REVIEW ARTICLE

Antibiotics in Milk and the Risk of Drug Resistance

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Abstract

The mammary glands of all mammals produce a biological fluid after giving birth known as milk. Intrinsic factors impacting drug transition to milk include animal breed, species, milk protein, fat content, and lactation period. Environmental conditions, disease, drug solubility, and drug-to-drug interaction are the extrinsic factors. Antibiotics are an important factor in animal feed production. Antibiotics are mainly administered in animals for disease prevention, treatment, and growth promotion. Antibiotic residues could be detected in animal products such as meat, egg, and milk. The side effects of antibiotic residues include immunopathological effects, antibiotic-resistant bacterial transfer to humans, allergy, nephropathy (gentamicin), mutagenicity, reproductive disorders, bone marrow toxicity (chloramphenicol), hepatotoxicity, and carcinogenicity (oxytetracycline, sulphamethazine, and furazolidone). Antibiotic-resistant bacterial transfer to humans because of the resistance mobile properties is the most important detrimental impact. This review addresses the antibiotics pharmacology in milk and the side effects of their residues on human health.

Keywords

Milk, Antibiotics, Antibiotic Residues, Public health, Antibiotic Resistance

INTRODUCTION

Mammalian births are followed by milk production from the mammary glands. Milk mainly comprises lactose, emulsified fat globules, and solution-forming soluble proteins in combination with the colloidal dispersed proteins. Milk is a nutritious food that contains different vitamins, minerals, dissolved gases, and enzymes[1].

The presence of antibiotics in mammalian milk have been documented in various literatures[2,3]. Active and passive diffusions are the two main mechanisms by which antibiotics passes from plasma to the milk of mammalians including humans[2]. For instance, higher nitrofurantoin and cimetidine concentrations have been reported in human milk and these drugs were passed from plasma to milk via the process called passive diffusion[4]. On the contrary, the passage of benzylpenicillin across the blood-milk barrier occurs through active transport[5]. However, probenecid can inhibit the organic acid's active transport at the epithelial barriers[6,7]. Other than the aforementioned

mechanisms, exocytosis and pinocytosis are effective drugs to milk transition mechanisms. The milk/plasma (M/P) ratio determines the drug into milk transition capability[8]. The drug's physicochemical characteristics and milk composition affect the M/P rate, which is calculated using octanol/water partition rate, drugs pKa, and binding to plasma proteins. High M/P ratio drugs are actively secreted into the milk[9]. The milk drug concentration is directly affected by the concentration of maternal plasma drug. Contrarily, the blood drug concentration is influenced by the maternal dose and maternal drug metabolism. The drug metabolism is assessed genetically and can vary among mammals. For instance, the clomipramine plasma concentration can exhibit a 50 times variation among dogs[10].

Antibiotic-contaminated milk (above maximum residue limit (MRL)) is toxic to humans and produces superbugs (multi-drug resistant) followed by life-threatening antibiotic therapy failures. Antibiotic exposure for a long duration could also change the gut microflora composition leading to enhanced disease occurrence[11]. Antibiotics residues could cause nephropathy (gentamicin), allergy, reproductive disorders, mutagenicity, carcinogenicity (furazolidone, oxytetracycline, sulphamethazine), and bone marrow toxicity (chloramphenicol)[12]. Furthermore, antibiotic-resistant bacterial transfer in humans is the most important side effect because of the mobile resistance properties. Therefore, antibiotic administration should be regulated in food animals to avoid detrimental impacts[13,14] (Figure 1).

FACTORS AFFECTING DRUG TRANSITION TO THE MILK

Hormonal changes are common during the pregnancy and lactation periods. Alterations in physiological factors affect the concentration of maternal plasma drugs during pregnancy[14]. The concentrations of plasma proteins (globulin and albumin) increase in the lactation period. A reduced blood protein concentration has been reported during the last trimester of pregnancy period whereas the levels of plasma protein concentration become normal during the lactation period[15]. The changes in drug pharmacokinetics during the lactation period resemble the drug pharmacokinetics alteration in pregnancy[14]. Contrarily, Santoshi and Papich (2000) did not observe any variation in the excretion, plasma distribution, and gentamicin drug exposure (AUC) between mares during the last pregnancy and lactation periods[16]. Hormonal changes, body mass/weight, and fat percentage can affect the drug pharmacokinetics during lactation

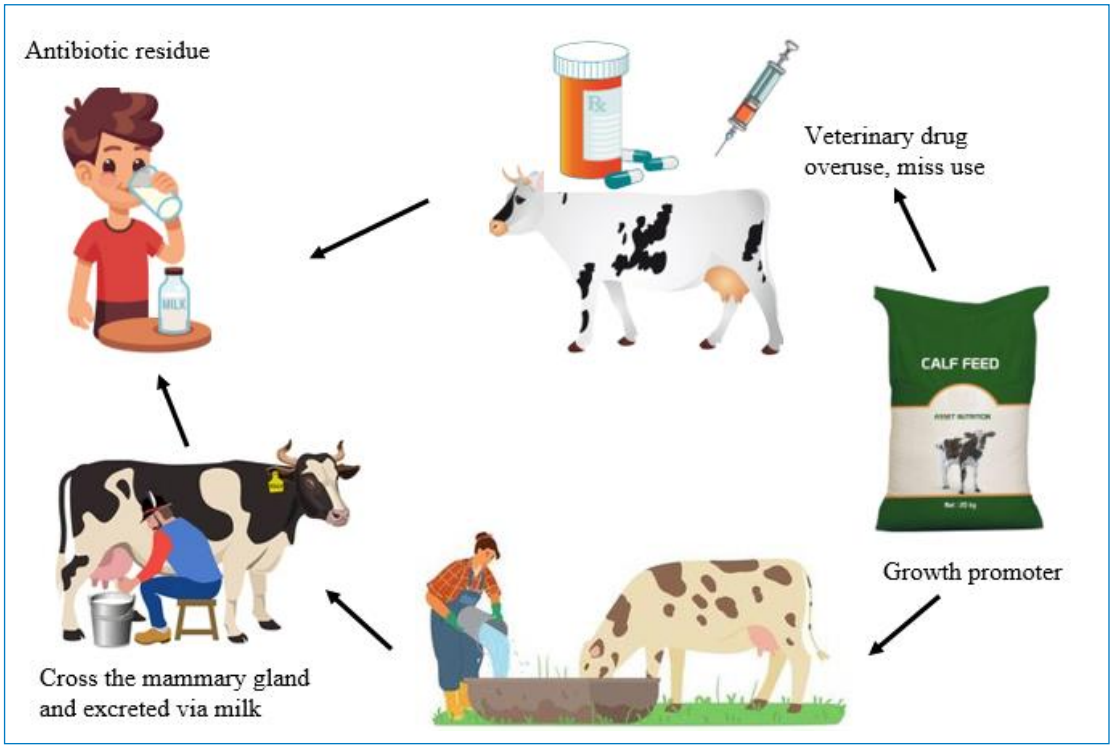

Figure 1. Antibiotic residue in milk.

and the postpartum period[14]. Lactation is known to cause more significant alterations in the drug plasma pharmacokinetics (half-life, clearance, increased distribution volume) than pregnancy[17].

Animals-Related Factors Affecting Drug Transition to the Milk

Species

Protein and fat content is high in sheep milk as compared to goat and cow. A high accumulation of doramectin has been reported in sheep milk than in goat milk, even at the same dose administration[18]. Danofloxacin investigations in lactating sheep and cows have also demonstrated similar findings with higher danofloxacin concentrations in sheep milk[19]. Lipophilic drugs could easily pass through high-fat sheep milk as compared to cow and goat milk.

Breed

The drug into milk transition varies with the breeds. Milk fat and protein contents are known to impact the drug transition. For example, fat and protein ratios are comparatively higher in the milk of Guernsey and Jersey breeds as compared to other breeds. Lipophilic drugs with high milk protein affinity become more concentrated in these breeds[20].

Nutrition

Ration's acetate/propionate ratio is related to the milk composition. Nutritional properties such as the roughage/concentrated feed ratio, herbage quality, and fat content in the feed could impact the composition of milk[21]. Nutrition imbalance (low energy/protein ratio) can reduce milk protein and fat[21]. The milk-fat ratio is lesser in the case of a higher concentrate feed ratio than the roughage feed. Cows fed on vegetable oil-rich rations produce milk with low fat[21].The milk fat ratio is negatively associated with the decreased medium and short fatty acid content in the ration. Soybean, having the highest feed value among legumes is broadly utilized in animal feeds. Soybean could inhibit the BCRP trans-membrane protein activity[22].

Disease

Breast tissue diseases and chemical and physical changes in the milk influence the drug transition to milk[23]. Edema and inflammation products disrupt drug distribution by creating pressure and clogging the milk ducts[24]. Pharmacologically, milk proteins-bonded drugs are considered ineffective. The reduction in milk protein (β-lactoglobulin, casein, and α-lactalbumin) increases the free drug in milk during mastitis[24]. Fibrosis can also alter the drug-to-tissue passage by decreasing the distribution of drugs in tissues[25]. These factors affect the drug pharmacokinetics in milk at differential levels. Milk yield can efficiently carry out drug excretion[26]. The cattle suffering from clinical mastitis produce lower milk yields, which lengthens the time of drug excretion[27]. The literature about the mastitis impact on the transporter-mediated drug secretions into milk is limited. Yagdiran et al. (2016) did not observe any significant difference in the BCRP gene expression after *Staphylococcus aureus* infection[28]. Contrarily, another study has reported a downregulated *Bcrp1* gene expression after *S. aureus*-induced mammary inflammation in a mouse model[29]. Endometritis could also impact the drug transitions in the milk. Kumar et al. (2010) demonstrated higher ceftriaxone concentration in the milk of healthy cows in comparison to endometritis cows after 12 and 24 h of drug administration. However, endometritis cows exhibited higher ceftriaxone milk concentrations than healthy cows after 36 h[30].

DRUGS-RELATED FACTORS

Administration Route

Different levels of each treatment drug are found in the milk. The administration route can affect the drug passage to milk. Parenterally applied drugs are rapidly absorbed as compared to orally administered drugs. Drug accumulation is high in the milk after intravenous drug administration as compared to various parenteral routes[31]. Intrauterine drug administration in lactating animals can also lead to drug residues in the milk[32].

Protein Binding

There are several antibiotics which are commercially available for veterinary use. These antibiotics administered to animals to treat different types of disease. The administered drugs can be found in bound or free form in circulation[33]. The free drugs can pass to biological fluids (milk) and tissue, whereas the bound drugs are unable to pass. Breast epithelial cells-generated specific milk proteins (α and β lactoglobulins, lactalbumin, casein) can bind the drug molecules. Milk

protein-binding drugs excrete at high rates and their distribution is low in tissues[19]. Milk protein percentage increases during mastitis disease[25]. Mastitis-suffering cows have demonstrated a higher ratio of drugs bonding with milk proteins after intramammary drug administration. Drug binding with the tissue proteins could prolong their excretion time through milk[26,34].

Ionization and pH

The drug ionization rates in aqueous media with weak basic or acid are related to the drug pKa and medium pH. Most non-ionic drugs demonstrate higher lipid solubility and can easily penetrate through the membrane. Plasma pH is constant, whereas the milk pH is variable. The milk pH turns alkaline during mastitis except for gangrenous mastitis whereas infection severity determines the drug ionization ratio in the milk. PKa value, pH (milk and plasma), and drug plasma concentration are used to assess the basic and weak acid drug excretion with the milk[35]. In the case of lower milk pH than plasma, the weak base drug accumulation is high in the milk as compared to weak acid drugs[35]. Sulfonamides have been used to investigate the pKa impact on the drug concentration in milk. Sulfacetamide exhibited a lower M/P ratio (0.08) because of the low pKa (5.4), whereas the pKa of sulfanilamide was 10.4 with an M/P ratio of 1.00[35].

Molecular Weight Transition

The molecular weight transition of chemicals and drugs in the milk is based on their molecular weight and size[35]. Drugs with smaller molecular weight and size could easily pass into the milk. Ethanol (molecular weight of 120) rapidly passes from the plasma to milk and reaches a high concentration. The transition of high concentrations of drugs with ≥ 600 molecular is impossible in milk. Due to higher molecular size, insulin (6.000) and Heparin (30.000) molecules are not detected in milk[35].

Solubility

Lipids mainly form the epithelial layer and alveolar structures in the mammary glands. The permeability of mammary tissues is high at the start of lactation. Therefore, lipophilicity plays an important role in the drug transition in milk[36]. The distribution of lipid-soluble, non-ionized, and free drugs is better in mammary tissues than other drugs[25].

Drug-Drug and Drug-Nutrition Interaction

Biological substances and xenobiotics could induce, inhibit, and compete for the breast cancer resistance protein (BCRP) leading to the alteration in BCRP substrate concentrations in the milk[37]. Real et al. (2011) have reported that ivermectin-based BCRP inhibition reduced the danofloxacin concentration, which serves as the BCRP milk substrate[38]. Triclabendazole and albendazole (BCRP inhibitors) can also change the pharmacokinetic parameters of BCRP substrates (moxidectin and enrofloxacin) in the milk[39]. BCRP-based drug-drug and drug-nutrition interactions could also impact the transition of biological substances and xenobiotics to milk[37]. Flavonoids (genistein and daidzein) containing soybean is a major protein source of animal feed. Genistein and daidzein are known to reduce the BCRP-substrate (nitrofurantoin, enrofloxacin, and danofloxacin) secretions to milk[39].

RESIDUES

Most of the administered antibiotics are metabolized inside the animal body followed by detoxification and excretion. Parent products and metabolites are mostly excreted through the urine whereas the excretion via feces is generally quite low. However, drug residues can persist in the meat, eggs, and milk for some period after excretion.

Antibiotic Residue (AR)

Administered antibiotics and their metabolites deposit in matrix and tissues, which are consumed by humans. The presence of drug concentrations more than the permitted levels for a specific period is referred to as residues[26,40]. Dry cow therapy and antibiotic administrations for mastitis treatment are the key reasons for antibiotic milk residues[41]. Milk residues pose a higher risk in developing nations as compared to developed countries. The absence of reliable food residue monitoring system and detection facilities pose a significant risk of antibiotic milk residues[42].

Maximum Residue Limit (MRL)

Maximum drug concentration in human or animal food that is permitted and considered non-hazardous by the regulatory bodies for a specific time is referred to as Maximum residue limit **(**MRL)[11]. MRL units are milligrams per liter and milligrams per kilogram for liquid and solid products, respectively[42]. Dairy

products with higher drug residues than MRL could be detrimental to the consumer's health[26]. The consumption of good-quality milk and dairy products is necessary for health[43]. However, antibiotic residues in these items could lead to hypersensitivity, cancer, and antibiotic resistance[44]. Antibiotic resistance is dangerous as it makes these drugs clinically ineffective[45]. The hazards of antibiotic residues can be avoided by maintaining a proper withdrawal time for consumable food products[45].

Withdrawal Time

Withdrawal time refers to the drug excretion time after administration to food animals where it reaches below MRL in marketed eggs, meats, organs, and other products. Drug administration routes and physical and chemical properties can affect the withdrawal time[46].

PUBLIC HEALTH IMPACTS

Drug residues pose either indirect-long term or direct-short term hazards depending upon the exposure time[47]. Direct-short-term hazards generally occur immediately after drug exposure, which include hypersensitive and allergic reactions in sensitive individuals immediately after consuming penicillin-contaminated milk[48]. Contrarily, long-term drug exposure leads to long-term hazards including reproductive abnormalities, carcinogenicity, and teratogenicity[49]. Drug residues in dairy products also cause aesthetic issues and reduce consumer acceptability[50].

Hypersensitive Reaction

There are IgE-mediated and non-IgE-mediated hypersensitivity reactions. IgE-mediated reactions include urticaria, angioedema, anaphylaxis, and bronchospasm, whereas non-IgE-mediated reactions include vasculitis, hemolytic anemia, serum sickness thrombocytopenia, and acute interstitial nephritis[51]. β-lactam antibiotics could cause severe allergic reactions (anaphylaxis, cutaneous, and serum sickness) in sensitive individuals[52]. Prior known penicillin exposure can lead to hypersensitive reactions. The unrecognized penicillin exposure through contaminated food (milk) might cause sensitization, which could develop into an allergic reaction after drug administration[53]. Even a lower penicillin amount can form reactive neoantigen leading to a hypersensitivity reaction (Type I) in urticaria. Approximately, 10–15% of humans are penicillin-hypersensitive and it has also been noted in animals[54,55].

Drug Resistance

Antibiotic administrations in livestock are linked to antimicrobial drug resistance (AMR) through the farm-to-fork food chain[56]. Long-term usage of subtherapeutic antibiotic doses as growth promoters is of greater concern[11]. AMR not only causes undesired direct impacts on consumers but also indirectly spreads resistance to human pathogens[57]. All drug-resistant bacteria are not human pathogens but they can transfer the resistance genes to pathogenic bacteria[51]. Long-term intake of antibiotics at low doses through contaminated dairy products could lead to antimicrobial resistance[12]. Bacterial pathogens and normal flora inside the consumers can become exposed to sub-therapeutic antibiotic residue concentrations[58]. This situation can ultimately develop multi-drug resistant bacteria (*E. coli*, Salmonella, Campylobacter, and Staphylococcus aureus (MRSA))[59]. These species can further transfer the resistance genes to the next generations as well as other species[58]. The resistant pathogens approach humans either directly (contact) or indirectly (animals-based foods including milk) to cause serious and difficult-to-treat infections[57,60]. Several pathogens have become insensitive to avoparcin and fluoroquinolones, which were previously quite effective against these microbes. Irrational usage of avoparcin has resulted in vancomycin-resistant enterococci development. Similarly, WHO is concerned about tetracycline, penicillin, and sulphonamide resistance in the agriculture sector[51,61].

Carcinogenicity

The term carcinogenicity refers to the cancer-causing ability of a chemical or drug with or without an initiator and promoter[35]. DDT, tetracycline, phenobarbital, furazolidone, and tamoxifen drugs can be carcinogenic to cause different kinds of cancers. Nitrofurans can release nitrosamines (carcinogenic metabolite) after reacting with nitrite. Therefore, the U.S. FDA has banned Furazolidone and its metabolites[50]. Chronic exposure to diethyl stilbesterol (synthetic estrogen analog) can cause benign abnormalities and vaginal clear cell adenocarcinoma in female offspring[51]. Similarly, prostate, breast, colon, ovary, and testes cancers have been documented after the ingestion of hormonal-residue-containing milk[62,63].

Teratogenicity

Teratogenicity is the toxicity of a chemical or drug to the developing fetus or embryo during pregnancy[64]. Embryotoxicity, developmental toxicity, and teratogenic impacts have been reported during pregnancy after exposure to some drugs. Teratogenic drugs include hormones (misoprostol, diethylstilbestrol), chemotherapeutic agents (thalidomide), antibiotics (aminoglycosides, tetracyclines), anthelmintics (albendazole), antiepileptics (carbamazepine), ACE inhibitors, methimazole, and cyclophosphamide[65].

Mutagenicity

Drug or chemical-based changes in DNA or cellular genetic component are known as mutagenicity[61]. Drug-based chromosomal damage or DNA mutation can cause infertility in humans[46]. Metronidazole, a nitroimidazole derivative, can exert genotoxic and mutagenic effects. DNA fragmentation and strand breakage by metronidazole have been reported in human hepatocytes and peripheral blood lymphocytes, respectively. Chloroquine, tinidazole, benzimidazole anthelmintic, and oxfendazole are also considered mutagenic[61].

Disruption of Normal Gut Flora

Gut flora competes with bacterial pathogens to prevent diseases. Milk residues of antibiotics (metronidazole, nitroimidazole, tetracyclines, tylosin, penicillin, and streptomycin) can disrupt the normal gut flora, which leads to gastrointestinal disturbance [66]. It allows the pathogens to penetrate and flourish in the host. *Clostridium difficile* associated diarrhea, pseudomembranous colitis, and life-threatening infections could occur in severe cases[67]. However, these conditions occur at therapeutic doses, and data about the effect of antibiotic residue range concentration on humans is limited[61].

Inhibition of Starter Culture

The presence of antibiotic residues in milk is of great concern in dairy industries. These residues can change the growth of starter cultures and thus affect the fermentation process during the production of cheese, yogurt, and other dairy products[46]. The side effects of chloramphenicol (brain abscesses and optic neuropathy) and fluoroquinolones (retinal detachment) have been documented[68]. Other drug residues-related hazards include immunodepression (chloramphenicol, tetracyclines), anemias (sulphonamides, chloramphenicol), endocrine disruption (HCHs), gastro-enteric disturbances (fluoroquinolones, erythromycin), photosensitization (tetracyclines), and chronic and acute toxicities of different body systems and tissues[47,63].

CONCLUSION

Milk is a widely consumed nutritious food that can be contaminated with different hazardous drug residues. The quality regulation of dairy products and the adoption of modern methods are crucial for the rapidly growing industry and public safety. Milk drug residues are of public concern as dairy products are almost daily consumed by adults, children, and infants globally. The complete elimination of residues from dairy products is practically impossible. However, the implementation of food safety measures can facilitate minimizing the drug residues in dairy products to a safe level.

Conflict of Interest

The author declared that there is no conflict of interest that is related to this study and this article.

Disclosure

The author did not receive any form of commercial support, including compensation or financial assistance, for this case report. Additionally, the author has no financial interest in any of the products, devices, or drugs mentioned in this article.

Ethical Approval

The study was approved by the Ethics Committee of the KAUH in Jeddah, Kingdom of Saudi Arabia, also known as the Institutional Review Board of Hospitals.

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