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ANTIBIOTIC RESIDUES: A GLOBAL CHALLENGE

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ABSTRACT

Presence of drugs or antibiotics residue in food above the maximum level has been recognized worldwide by various public and government authorities. 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 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 general increase of chemicals and drugs in the food supply. The frequent use of antibiotics may result in drug residues that can be found at different concentration levels in products from animal origin, such as milk, meat and other food products. In general, harmful effects of drug and chemical residues may be carcinogenic, teratogenic, reduction in reproductive performance, drug allergy and acute toxicity or poisoning. 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.

KEYWORDS: Antibiotic, Residue, Health.

INTRODUCTION

Residues of veterinary drugs have been recognized as an important aspect of food safety because residues may persist for longer periods after withdrawal of the drug treatment. Chemicals and drugs including antibiotics employed for chemotherapeutic and prophylactic purposes are also used as feed additives to promote growth, improve feed efficiency and synchronize the reproductive cycle and breeding performance which may further lead to residue toxicity. In general, harmful effects of drug and chemical residues may be carcinogenic, teratogenic, reduction in reproductive performance, drug allergy and acute toxicity or poisoning.

The use of antibiotics expanded during the period between 1950 and 1960. Antibiotics are frequently used to compensate for poor production practices. Most of the antibiotics used in food animals are the same as or belong to the same classes as those used in humans. Sweden banned the use of microbial growth promoters in food producing animals [5]. As a result of the ban, the use of antibiotics decreased by approximately 55% during the last more than a decade.

The Swann committee in UK in 1969 found that the use of antibiotics to promote growth in livestock has led to the production of resistant strains of microorganisms which can transmit this resistance to other bacteria. They recommended that the antibiotics in feed be restricted to those which are of economic value in livestock production have little or no application as therapeutic agents in man or animals and will not impair the efficacy of the prescribed therapeutic drug through the development of a resistant strains of organisms.

Swann [31] highlighted the possible adverse effects of antibiotics on human health by prolonged feeding of sub-therapeutic levels of antibiotics to food animals. Antimicrobial classes used to treat chickens included quinolones, tetracyclines, beta-lactanes, aminoglycosides, macriolides, polypeptides and sulphonamides [29]. In spite of the ban on use of antibiotics in Swden, antibiotic resistance continued to exit in a proportion of microbial flora [33].

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 [22]. The mechanism of action of antimicrobial agents as growth promoters is related to interactions with intestinal microbial populations [7].

Antimicrobial growth promoters (AGP) are used to help the animals to digest their food more efficiently, get maximum benefit from it and allow them to develop in to strong and healthy individuals. As prevention of diseases, enhancement of growth and feed efficacy are crucial to vital animal husbandry business, the use of AGP is increasing day by day [9]. AGPs are typically administered in sub-therapeutic doses for long periods of time (usually greater than 2 weeks) and sometimes for the entire duration of production cycle. It was thought that AGPs improve production by 2-10%. Safe and effective use of antibiotic in animal production has received considerable attention in most of the countries in the world. The drug resistance has gained its importance due to the transmission of antibiotic resistance factor to other enteric organisms which have posed a serious public health problem.

The antibiotic residues occur in food mainly as a result of therapeutic treatment for animals or supplementation of animal feed. A limited amount of these arise by the addition of these antibiotics in preservation of milk, meat, fish and poultry. Microbial resistance to antibiotics results from prolonged ingestion of small amount of contaminated food. Many of the antibiotics used to treat bacterial infections in humans have veterinary applications:

prophylactics and growth promoters. In these two cases, the antibiotics are used at a concentration lower than the therapeutics concentrations for a longer period of time, a potentially dangerous practice since it is one of the strongest selective pressures leading to emergence of antibiotic resistance strains of bacteria, induction of allergic reactions in humans and technological problems of fermented meat products [23].

The frequent use of antibiotics may result in drug residues that can be found at different concentration levels in products from animal origin such as milk or meat. Presence of drugs or antibiotics residues in food above the maximum permissible level has been recognized worldwide by various workers [14]. Existence of antibiotic residues in food stuff can pose hazards to human health. Among them are sensitivity to antibiotics, allergic reactions, imbalances of microflora, bacterial resistance to antibiotics in microorganisms and losses in to the food industry.

In 1969, the US Food and Drug Administration issued a warning that use of antibiotic in food producing animals will be regulated more closely owing to the potential health hazard from residues in milk, meat and eggs. They have entirely prohibited the use of food products containing antibiotic especially penicillin and the product must be discarded for human consumption. Chloromycetine although a useful antibiotic, has been proved as one of the most dangerous because it has been considered responsible for fatal blood dyscrasis. It has also been regarded as toxic to premature infants.

Antibiotic residues in chicken meat

The worldwide commercial poultry industry is the largest supplier of animal protein in the form of meat and eggs. Its significance is even greater in the developing countries, usually providing both protein and income for small family [15]. In poultry, usage of antibiotics had facilitated their efficient production and also enhanced the health and well being of poultry by reducing the incidences of diseases but unfortunately, unauthorized use of these antibiotics, the failure to follow label directions or inappropriate withdrawal period of time before slaughtering of poultry could lead to contamination of edible poultry tissues with antibiotic residues, with potential adverse effect on human health [8]. Antibiotic residues in foods of animal origin are one of the sources of concern among the public and medical health professionals [1]. Al-Ghamdi [3] studied the presence of antibiotic residue of muscle, liver and egg samples collected from 33 broiler and 5 layer farms in the eastern province of Saudi Arabia. Antibiotic residue positive samples were identified in the products of 23 (69.7%) broiler and 3 (60%) layer poultry farms. All the antibiotic residue positive broiler farms were positive for at least one tetracycline compound in raw muscle (87%) and liver (100%), respectively while, 73.9% broiler farms were positive for two or more tetracycline in these two tissues.

Alhendi *et al.* [2] studied drug residues in broiler chickens fed with antibiotic in ration. They observed that daily oral administration of two dose levels of 1 and 2 mg/kg body mass of ampicillin (A), 50 and 100 mg/kg body weight of OTC (O) and 50 and 100 mg/kg of sulphadimidine(s), in broiler feed resulted in an immediate increase in concentration of antibiotics in plasma and tissues from day 1 until day 40 of the treatment. At day 40, a range of 0.61 to 1.94, 0.24 to 2.25 and 1.30 to 6.70 ug/g or ug/ml was observed in samples of respective groups. Pavlov *et al.* (2005) studied the residue levels of tobramycine in muscle (115), liver (192) and kidney (155) samples of poultry stored at -18^{0}C. They observed that residues of tobramycine were found to decrease during storage period of 60 days. They found that 4% muscles, 17% livers and 33% kidney samples were positive for antibiotic residues. Sahid *et al.* (2007) studied on 100 tissue samples (33 liver, 33 kidney and 34 muscles) collected from local market of Rawalpindi and Islamabad. They observed that 13 (39.4%) liver, 9 (27.3%) kidney and 7 (20.6%) muscle samples were positive for antibiotic residues. Salehzadeh *et al.* [26] collected 270 chicken muscle, liver and kidney samples from 90 broiler farm in Tehran province and observed that samples from 22 (24%) of farms showed residue above maximum residual limits (MRLs). The enrofloxacine positive samples which showed residues of enrofloxacine above MRLs were 8 (8.88%), 12 (13.33%) and 22 (22.44%) of muscle liver and kidney samples. The mean concentrations of enrofloxacin in muscle, liver and kidney samples were 18.32, 18.34 and 26.06 ng/g, respectively.

Table: 1. Maximum permissible level of antibiotics in meat in the USA

Antibiotics	Animal species	Level (mg/kg)
Penicillin	Cattle, calves	0.050
Tetracycline	Calves, sheep, goats, pigs	0.25
Tylosine	Cattle, calves, pigs	0.20
Erythromycine	Pigs	0.10
Neomycine	Calves	0.25
Oxytetracycline	Cattle, calves, pigs	0.10
Chlortetracycline	Cattle	0.10
Chlortetracycline	Calves and pig muscle	1.00
Chlortetracycline	Calf liver and kidney	4.00
Chlortetracycline	Pig liver	2.0
Lincomycine	Pigs	0.10

Trivedi [32] observed wide use of antibiotics like tetracyclines, fluoroquinolones, beta-lactanes and macrolide antibiotics in the poultry farms at the surroundings of Jabalpur. In his study among three antibiotics, enrofloxacin was the most predominant antibiotic (20.55%) detected in 180 chicken meat samples followed by OTC (12.78%) and amoxycillin (8.89%). The concentration of three antibiotics (enrofloxacin, oxytetracycline and amoxicillin) was maximum to the extent of 61.66% in kidney samples of chicken, followed by 51.66% in liver and 38.33% in muscle samples. Out of 180 samples, the residue concentration of three antibiotics in 19 samples (10.55%) was found to be above the Maximum Permissible Limit (MPL). Among the three antibiotics studied, oxytetracycline was largely inactivated by heat while amoxicillin was partially heat labile and enrofloxacin was found resistance to heat. Maximum permissible level of antibiotics in meat in the USA is given in Table 1.

Antibiotic residues in milk

The prevalence of antibiotic residue in milk product had been observed due to indiscriminate use of various antibiotics in the treatment of mastitis. Sundlof *et al.* [30] observed that pencillins, tetracyclines, sulphonamides and aminoglycosides were most frequently used in lactating animals, which led to occurrence of their residues in milk. Several workers have reported the presence of antibiotic in the milk after the treatment of mastitis cases.

In a survey carried out by NIN [21] in Hyderabad and surrounding villages indicated that the usage of oxytetracycline (OTC) was higher in Hyderabad in comparison to suburban villages. Among the samples of buffalo milk collected from private dairy farmers, 73% had OTC levels ranging from 0.2-2.67 ug/ml and among the samples collected from the market milk vendors, 9% had OTC level ranging from 0.2-1.4 ug/ml. The milk samples obtained from the Govt. dairy farm did not contain any drug residues. The OTC residues in milk collected from Hyderabad were 2 to 67 times higher than the safe limit of 0.1 ug/ml indicated the indiscriminate use of veterinary drugs by dairy farmers at Hyderabad. Antibiotics used as therapeutic agents or as feed supplement in milch animal lead to secretion of their residue in milk [29]. These residues not only create problems in dairy industry but also have immense public health significance. Hamann *et al.* [13] reported that presence of antibiotic residues in milk is influenced by following factors:

a. concentration and type of antibiotic used
b. carrier employed in the preparation of antibiotic
c. amount of milk drawn from the gland
d. time interval between treatment and milking
e. absorbance of udder tissues
f. milk yield
g. individual factors.

The antibiotic residues in milk are of concern in two respects. First they may curtail proper lactic acid fermentation in cultured products resulting in spoilage and the possibility that staphylococci may proliferate before curd formation. Secondly, the ingestion of antibiotic contaminated milk may cause a reaction in human already sensitized to the contaminants. The potential hazards of ingesting antibiotic residues in contaminated milk include “allergic reactions, interference in the intestinal flora and resistance population of bacteria in the general population [4]. Allergies to antibiotic occur when the body’s immune system attacks the antibiotic, which is often a haptenic metabolite of the antibiotic and some carrier tissues. Small levels of antibiotics can be very hazardous to susceptible humans causing acute to severe reactions.

Penicillin raises most apprehensive in this respect because it strongly inhibits lactic acid bacteria and because it may trigger anaphylactic shock in unusually sensitive patients to whom it has been administered previously. Other antibiotics may cause similar reactions but evidences indicate that penicillin is of great concern. It has been suggested that the present recommended limit of 0.05 IU of penicillin/ml of milk is too high and offers no guarantee of safety.

The presence of even small quantities of antibiotics in milk is found to create problems in dairy industry [18]. The commonly encountered problems included:

a. Inadequate curdling of milk and improper ripening of cheese during their production.
b. Decreased and flavour production in cultured products
c. Interferences with starter culture resulting in loss of production. Antibiotic residues may cause partial or complete inhibition of starter cultures used in fermentation, leading to interference in the production of fermented products like Yogurt and cheese.
d. Difficulties in validation of certain quality control test.

Colins [6] reported that about 28% of commercial milk supply in the US indicated the presence of antibiotic residues. Approximately 4.2 million milk samples were tested for antibiotic residues and 30.9 million kg of milk was dumped because of positive assay result. Lee *et al.* [16] examined antibiotic residues in milk after I/M injections, I/U injections and oral administration in dairy cows. Amoxicillin residues were detected in milk after intramuscular injection. They concluded that type of antibiotic, dosage and route of administration influences the duration over which antibiotic residues could be detected in milk. They further concluded that milk yield on the sampling day and lactation stage had no influence on the duration over which antibiotic residues could be detected in milk. Podhorniak [24] observed that no loss of cloxacillin residues in milk was observed after 48 hrs storage at 4^0 C or 24 hrs at 25^0 C. Slight loss was noted after 72 hrs storage at 4^0 C and 48 hrs storage at 25^0 C.

Lack of awareness of withdrawal times or deliberate abuse may lead to elevated levels of drug residues in the milk. The most common causes of occurrence of drug residues in milk are insufficient identification of treated cows, insufficient knowledge about withdrawal periods and failures due to hired staff. Singh [28] reported that raw milk samples collected from dairy farms at Jabalpur were free from residue concentration of amoxicillin and cloxacillin. He also observed that animals treated with amoxicillin and cloxacillin showed significant level of residues concentration of amoxicillin and cloxacillin on day one (post-treatment). However, similar animals did not show residues of amoxicillin and cloxacillin in milk samples collected on day 5 post- treatment. He recommended that a withdrawl period of atleast 24 hrs is needed after administration of amoxicillin and cloxacillin. Thus, milk from these antibiotic treated animals should not be used for human consumption for 24 hrs post-treatment.

Toxicity of Antibiotic residues

Possible adverse effects of antibiotics residues have been suggested. These includes allergic/anaphylactic reactions to residues, chronic toxic effects occurring with prolonged exposure to low levels of antibiotics, development of antibiotic resistance bacteria in treated animals and disruption of normal human flora in the intestine. There are few reports which indicate that sensitive individuals may experience allergic reactions to antibiotic residues, particularly of penicillin residue. Anaphylactic reactions have been reported to result from the consumption of meat containing penicillin [13]. Estimates of the prevalence of drug sensitivity vary but are estimated to be around 7% in the general population.

Symptoms of chronic exposure to OTC include blood changes such as leucocytosis, atypical lymphocytes, lung congestion, toxic granulation of granulocytes and thrombocytopenia purpura. Liver injury and delayed blood coagulation may also occur. It can damage calcium rich organs like teeth and bones and sometimes erosion of nasal cavities. Children under 7 years of age may develop a brown discolouration of the teeth. Infants born from the mothers treated with OTC during pregnancy may develop discolouration of the teeth. Beta-lactum antibiotics usually clear rapidly from the blood via the kidneys and excreted in to the urine (residues in kidney and liver are about 100 times higher than muscles). Estimate shows that 10 IU (0.6 ug) of penicillin could cause an allergic reaction in a sensitive individual; 0.01 IU/ml of milk in a very sensitive individual. Enrofloxacine a fluroquinolone antibiotic acts by inhibition of bacterial DNA gyrase. Embryo lethality and teratogenecity of fluroquinolone in rats and rabbits has been suggested [12].

The Food and Drug Administration center for Veterinary Medicine has proposed to withdraw approval for use of fluoroquinolone antibicrobial, enrofloxacine in poultry. Their decision is not based on drugs direct toxicity but on potential for increasing human pathogen resistance.

Lemus [17] suggested that antibiotic residues that may be present in carcasses of medicated livestock could pass to and greatly reduce scavenger wild life populations. They found high concentrations of antibiotics in the plasma of many nesting cinereous (57%) and Egyptain (40%) vulture. Enrofloxacine and ciprofloxacine were also found in liver samples of all dead cinereous vultures.

Antibiotic resistance threat to human health

Antibiotic resistance is a global public health concern today. The U.S. Centers for Disease Control and Prevention has described resistance as one of the world's most pressing health problems, because the number of bacteria resistance to antibiotics has increased in the last decade and many bacterial infections are becoming resistance to the most commonly prescribed treatment. The WHO has identified antibiotic resistance as one of the three greatest threats to human health.

Microorganisms resistance to antibiotic drugs emerged and spread soon after the introduction of those drugs and in parallel with their use. Many well known antibiotics are no longer effective to treat common infections such as otitis, pneumonia, gonorrhoea and tuberculosis. Thus, microbial resistance is the main cause of newly emerging and reemerging infectious diseases.

In 1993, WHO declared tuberculosis a global emergency, it was stated that it is a leading infectious killer of adults and will have killed at least 30 million people within the next 10 years if current trends continue. A cost effective and proven drug treatment exits but careless tuberculosis treatment practices are triggering bacilli that are resistance to once effective drugs. Multidrug resistance tuberculosis develops when doctors or other health workers prescribed the wrong drugs or wrong combinations of drugs [27]. Antimicrobial resistance results in higher costs due to the use of more expensive combinations of antibiotics to increased rate of hospitalization for infections once easily treated and an outpatient basis.

Drug use in livestock is implicated in antimicrobial resistance in humans because many antibacterial drugs used for livestock are same as or similar to drugs used for humans. Some pathogens can pass from livestock to humans, either directly through contact [10] or through food products that are improperly processed, handled or prepared. Some food born illness in humans caused by resistant pathogens have been traced in livestock products and have been linked to live animals on farms.

Tragically *Salmonella* bacteria are only one of many diseases producing organism that are becoming increasingly resistant to antibiotics due to the continuous feeding of these antibiotics to livestock. For example in 1990s less than 10% *Staphylococci* bacteria were resistance to penicillin but in 2000 over 90% of the *Staphylococci* became resistance to penicillin. The chronic use of antibiotics in factory forms has created the likelihood of an epidemic of untreatable *Salmonella* food poisoning [20]. A recent example is a clone of *S. typhimurium* DT104, resistance to tetracyclines, ampicillin, streptomycine, chloramphenicol and sulphonamides which have become prevalent in many countries. An outbreak of human nalidixic acid resistant *S. typhimurium* DT 104 infection in Denmark was traced in a pig farm. Another outbreak of the same infection, reported in the United Kingdome was traced in a dairy farm where fluroquinolones had been used in the cattle a month before the outbreak. Following the introduction of fluroquinolones for use in food producing animals, the emergence of *Salmonella* serotypes with reduced susceptibility to fluroquinolones in humans has become a cause for particular concern [19]. Following the introduction of fluroquinolones for use in poultry there has been a dramatic rise in the prevalence of fluroquinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans [34].

The use of avoparcine as a growth promoting feed additives in animal husbandry has contributed to the reservoir of transferable resistance genes to glycopeptides including vancomycine, in the commensally enterococci of animals. Glycopeptides-resistant enterococci cause serious infections in hospitalized immune impaired patients. In this setting they contribute to increased morbidity and mortality, in part because of limited therapeutic options.

Multiresistant *Escherichia coli* have been evolved by the use of broad spectrum antimicrobials in both livestock and humans. The development of antimicrobial resistance in *E. coli* creates problem due to their propensity to disseminate antimicrobial resistance genes. Resistance genes have been traced from *E. coli* in animals to *E. coli* in humans Certain *E. coli* are food borne pathogens and most of these strains are currently susceptible to antimicrobials. Erythromycine, should not be used in livestock within 48 hrs of slaughter for human consumption. Lincomycine and spectinomycine combined are valuable antibiotics in the prophylaxix and therapy of chronic respiratory diseases associated with mycoplasma in poultry as are administered in the drinking water, treatment must be discontinued 48 hrs before slaughter. The WHO has recommended that antibiotics which are also licensed in human medicine should not be used any more as growth promoters in livestock.

Not only is there a risk to human health from direct toxicity and from allergic reactions in persons sensitized to the antibiotics involved but antibiotic residues may also interfere with any microbial examinations which may be necessary in assessing the fitness of the carcass. The age restrictions have been imposed for feeding of antibiotics in animals. It is given in Table 2. If use of antibiotics is necessary as in treatment of animals a withholding period must be allowed till residues can no longer be detected. The withdrawal time and tolerance level of antibiotics in different species of animals is furnished in Tables 3, 4, 5 and 6.

Table: 2. Age restriction on feeding antibiotics

Species	**Age**
Swine	4-6 weeks
Poultry	8-10 weeks
Lamb	2 months
Fur bearing animals	2-3 months
Calves	3 months
Beef Cattle	18 months

Table: 3. Withdrawal time and tolerance level of antibiotics in cattle

Drugs	Pre-slaughter withdrawal time (days)		
	Oral	Injectables	Tolerance level (ppm)
Ampicillin	15	6	0.01
Bacitracin	0	-	0.05
Chlortetracycline	10	10	0.10
Dihydrostreptomycine	10	30	-
Erythromycine	-	14	0
Neomycine	-	-	0.10
Procain penicillin	-	10	0.05
Oxytetracycline	7	22	0.10
Sulphamezathine	21	-	0.10

Table: 4. Withdrawal time and tolerance level of antibiotics in sheep and goats

Drugs	Pre-slaughter withdrawal time (days)		
	Oral	Injectables	Tolerance level (ppm)
Dihydrostreptomycine	-	30	-
Erythromycine	-	3	-
Procain penicillin G	-	9	0
Chlortetracycline	2	-	-
Sulphamezathine	10	10	-
Sulphaquinoxaline	10	-	-

Table: 5. Withdrawal time and tolerance level of antibiotics in swine

Drugs	Pre-slaughter withdrawal time (days)		
	Oral	Injectables	Tolerance level (ppm)
Ampicillin	1	15	0.01
Bacitracin	0	-	0.05
Chlortetracycline	7	-	1.0
Dihydrostreptomycine	30	30	0
Erythromycine	7	7	0.10
Lincomycine	6	2	0.10
Procain penicillin	-	7	0
Oxytetracycline	26	26	0.10

Table: 6. Withdrawal time and tolerance level of antibiotics in chickens

Drugs	Pre-slaughter withdrawal time (days)	Tolerance level (ppm)
Bacitracin	0	0.05
Chlortetracycline	1	0
Erythromycine	2	0.125
Gentamycine	35	-
Streptomycine	4	0.10
Carbomycine	1	0
Monensine	5	0.05
Tylosine	5	0.20

CONCLUSION

It is concluded that 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 and mostly after 4-5 days of administration secretion of residues are negligible. Hence, the withdrawal time of different drugs should be strictly followed and during this period milk, meat and other animal products like liver and kidney should not be used for human consumption. Use of antibiotic as growth promoter should be strictly prohibited and whenever they are used for therapeutic purpose must be used in proper doses and for proper time. Thus, by observing proper scientific guidelines and precautions we can minimize the harmful effects of antibiotic residues.

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