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Behaviours of Drugs in the Milk - A Review

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Abstract: Milk is a food containing many biologically active substances that have an important place in the nourishment of newborns and adults. The transition of the drugs used in the treatment, as well as the environmental pollutants to milk cause a potential risk for consumer health as well as economical losses due to exceed of the legal limits of these compounds set by authorities. The transition of these chemicals to milk is complex; while active transport and passive diffusion play were found to have an important role. The transition abilities of the drugs into milk are defined by milk/plasma ratio. The M/P ratios of the drugs are affected by the composition of the milk and the physicochemical properties of the drug. The concentration of the drugs in the milk depends on the factors of the drug (protein binding, ionization, molecular weight, lipophilicity, drug-drug and drug-nutrient interactions) and organism (race, species, lactation period, parity, disease and nutrition). If the transition properties of the compounds of concern are known or able to be modelized in kinetic applications, it can be useful for preventing milk from drug residues.The success of mastitis treatment depends on the proper use of drugs and knowing of the behaviour of drugs in the milk.

Keywords: Behaviour, Drug, Factor, Milk, Transition.

İlaçların Sütteki Davranışları - Derleme

Öz: Süt, yeni doğanlar ve yetişkinlerin beslenmesinde önemli yeri olan birçok biyolojik aktif madde içeren bir besindir. İnsan ve hayvanların tedavisinde kullanılan ilaçların ve çevresel kirleticilerin süte geçme yeteneği, sütü sağlık ve ekonomik açıdan sorunlu hale getirmektedir. Kaliteli ve güvenli gıda üretimine yönelik yasal ve bilimsel uygulamalar bu sorunları önlemeyi amaçlamaktadır. Aktif transport ve pasif difüzyon, ilaçların süte geçişinde önemli rol oynamakla birlikte diğer mekanizmaların da etkin olduğu bilinmektedir. İlaçların süte geçişlerisüt/plazma oranı ile belirlenir. Süt/plazma oranı sütün bileşiminden ve ilacın fizikokimyasal özelliklerinden etkilenir. Sütteki ilaç konsantrasyonu, ilaca (proteine bağlama, iyonizasyon, molekül ağırlığı, lipofiliklik, ilaç-ilaç ve ilaç-besin etkileşimi) ve canlıya (ırk, tür, laktasyon periyodu, doğum sayısı, hastalık ve beslenme) bağlı olarak değişiklik gösterir. Söz konusu bileşiklerin geçiş özelliklerinin bilinmesi veya kinetik uygulamalarla modellenebilmesi sütte ilaç kalıntılarının önlenmesinde faydalı olabilir. Mastitis tedavisinin başarısı, ilaçların doğru kullanılması ve ilaçların sütteki davranışlarının bilinmesine bağlıdır.

AnahtarKelimeler: Davranış, Faktör, Geçiş, İlaç, Süt.

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INTRODUCTION

Milk is defined as the biological fluid that is produced in the mammary gland following by birth in all mammalian species. The composition of the milk consists of mainly emulsified fat globules, lactose and soluble proteins that form solutions with colloidal dispersed proteins. Milk also contains various minerals, vitamins, enzymes and dissolved gases. The passive diffusion is primary mechanism that plays the key role in the transition of drug from plasma to milk. In the transition of drugs to the milk, there are transport mechanisms other than passive diffusions. Milk concentrations of cimetidine and nitrofurantoin are founded higher than predicted concentrations in humans (1,2). Active transport plays an important role in the passage of organic compounds such as benzylpenicillin across the blood-milk barrier. However, probenecid is a known inhibitor of active transport of organic acids at epithelial barriers. In an experimental study, probenecid has reduced the excretion of benzylpenicillin from kidney (3). The existence of carrier-mediated transport system/systems in the mammary gland has been revealed in experimental studies using rats. In these studies, it has been indicated that dipyridamole reduced more the milk/serum ratio of nitrofurantoin than 60% and the cimetidine than 80% (4,5). Other mechanisms such as pinocytosis and exocytosis are effective mechanisms for the transition of drugs into the milk. It has been demonstrated that non-linear kinetic (saturation) is possible in the transition of compounds to milk such as aminopyrine, N-acetylated paraaminohippuric acid and N-acetylated sulfanilamide (5). ATP-binding-cassette (ABC) is a transmembrane protein that is actively involved in the transport of biological substances and xenobiotics. P-glycoprotein and Multi-Drug Resistance Protein (MRP), particularly the Breast Cancer Resistance Protein (BCRP) from the ABC family, play a role in the transit of the drug to milk. BCRP is highly expressed in breast tissue especially during the last period of pregnancy and lactation period (6,7). Bcrp1 substrate concentrations in wild type lactating mouse milk has been higher compared to transgenic lactating mice without Bcrp1 transmembrane protein (Bcrp1 -/-) (6). Genetic variations of BCRP should also be assessed in the transit of the drug to milk. Variations in the expression and/or function of BCRP could be lead to significant changes in the pharmacokinetics of the BCRP substrates in the milk. Y581S is one of the BCRP polymorphisms, which have caused to increase transition of danofloxacin to the milk. In addition, the heterozygous variant Y/S of the Y581S polymorphism have increased to transition of danofloxacin to milk much more than homozygous variant Y/Y (8). Otero et al. (9) found that riboflavin transports more efficiently *in vitro* by the Y581S. Also the same authors have determined that uric acid and enterolactone (substrates *in vitro* of the bovine ABCG2 variants) are actively secreted into milk with a two-fold increase in the milk/plasma ratio for Y/S with respect to Y/Y cows. Y581S polymorphism is responsible for production and composition of milk (10). BCRP variants can be also different between species. The metabolites of triclabendazole (triclabendazole sulphoxide and sulphone) have lower inhibitor effect on BCRP variants in sheep than in cattle. Especially, these metabolits inhibite the bovine Y581S variant (11). The *in vitro* transport of ciprofloxacin by the S581 variant has been more efficient when compared to the Y581 variant. Also the administration of enrofloxacin to Y/Y 581 and Y/S 581 cows has revealed that the plasma concentrations of enrofloxacin and ciprofloxacin are significantly lower in Y/S animals (12). The transition ability of the drugs into milk is defined by milk/plasma (M/P) ratio. M/P rate is affected by composition of the milk and physicochemical properties of the drug. M/P ratio can be estimated by using the values of octanol/water partition rate, binding to plasma proteins and the pKa of drugs. The drugs with a high M/P ratio are actively secreted to the milk (13). Maternal plasma drug concentration directly affects drug concentration in the milk. On the

other hand, the drug concentration in the blood is not affected only by the maternal dose; this ratio can be changed by the maternal drug metabolism. The drug metabolism is genetically determined and shows variation in mammals. Plasma concentration of clomipramine can be shown difference by more than 50 times among the dogs (14).

1. Factors Affecting Drug Transition to the Milk

Physiological changes such as hormonal changes are observed during pregnancy and lactation period. In pregnancy, maternal plasma drug concentration is affected by changing physiological factors. Some plasma proteins such as albumin and globulin increase during the lactation period. Researchers have indicated that there is a decreasing in concentration of blood protein during the last period of pregnancy and plasma protein concentration reaches normal levels during lactation (15). Changes in the pharmacokinetics of drugs in lactation period are often similar to changes in the pharmacokinetics of drugs in pregnancy. Contrary to indicated above Santschi and Papich (16) have found that there is no difference in the plasma distribution, excretion, and drug exposure (AUC) of gentamicin between mares in the last period of pregnancy as well as in the first period of lactation. The pharmacokinetics of the drugs can be affected by hormonal changes during postpartum and lactation period, also body fat percentage, body weight and body mass. It has been shown that lactation causes significant changes in plasma pharmacokinetics (clearance, increased volume of distribution and half-life) of drug when compared with pregnancy (17).

2. Factors Related to Living Organism

2.1. Species

Sheep milk contains more fat and protein than cow and goat milk. In two different experimental studies, doremectin has been found to accumulate more in the milk of sheep than in the milk of goat, despite the same dosage regimen (18,19). Similar results have been obtained for danofloxacin studies in lactating cows and sheeps, the concentration of danofloxacin in sheep milk has been shown to be higher (20,21). It can be said that lipophilic drugs are more likely to pass sheep milk, which has a higher fat rate than goat and cow milk.

2.2. Disease

Physical and chemical changes in the milk and breast tissue diseases affect the drug transition to milk. Inflammation products and edema disrupt the distribution of drugs by clogging milk ducts and creating pressure. Drugs bonded to milk proteins are pharmacologically ineffective. Since the amount of milk protein (casein, α-lactalbumin, β-lactoglobulin) reduce, the amount of free drug in milk increases in mastitis cases. The other change, which can affect drug passage into tissue, is fibrosis. Fibrosis decreases the drug distribution in tissues. Depending on these factors, the pharmacokinetics of drugs in milk can be affected at different levels. Yield of milk could be effective on the excretion of drugs by milk.The withdrawal times of drugs from the milk takes more time because of reduced milk yield in cattle with clinical mastitis (22). In an experimental study conducted on healthy and mastitic cows, the withdrawal time of azithromycin has been found to be prolonged in mastitic cows (23). Although administered in the same dosage regimen, cefacetrile accumulates in mastitic cows milk than healthy ones (24). Sezgin and Tras (25) have determinated that mastitis cause the change in pharmacokinetic of albendazole in milk [area under the curve (AUC), biological half-life and M/P ratio] but mastitis hasn't changed pharmacokinetic of triclabendazole and fenbendazole. After intravenous administration, milk concentration of flunixine meglumine have found different in mastitic and healthy cows at all time points (26). The same authors have stated that concentration of flunixine meglumine in mastitic cow milk has been higher than healthy ones. In contrast to the parent drug, 5-hydroxy flunixin concentrations have been significantly higher in healthy cow milk at both 2 and 12 hours. The results of another experimental study have reported that the AUC of norfloxacin in milk is significantly lower in the infected quarters of the

mastitis groups (subclinical and clinical group) when compared to the values in milk from healthy quarters of the same udder. Also, they determined concentration of norfloxacin in milk is higher than in serum (27). There are not enough studies about the effect of mastitis on transporter-mediated secretions of drugs into milk. Yagdiran et al. (28) have found that no significant differences were observed for gene expression of BCRP after *S.aureus* challenge. On the other hand, another study revealed that the gene expression of Bcrp1 has been downregulated in mouse model of *S.aureus*-induced mammary inflammation (29). Other diseases such as endometritis can also affect the drug behaviours in the milk. Kumar et al. (30) have determinated that concentration of ceftriaxone in milk is greater in healthy cows than endometritic cows at 12 and 24 h after drug administration, whereas endometritic cows had greater ceftriaxone concentrations in milk compared to healthy cows at 36 h.

2.3. Lactation Period and Parity

Rates of milk protein and fat at different periods of lactation have been shown to alter drug excretion from milk (31). There is a positive relationship between amounts of protein and fat in the milk. In cows, milk yield increases parallel to the increasing of parity and milk yield reaches the maximum level at 4-5th births. This increase is related to breast volume. The raising in milk yield causes to increase the excretion of drug by milk (22).

2.4. Breed

Breeds can affect the drug transition into milk. It has already been mentioned that the rate of milk protein and fat is effective on the transition of drugs to milk. For example, milk protein and fat ratios of Jersey and Guernsey breeds are higher than other breeds. Lipophilic drugs, which show affinity to milk proteins, can be more concentrated in the milk of these breeds (22).

2.5. Nutrition

Milk composition is related to acetate/propionate ratio of the ration. In addition, nutritional characteristics such as the herbage quality, the roughage/concentrated feed ratio and the amount of fat in the feed can affect the milk composition. Imbalances in nutrition (low energy/protein ratio) can decrease rates of milk fat and protein. If the concentrate feed ratio is higher than the roughage feed, the milk fat ratio tends to decrease. Cows fed with rich rations from vegetable oil have low milk fat. Decreasing in short and medium chain fatty acid content in the ration affects milk fat ratio negatively. Soybean, which has the highest feed value among legumes, is widely used in animal feeding. Soybean has an inhibitory effect on activity of BCRP tranmembran protein (32).

3. Factors Related to Drugs

3.1. Route of Administration

Every drug used in treatment passes to milk at more or less levels. The route of administration affect to passage of drugs to milk. Parenterally applied drugs are absorbed easily and rapidly than oral administered drugs. Intravenous administered drugs more accumulate in the milk compared with different parenteral routes (23). Also, it should also be considered that intrauterine drug application to lactating animals can cause drug residue in milk (33).

3.2. Protein Binding

Drugs are found as free or bound form in the circulation. While free drugs can pass to tissue and biological fluids such as milk, bound drugs can't. There are specific proteins (casein, lactalbumin, α and β lactoglobulins) in milk produced by the breast epithelial cells which bind drug molecules. The excretions of drugs that bind to milk proteins at high ratios are rapid and distribution to tissues is low (22). In mastitis disease, the percentage of milk protein is increased. In a study conducted on cows with mastitis, it has been found to be increasing in proportion of drugs bonded to milk proteins following intramammary drug administration. Also, it has been concluded that binding to tissue proteins could prolonged the withdarawal time in the milk (27).

3.3. Ionization and pH

Ionization rates of drugs with weak acid or basic in aqueous media are related to the pH of medium and the pKa of drugs. Most of non-ionic drugs have higher solubility in lipid and pass across the membrane easily. While the pH of the plasma is constant, the pH of the milk is variable. Except of gangrenous mastitis, the pH of the milk shifts to alkaline in mastitis cases. The ionization ratio of the drug in the milk is also dependent on the severity of the infection. Excretion of weak acid and basic drugs with milk are determined by the pKa value and plasma concentrations of drug and the pH of the plasma and milk (34). As the pH of the milk is lower than the pH of the plasma, weak base drugs accumulate in milk more than weak acid drugs. Tras et al. (35) found that the sulphadoxin concentration in mammary quarters applied basic solution was higher than in quarters applied acidic solution and the difference was to be significant. Due to the increased vascular permeability in inflammatory diseases, drug transition from plasma to milk increases. In mastitis cases, intramammary drug administration causes increase in drug transition from milk to plasma. The effect of pKa on drug concentration in milk has been demonstrated in studies with sulfonamides. Sulfacetamide has a low M/P ratio (0.08), because of a low pKa (5.4), sulfanilamidine has a pKa of 10.4 so M/P ratio is 1.00 (36).

3.4. Molecular Weight

Transition of drugs and other chemicals into milk depends on the molecular size and molecular weight. Drugs with small molecular weight and molecule size pass to milk more easily. Ethanol (molecular weight 120) passes rapidly from the plasma to milk and reaches a high concentration in the milk. It is not possible for drugs of ≥ 600 molecular weight to transition at high concentrations into the milk. Heparin (30.000) and insulin (6.000) molecules are not found in milk because their molecular sizes are high (34).

3.5. Solubility

The structure of alveolar and epithelial layer of the mammary gland is mostly formed from lipid. Mammary tissue is very permeable at the beginning of lactation. Therefore, lipophilicity is important in drug transition to milk. Non-ionized, free and lipid-soluble drugs have a better distribution into mammary tissue. In an experimental study, pharmacokinetic behaviours of doramectin and ivermectin have determined in milk and it has been found that C_{max} and AUC values of doramectin in milk are 6 and 4-fold higher than the ivermectin, respectively (37).

3.6. Drug-Drug and Drug-Nutrition Interaction

Xenobiotic and biological substances cause the inhibition or induction of BCRP and also compete for BCRP. Thus, concentrations of BCRP substrates can change in milk. Real et al. (38) have indicated that inhibition of BCRP by ivermectin reduced the concentration of danofloxacin which is BCRP substrate in milk. Similarly, BCRP inhibitors such as albendazole and triclabendazole have caused changes in milk pharmacokinetic parameters of enrofloxacin and moxidectin which are BCRP substrates (11,39). BCRP can also alter transition of xenobiotic and biological substances to milk through drug-nutrition interactions as well as drug-drug interactions. Soybean is widely used as a protein source in animal feed; it contains flavonoids (daidzein and genistein). It has been indicated that daidzein and genistein reduce the secretion of BCRP substrates such as danofloxacin, enrofloxacin and nitrofurantoin to the milk (7,40,41). The concentration of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) which is abundantly present in cigarette smoke and well-heated meat has been determined high level in wild type mice milk compared to Bcrp1 -/- mice (6). van Herwaarden et al. (42) have found that milk secretion of riboflavin had reduced >60-fold in Bcrp1 -/-mice compared to in wild-type mice. Also, flavinmononucleotide (FMN) levels have been found 6-fold lower in milk of Bcrp1 -/- mice than wild-type.

But flavin adenine dinucleotide (FAD) levels have been unchanged. In the same study, the concentrations of different vitamins (vitamin A, B_1, B_6, B_9, B_{12}, C, E, H, K_1) in milk have been investigated in Bcrp1 -/- mice and the level of biotin (vitamin H) has been found 3-fold lower in Bcrp1 -/- mice. Carcinogenic and mutagenic chemicals such as heterocyclic amines 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and aflatoxin B1 pass into the milk easily. Milk/plasma ratios of these compounds have found 3.4, 2.6 and 3.8–fold higher in wild type mice than Bcrp1 -/- mice, respectively (13). PCB 126 is a dioxin-like PCB which may contaminate milk and dairy products and is also known human carcinogen. Manzini et al. (43) have found that PCB 126 increases bABCG2-mediated excretion of Hoechst H33342 in Madin-Darby canine kidney-bovine ABCG2 (MDCKII-bABCG2) cells line. Also, in the same study the incubation of PCB126-pretreated cells with AFM1 has been found to reverse effect of PCB 126 on bABCG2 efflux activity. Manzini et al. (43) have stated that AFM1 is as likely a substrate of bABCG2. The fumitremorgin C (FTC) and equol known as ABCG2 inhibitor have been found to cause a significant reduction in PhIP transport in MDCKII-bABCG2 and cABCG2 cells (44). On the other hand, only equol has been reported to cause a significant reduction in transition of enrofloxacin in bABCG2 as well as in cABCG2 cells. Also, FTC and equol have been decreased efflux rate of sodium salicylate in MDCKII-bABCG2 cells, but are not decreased in MDCKII-cABCG2 cells. Mahnke et al. (45) have found that the tranport of monopental sulfon (MNPSO2), which is a metabolite of monopental known as bovine ABCG2 (bABCG2) substrate, has been significantly inhibited by FTC, enrofloxacin, oxfendazole and moxidectin in bABCG2 cells compared to untreated MDCKII bABCG2 cells. Clinical effectiveness in treatment of mastitis cases can be enhanced by the use of BCRP substrate drugs. At the same time, the addition of BCRP inhibitor to feeds can provide economic contribution by reducing passage of the drugs and toxins into milk.

CONCLUSION

The transition of drugs and substances with carcinogenic properties such as environmental pollutants and mycotoxins (aflatoxins) to milk cause an important health problems and economic losses. The residue problem in animal foods is a global problem with incremental predication. In recent years researchers have shown that not only passive diffusion but active transport and specific transmembrane proteins are involved in the transition of drugs to the milk. The pregnancy and lactation period cause significant changes in the pharmacokinetics of drugs. In particular, it can be stated that diseases such as mastitis cause differences in drug concentration in the milk. It can be useful to investigate the effects of pregnancy and lactation on transition of drug to milk in all species and whether the other diseases affecting milk yield except mastitis may affect the behaviour of the drug in the milk. Milk composition, which varies according to species and breeds, may also affect drug behaviour in milk. There is a BCRP- mediated interaction, which can lead to change concentrations of substances in milk, among xenobiotics, biological substances and nutrients. Clinical efficacy can be improved by combining BCRP substrate drugs used in the treatment of mastitis with a related transmembrane protein inducing compound.The addition of BCRP inhibitor to feeds can minimize the passage of the xenobiotics in order to control the residual levels.

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