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Antibiotic residues in animal products and its effect on human health

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Abstract
Antibiotics are mainly employed for chemotherapeutic, prophylactic purposes and also used as feed additives to promote growth and improve feed efficiency. However, antibiotic residues in animal origin products usually found when administration of drug in extra label fashion and does not follow withholding period after treatment. The usage of antibiotic that resulted into deposition of residues in meat, milk and eggs must not be intended for human food consumption. If use of antibiotics is necessary as in prevention and treatment of animal diseases, a withholding period must be observed until the antibiotics residues are negligible to none detected. The concern over antibiotic residues in food of animal origin occurs in two aspects; one which produces potential threat to direct toxicity in human whereas the low levels of antibiotic exposure would result in alteration of microflora, cause disease and the possible development of resistant strains which cause failure of antibiotic therapy in clinical situations second concern of time. The establishing regulatory standards and good management practices that reduce the risk of antibiotic residues in milk supply are essential components of human food safety.

Keywords: Antibiotic, residues, animal products, human health

Introduction
The problem of satisfying the dietary requirements of growing world's population is become increasing acutely. Drugs that improve the rate of weight gain, increasing feed efficiency, prevent or treat the diseases in food producing animals are critically needed to meet the challenge of providing adequate amounts of food for that population. The frequent antibiotics use causes the occurrence of antibiotic residues in various food products of animal origin including milk, egg and meat. Antibiotic residues in milk are of great public health concern since milk is being widely consumed by infants, youngster and adults throughout the globe (Khaniki, 2007) [12]. Presence of drugs or antibiotics residues in food above the maximum acceptable level has been recognized worldwide by various public authorities (Kempe and Verachtert, 2000) [11]. Intramammary infusions of antibiotics for treating mastitis (92%), injections (6%), and other causes 2% are the responsible for the antibiotic residue in milk (Booth, 1988). Food Safety and Standards Act, 2006 defines veterinary drug residues as "The parent compounds or their metabolites or both in any edible portion of any animal product and include residues of associated impurities of the veterinary drugs concerned" (FSSA, 2006) [5]. The residues are the substances having a pharmacological action, their metabolites and other substances transmitted to animal products that are likely to be harmful to human health (Serratosa *et al*., 2006) [20]. The Food and Drug Administration's Center for Veterinary Medicine (CVM) announced a Milk Drug Residue Sampling Survey in November of 2010 with the purpose of determining if dairy farms with a previous tissue residue violation have more drug residues in raw milk than other dairy farms. Samples were collected from dairy farms with a previous tissue residue violation (targeted farms) and from a comparable number of randomly selected dairy farms that were not selected for inclusion in the targeted list (non-targeted farms). Samples were tested for 31 different drug residues. A total of 15 milk samples (0.78%) were confirmed positive out of the 1912 analyzed (one sample contained two confirmed drug residues). The final results include 11 confirmed positive milk samples out of 953 (1.15%) targeted milk samples representing a total of 12 confirmed positive milk residues in the targeted sample group, including the sample that contained two confirmed drug residues. Out of the 959 non-targeted samples, four of the samples were confirmed positive (0.42%) representing a total of four confirmed drug residues in the non-targeted group. In India several measures have been initiated by the Indian government to increase the productivity of

livestock through various schemes and policies including Delhi Milk Scheme (DMS), Key Village Scheme (KVS), Integrated Cattle Development Project (ICDP) and some other programs were launched to improve breeding, feed and fodder availability and effective disease control which has resulted in increasing the milk production significantly and at present, India stands first in the milk production (Kumar *et al*., 2011) [14]. The average growth in the milk production is about 5 % per annum with sustained growth in the availability of milk and milk products for the growing population.

Public health aspect and harmful consequences of antibiotic residues

Considering the issue of public health hazards, milk and milk products contaminated with antibiotics and other chemical contaminants beyond a given residue levels, are considered unfit for human consumption (Hillerton *et al.*, 1999; Goff ova *et al*., 2012) [9, 6]. Occurrences of veterinary drug residues pose the broad range of health consequences in the consumers. The residues of antibacterials may present pharmacological, toxicological, and microbiological and immune pathological health risks for humans (Dracokva *et al*., 2009) [3]. In rare situations, the pathogens against which the antibiotics are being used have less public health hazards than those posed by the improper use of antibiotics. To enlist one example, mastitis pathogens in milk pose a lower threat to public health if milk is pasteurized. On the other hand, the careless antibiotic therapy to eliminate mastitis pathogens becomes a public health concern due to their residues in milk (Hameed, 2006) [8]. Antibacterial causes broad range of health effects, to summarize they can cause development anomalies e.g. bone marrow aplasia (chloramphenicol) and can alter the normal gastrointestinal microflora resulting in GI disturbances (intestinal dysbiosis) and development of resistant strains of bacteria. Therefore, the use of anti-bacterials may result in emergence of antibiotic resistant strains of pathogens, complicating the treatment for both human and animal diseases (Dewdney *et al*., 1991; Goffova *et al*., 2012) [2, 6]. In addition some of the antibacterial may act as carcinogens and pro-carcinogens (Oxytetracycline and furazolidone). Carcinogenic and genotoxic effects in consumers could be possible at very low exposure levels, especially if the chemical in question is ingested regularly over a long period of time. Oxytetracycline can react with nitrite and the combination thereof called as nitrosamine is a potential carcinogen (Mitchell *et al*., 1998) [15]. In the year 1995 European Union (EU) prohibited the use of nitrofurans for the treatment of bacterial diseases in livestock production, due to concerns about the carcinogenicity of their residues in edible tissue (Vass *et al*., 2008) [21]. In subsequent years Australia, USA, Philippines, Thailand and Brazil also prohibited the use of nitro furans in food animals (Khong *et al*., 2004) [13].

These hazards can be categorized in to two types as direct-short term hazards and indirect-long term hazards, according to duration of exposure to residues and the time onset of health effects (Muhammad *et al*., 2009) [16]. The direct health hazards includes the health effects caused due to excretion of drug in milk, as an example the beta-lactam group of antibiotics regardless of their low concentration in milk causes allergic hypersensitive reaction in sensitized individual immediately after consumption (Paige *et al*., 1999; Sierra *et al*., 2009) [17, 19]. Another example includes the aplastic anemia caused by chloramphenicol not related to level of exposure (Rich, 1950; Granowitz *et al.*, 2008) [18, 7]. Several antibiotics are potent antigens or act as a haptens and occupational exposure on a daily basis can lead to allergic reactions. Most of the reported allergic reactions are related to ß-lactam antibiotic residues in milk or meat and the allergic reaction has been associated with exposure to antibiotic residues in foods. Many of the cases refer to people previously treated with antibiotics and hyper sensitized to a degree that subsequent oral exposure evoked a response. A hypersensitivity reaction to a drug is either IgE-mediated or Non–IgE-mediated reactions. IgE-mediated reactions occur shortly after drug exposure. Instances of IgE-mediated hypersensitivity reactions include urticaria, anaphylaxis, bronchospasm and angioedema. Non IgE-mediated reactions include hemolytic anemia, thrombocytopenia, acute interstitial nephritis, serum sickness, vasculitis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (Granowitz *et al*., 2008) [7].

Indirect and long term hazards are the effects caused by long term exposure of an individual to residues and include carcinogenicity, teratogenicity and reproductive effects. Long term exposure to diethyl stilbesterol can cause vaginal clear cell adenocarcinoma and benign structural abnormalities. The long term exposure to antibiotic residues in milk may result in alteration of the drug resistance of intestinal microflora. The use of the antibiotic avoparcin as a growth promoter in food animals resulted in the development and amplification of vancomycin resistant enterococci. Subsequent colonization in human intestine of these resistant strains causes the clinical disease that would be difficult to treat. Even if the resistant strains bacteria are not human pathogens, they may still be dangerous because they can transfer their antibiotic resistance genes to other pathogenic bacteria. Antibiotic resistant strains of bacteria, including *Salmonell*a, *E. coli* and *Campylobacter* spp., have been isolated from farm animals in many countries.

Antibiotics used in dairy animals

Antibacterial agents like tetracyclines, nitrofurans and sulfonamides are used as feed additives in cattle feed which may excrete in milk and sometimes associated with toxicological effects in human. Carcinogenic and mutagenic effects were demonstrated on animals due to nitrofurans used at high and lengthened doses. These antibacterials are now prohibited in most countries for veterinary use in animal production. The other substances considered as potentially carcinogenic are antibiotic additives: quinoxaline, carbadox and olaquindox (FAO/WHO, 1995) [4]. In long term animal studies, amoxicillin, chloramphenicol, doxycycline, gentamicin and rifampin, have shown effects on reproduction performance in parents and developmental toxicity in their offspring's. This data hold functional insight on possible adverse effects of these antibacterial in pregnant and lactating women and to their young ones. Recently in a study, postulated the risk of retinal detachment in individuals upon continued exposure to fluoroquinolones. Chloramphenicol is also associated with optic neuropathy and brain abscess with varied intensities and clinical manifestations. Apart from the health hazards, antimicrobial residues in milk are responsible for interference with starter culture activity and hence disrupt the manufacture process of milk products (Katla *et al*., 2001) [10]. In the fermented dairy products manufacturing plants, such as cheeses and yogurts, the presence of antimicrobial agents can lead to the partial or total inhibition of the lactic bacterial growth. Antibiotic residues can also interfere with the methylene blue test, intended to estimate the total

microbial load in milk. The time taken for reduction of the dye will be increased, hence causing under estimation of the microbial load. All of these concerns may result in major economic losses to the dairy industry.

Antimicrobial residues and regulatory issues in India

Milk offered for sale is a specific food item that requires strict control and enforcement by all legal regulations and relevant authorities that must allow its marketing at home country and abroad only through special and official permission. In regard to dairy animals in developed countries, to avoid risks related to drug residues in milk, in many countries maximum residue limits (MRLs) have been established for each antimicrobial agent by law, below which it is considered that the drug may safely be used without harming the consumer.

Possible strategies for prevention of antibacterial residues in Indian scenario

Preventing drug contamination of milk is the responsibility of every farm. Drug residues can be avoided by a well-planned drug use program. The sale of contaminated milk will cause the responsible party to be subjected to severe penalties, including suspension of permits and monetary loss. Milk with drugs can adulterate a whole truckload or holding tank of milk.

A. Establishment of pharmacokinetics and withholding time for antibacterial used in dairy animal to describe metabolism and distribution of drugs in different tissue and milk. Withholding periods after treatment of cows with veterinary drugs should be valued. The pharmacokinetics of a drug is also dependent on the vehicle used in a certain drug formulation. Therefore the withholding time is valid for the specific drug. Different withholding periods may be appropriate for two drugs containing the same antibiotic.
B. One practical approach to cut down the residues in milk would involve good hygiene and good management practices at farm and the milk processing units. Modifying and implementing the good management practices is also very important for preventing the spread of disease among livestock which could reduce the need of antibacterial use.
C. Evaluation and use of alternative to antibiotic growth promoter e.g. probiotic microorganisms, immune modulators, organic acids (acidifiers) and other feed suppliments.
D. Although, Directorate General of Health Services under Ministry of Health and Family Welfare has set out the policy for use of antimicrobials to combat antimicrobial resistance in human and animal in India, there is no regulation or policy regulating the use of antibacterials in animals for treatment or as growth promoter. Establishing the use policy for antibacterial in animals will help for monitoring and surveillance of the usage of these drugs.
E. Pharmacovigilance programme would be developed for veterinary pharmaceuticals concerning the safety of veterinary medicines used for the treatment, prevention or diagnosis of disease in animals.
F. Establishment of pharmacovigilance working group and an effective reporting system involving veterinarians, immunologists, pharmacologists, toxicologists and Eco toxicologists is an important prerequisite for the risk assessment of antibacterial drug residues for human and environment.
G. Maintaining treatment records of cows in order to determine appropriate withholding periods. This will also help to treat dry cow with long acting substances so the withholding period can be adjusted if the dry period is shorter than expected.
H. Recommendations of the drug manufacturer regarding dosage, route of administration, treatment intervals and storage condition of antimicrobials should be followed intimately because any deviation may contribute to extended withholding periods.
I. Development and validation of rapid screening tests for detection of antimicrobial residues in milk at individual cow basis to make sure that milk of individual cows is free of inhibitors after the end of the withholding period.

Conclusion

Use of antibiotics as feed additives at sub therapeutic dose should be strictly prohibited. For therapeutic purpose, it must be used in proper dose for proper time. The establishing regulatory standards and good management practices that reduce the risk of antibiotic residues in milk supply are essential components of human food safety. Within the last decade an increasing number of investigations covering antibiotic input, occurrence, fate and effects have been published, but there is still a lack of regulations and guidelines regarding use of antibiotics in veterinary practice in India. The issue of antibiotic residues in food chain warrants the further policies and guidelines to address the possible risk to public health and environment.

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