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Antibiotic residues and human health hazard – review

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Abstract

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Use of antimicrobials to food animals for treatment, prophylaxis and as growth promoter's results in deposition of their residues in animal products. Consumption of these residues through animal products may cause development of antimicrobial drug resistance, hypersensitivity reaction, carcinogenicity, mutagenicity, teratogenicity, bone marrow depression, and disruption of normal intestinal flora. Withdrawal periods and rules pertaining to antimicrobial residues should be strictly followed to make the animal products safe for human consumption. The present review aimed to show human health hazard after consuming food of animal origin with antibiotic residues.

Keywords: antimicrobials; antibiotic residues; food animals; health hazard

Introduction

Antimicrobials also known as antibiotics, anti-infectives, antibacterials or chemotherapeutics, include synthetic and natural compounds. They are substances with low molecular weight produced by fungi and bacteria. Antimicrobials are widely used to control, prevent, and treat infection, and to enhance animal growth and feed efficiency (Schwarz et al., 2001). As a result of their extensive use, residues are often found in animal products – meat, milk and eggs.

The use of antibiotics in food animals

Antibiotics as growth promoters

The antibiotic effect as growth promoters is related to interactions between the antibiotics and the intestinal microbiota (Bates et al., 1994). The low doses of antibiotics are sometimes added to poultry, cattle and swine feed to increase their weight. For example, sulphonamides are used as growth promoter in poultry.

Antibiotics as therapy and prophylaxis

In animals, antibiotics may either be administered to prevent disease or during an infection. According to Tollefson & Miller (2000), the increased nurture of livestock or poultry can lead to frequently prophylactic and therapeutic antimicrobial use. Therapeutic use of antimicrobial drugs is essential for maintaining animal health. In this livestock sector, almost 90% of the antimicrobial drugs is used at subtherapeutic levels for disease prevention or growth promotion. Today, major cases requiring antibiotic use include intestinal and respiratory infections, mastitis in dairy cows and skin and organ abscesses (Teuber, 2001).

In 2008, Nisha (2008) summarized the adverse consequences of the presence of antimicrobial residues on the consumer. That is transfer of antibiotic resistant bacteria to the human, immunopathological effects, autoimmunity, carcinogenicity (Sulphamethazine, Oxytetracycline, Furazolidone), mutagenicity, nephropathy (Gentamicin), hepatotoxicity, reproductive disorders, bone marrow toxicity (Chloramphenicol) and allergy (Penicillin).

Sony (2012), in turn, divides into two types of risks related to antimicrobial residues. These are direct or short-term risks as well as indirect and long-term risks. To the first category, the concern toxic and allergic reactions as well as hypersensitivity reactions and in the second group – carcinogenicity, teratogenicity, microbiological effects (resistance) and reproductive toxicity.

Priyanka et al. (2017) described in detail risks, according to duration of exposure to residues and the time onset of health effects. The article shows the risks of residues of antibiotics in milk. As an example to the direct risks of the authors includes the beta-lactam antibiotics regardless of their low concentration in milk causes allergic hypersensitive reaction in sensitized individual immediately after consumption. Chronic toxic effects occurring with prolonged exposure to low levels of antibiotics include everything listed by Sony above and add disruption of normal intestinal flora.

According to Lee et al. (2001) there are again two main types of adverse effects from the presence of residues of antibiotics in food of animal origin in terms of human health. The first is hypersensitive (immunological, allergic) reactions. Immunological reactions may range from a weak reaction such as rash to direct life-threatening as anaphylactic shock. The second type of negative impact is the development of antibiotic resistance.

Antimicrobial drug resistance

Antimicrobial resistance is now recognized as one of the most serious global threats to human health in the 21st century. For this reason, the number of published articles for antimicrobial drug resistance has increased markedly in the last decade. Livestock is known as an important reservoir of antimicrobial-resistant zoonotic bacteria. In his review from 1986, Okolo (1986) draws attention to the creation of antibiotic-resistant microorganisms after the uncontrolled use of antibiotics.

In studies conducted by Bates et al. (1994) and Kruse & Rorvik (1996), the authors found that the purchased raw chicken meat and chickencarcasses were a source of vancomycin – resistant enterococci (*Enterococcus faecium*) and concluded that the animals could serve as a source of vancomycin-resistant enterococci that can enter the human food chain.

In other study of Kruse et al. (1999) proved a strong and statistically significant association between the use of the avoparcin as a growth promoter in Norwegian poultry production and the occurrence of vancomycin-resistant *Enterococcus species* (VRE). VRE had been isolated from 30% investigated broiler carcasses.

As reported by Constable et al. (2017), following the ban of usage of avoparcin in EU, in Italy decrise VRE prevalence in poultry carcasses and in Hungary a decline in prevalence of VRE among slaughtered cattle, swine and poultry.

According to Beyene (2016), humanity develop drug resistant to bacteria such as *Staphylococcus*, *Campylobacter* and *Salmonella* after consuming food of animal origin. The author indicates of drugs as fluoroquinolones and avaoparin that have been shown to cause the growth of resistant bacteria.

The results of current study showed basic information on relationship between antibiotic residue and resistance for 6 compounds in 13 chicken samples. The authors investigated the correlation between the level of 17 antibiotic residues and 6 antibiotic resistances of *Escherichia coli* isolates in chicken meats Lee et al. (2018). On the other side, Warren et al. (2008) proved that imported chicken breasts from Brazil and South America are a potential source of quinolone-resistant *Escherichia coli* in the UK. Some studies reported about quinolone-resistant *Salmonella* spp. and *Campylobacter* spp. These bacteria can enter the human food chain through the food offered and after contact with animals (Radostits & Rubinstein, 2002; Fàbrega et al., 2008).

Phillips et al. (2004) described multiresistant *Salmonella*, macrolide – and fluoroquinolone – resistant *Campylobacteria*, glucopeptide – and streptogramin – resistant *Enterococci* and multi-resistant *E. coli*, which the mode of transmission is the food chain.

Skockova et al. (2015) in their study found that some strains of *Escherichia coli* isolated from poultry, pork, beef and venison meat were resistant to one or more groups of antimicrobial agents (tetracycline, b-lactams and quinolones). The same and another study reported that due to the frequent use of antibiotics in livestock production, bacteria originating from food animals frequently carry a resistance to a range of antimicrobial agents, including those commonly used in humans (Hammerum & Heuer, 2009; Skockova et al., 2015).

Hypersensitivity (immunological or allergic) reaction

Drug hypersensitivity was defined as an immune arbitrated response to a drug agent in a sensitized patient. Allergic reactions to drugs may include cutaneous reaction, serum sickness and the most severe allergic reaction is hypersensitivity leading to anaphylactic shock. This is a severe, sudden and systemic allergic reaction, usually affecting more organs, which may have a fatal outcome within minutes. Numerous data are available in the literature for reported cases of allergic reactions to antimicrobial agents. According to Paige

et al. (1997) β-lactam antibiotics, and especially penicillin and cephalosporins, cause mild allergic reactions, such as skin rashes and allergic dermatitis, but can also lead to anaphylaxic conditions. Baynes et al. (2016) also confirmed risk of developing allergy after consuming meat products having penicillin residues which can manifest as a skin rash or even severe anaphylaxis. Also an anaphylactic reaction following consumption of pork containing penicillin was reported by Kanny et al. (1994) and Raison-Peyron et al. (2001). Some studies reported about allergic reactions in sensitized individuals provoke by penicillin residues in milk (Swann, 1969; Dewdney et al., 1991). In conclusion, about 10 per cent of the human population was considered hypersensitive to penicillin. Similar results for allergic hypersensitive reaction after consumption of milk with residues of beta-lactam antibiotics showed the studies of Sierra et al. (2009). Most of the reported allergic reactions are related to beta-lactam antibiotic residues in milk include serum sickness, erythema multiforme, hemolytic anamia, thrombocytopenia, vasculitis, acute interstitial nephritis, Stevens-Johnson syndrome and toxic epidermal necrolysis Granowitz et al. (2008).

Carcinogenicity

The term carcinogen refers to an effect produced by a substance having carcinogenic activity. According to the International Agency for Research on cancer (IARC) and Bendesky et al. (2002) evidence abounds to suggest that metronidazole is carcinogenic in animal, but insufficient to do so in humans. The following facts prove carcinogenic of metronidazole to humans: it is a mutagen in bacterial systems, it is a genotoxic to human cells and also it is carcinogenic to animals. Carcinogenic veterinary drugs in many countries are quinoxaline, nitrofurans and nitromidazoles. It is proved that these drugs might be acquired via food of animal origin as antimicrobial residues (Booth & McDonald, 1988). Similar results for carcinogenic and genotoxic effect of oxytetracycline and furazolidone showed the studies of Mitchell et al. (1998). The authors specified that when oxytetracycline reacted with nitrite as nitrosamine, the same is potential carcinogen.

Mutagenicity

The term mutagen was used to describe physical or chemical agents that can cause a mutation in a DNA molecule. These agents can also damage the genetic component of a cell or organisms. In his study, Beyene (2016) pointed drugs as a probable threat to the human population that might have adversely affects human fertility. As reported by Botsoglou & Fletouris (2001) several drugs including doxorubicin have been shown to elicit mutagenic activities.

Teratogenicity

The term teratogen applies to drug or chemical agent that produces a toxic effect on the embryo or fetus during a critical phase of gestation. According to Beyene (2016), consequently was produced a congenital malformation, which affects the structural and functional integrity of the organism. For example, when benzimidazole had been given during early stage of pregnancy, it is proved that it has embryo toxic and teratogenic effect. In addition to embryo toxicity; the oxfendazole has also unveiled a mutagenic effect.

Some drugs or their residues taken in the long term, but at low doses, may produce reproductive and teratogenic effects. This is confirmed by Sundlof (1994), who reported that residues of nitroimidazoles and 3-nitrofurans cause human neoplasia and the presence of residues of certain hormonal preparations, the author points out as causing vaginal adenocarcinoma and benign abnormalities of the uterus.

Disruption of normal intestinal flora

Intestinal microflora plays an important role in human physiology and human health. Microflora in the gastrointestinal tract of human is an extremely and relatively stable complex of microorganisms consisting of 500 to 1000 species. Neish (2009) and Pimentel (2012), affirmed that. According to Gibson & McCartney (1998), some antibiotics kill over 99% of beneficial bacteria in the gastrointestinal tract and their recover can be for months.

The broad-spectrum antibiotics might adversely affect a wide range of intestinal flora and subsequently cause gastrointestinal disturbance. Flunixin, streptomycin and tylosin are drugs used in animals and also use of vancomycin, nitroimidazole and metronidazole in humans are known with this effect and were describes by Beyene (2016). There was little scientific information on the effect of antimicrobial residues on the bacterial flora of the human intestinal tract. Cabello (2006), in his study reports that detected residual amounts of antibiotics in salmon samples may lead to a change in normal human microflora. In a similar article Linge et al. (2007), describe intestinal dysbiosis and also allergic reactions and resistant populations of bacteria after the presence of antibiotic residues in milk.

Other affects

In addition to the above-listed adverse effects, residues of antibiotics may still cause nephropathy (Gentamicin), and exposure to chloramphenicol residues in foods can rarely cause a fatal blood dyscrasia in individuals (Settepani, 1984).Granowitz et al. (2008) reported for aplastic anemia caused by antibiotic residues (chloramphenicol) in milk.Oth-

er literature data indicates bone marrow depression, hepatic disorders, reproductive disorders and myelotoxicity (Nisha, 2008). Robert (1996) reported that a significant percentage of the administrated tetracyclines are excreted in bovine milk and cause except those listedabove harmful effects on consumers (allergic reactions, disruption of normal intestinal flora, development of antibiotic-resistant bacteria) and liver damage and yellowing of teeth. Similar results associated with toxicological effects such as leucocytosis, lung congestion, atypical lymphocytes, thrombocytopenia purpura, toxic granulation of granulocytes and brown discolouration of the teeth after consuming milk with tetracyclines, nitrofurans and sulfonamides residues are reported by Ram et al. (2000) and Vragovic et al. (2012).

Conclusion

Veterinary drugs are used to control, prevent, treat infection and enhance animal growth and feed efficiency. Some literature dataindicate that about 80% of all livestock receive drugs for part or most of their lives. The use of antibiotics in food-producing animals may result in residues in food product from animal origin, such as meat, milk, eggs and honey. It should be noted that, in addition to the positive effect on human and animal health control, antimicrobials can also be dangerous for humans. Literature data demonstrate the harmful effects of residues in animal products; therefore the prudent and responsible use of antibiotics is an essential part of the ethical approach to improving animal health and food safety.

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