal blood dyscrasia in individuals (Settepani, 1984) [22]. Hepatic disorders, reproductive disorders, myelotoxicity (Nisha, 2008; Demoly and Romano, 2005) [20].

For guarding humans from exposure to any veterinary drugs residues, withdrawal times have been determined. The withdrawal time is defined as the time interval from administration of a drug to animal until slaughter to assure that drug residues in meat are below the maximum residue limit.

Regulations and laws on antimicrobial residues in India

Under the Food Safety Standards Authority of India (FSSAI), antimicrobial tolerance limit for meat and meat products has not been established, but Ministry of Health and Family Welfare amended the Drugs and Cosmetics Rules, 1945, which as per sub rule 3 of rule 97, established withdrawal periods for the drugs used in animals. Drug manufacturing companies must mention withdrawal period on the container of drugs which is intended to be sold. If not otherwise mentioned, the withdrawal periods should not be less than 28 days (Table, 1) (FSSAI, 2011) [11].

Export Inspection Council of India (EIC) ensures food safety and quality for fresh poultry meat and poultry meat products for export to European Union (EU). EIC has followed the EU directive regulations and Maximum Residue Limit (MRL) for antimicrobials (Table. 2), but EIC has not set any residue level for sale of fresh poultry meat and poultry meat products in India (EIC, 2012) [9].

Leads for future

Conduct surveillance programme of antimicrobials used in food animals. Collect surveillance data of antimicrobial resistance in animals, humans and food chain at national level. Establish universally applicable standards for the maximum residue levels in food animal tissues. Development of simple and economic test to identify drug residues in meat and meat products in field situations. Need to develop toxicological effects of metabolites of antimicrobials in human beings.

Table 1: Withdrawal time of commonly used antimicrobials.

Antimicrobials	Pre-slaughter withdrawal time (days)			
	Cattle	Sheep	Swine	Chicken
Ampicillin	06	-	15	-
Amoxicillin	25	-	-	-
Procaine penicillin G	10	9	28	05
Dihydro streptomycin	30	30	30	-
Erythromycin	14	03	07	02
Oxytetrcycline	03	-	28	05
Chlortetracycline	10	0	0	01
Sulfadimethoxine	-	-	-	05
Sulfamethoxypyridazine	16	-	-	-
Sulfamethazine	07	-	15	-
Sulfaquinoxaline	-	-	-	10
Tylosin	21	-	14	03

(Prescott and Baggot, 1993)

Table 2: Maximum residue limit for commonly used antimicrobials in beef.

Antimicrobial	Muscle (µg/kg)	Liver (µg/kg)	Kidney (µg/kg)	Fat (µg/kg)	Cow milk (µg/L)
Amoxicillin	50	50	50	50	4
Benzyl penicillin	50	50	50	50	-
Chlortetracyclin/Oxytetracyclin /Tetracyclin	200	600	1200	-	100
Gentamycine	100	2000	5000	100	200
Streptomycin	600	600	1000	600	200
Erythromicin	-	-	-	-	-
Neomycin	500	500	1000	500	1500
Sulfadimidine*	-	-	-	-	25
Tilmicosin	100	1000	300	100	-
Tylosin	100	100	100	100	-

Note: * A common MRL of 100 µ/kg suggested for all tissues (CAC, 1993)

Conclusion

The use of veterinary drugs in food-producing animals has the potential to generate residues in animal derived products and poses a health hazard to the consumer. The 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. Withdrawal periods should be strictly followed and rules pertaining to antimicrobial residue limits should be strictly enforced to make the meat safe for human consumption.

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