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Pharmacotherapy and Nursing Approaches in Neonates

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ABSTRACT

Pharmacotherapy gains importance in newborns due to the differences in body physiology. Newborns need special drug treatments due to their anatomical, physiological, and biochemical differences that change the pharmacokinetics and pharmacodynamics of various drugs. Factors such as gastric pH and emptying time, intestinal transit time, immaturity of secretion, total body water, immaturity of the neurological and the urinary systems may result in age-related changes in pharmacokinetics and pharmacodynamics. Due to the immaturity of the body systems of the newborns, the absorption, distribution, metabolism, and excretion of the drugs from the body are different from that in adults. Knowing the pharmacokinetics of the drugs in medicaments and their appropriate treatment is of great importance in the prevention of drug errors. From these perspectives, neonatology nurses have crucial roles to play in providing patient safety in their care. The aim of this review is to develop a guide regarding the essential principles of pharmacokinetics in newborns and safe drug administrations. In this review, the newborn pharmacokinetics and nursing approaches are examined under three subtitles: (1) pharmacological definitions-principles, (2) pharmacokinetics in newborns, and (3) responsibilities of the nurse. It is expected that this study will guide neonatal nurses in practice and shed light for further research and new studies on pharmacotherapy and safe drug administrations.

Keywords: Newborn, nurses, pharmacotherapy

Introduction

The purpose of treatment with medication is to prevent various diseases, reduce or control the disease effects. In order to achieve this goal, it is necessary to deliver sufficient doses of drugs to the target tissues so as not to become toxic. It is necessary for the desired drug to reach the target tissue to be able to have the expected effect and to keep the adverse effects at the lowest level.[1-3] Especially, as pharmacotherapy in this sense is important in every age group, it gains further importance in newborns due to the differences in their body physiology.

Newborns need special treatment for drug administration due to their physiological differences that affect the pharmacokinetics and pharmacodynamic properties of various drugs.[4,5] As the body systems of the newborns are immature (not fully developed), the absorption, dissemination, metabolism, and excretion of the drugs from the body are different from that in adults. Newborns, especially premature infants, have limited ability to metabolize drugs due to their physiological immaturity.[1,5,6]

Knowing the principles of drug therapy in newborns ensures the safe use of drugs. Also, safe usage of drugs, pharmacodynamic properties, efficacy, and side effects of the drugs.[6,7] Wang et al[8] conducted 43 drug studies in newborns and specified that only 10 of 43 drugs are pharmacokinetically safe in newborns.[8]

Drug administration should be carried out by a multidisciplinary team in order to be able to administer the drugs safely and to keep the side effects of the drug at a minimum level.[9,10] As a member of a multidisciplinary team, the newborn nurse has a role to play in every process from the preparation of the drugs to the administration of the drugs and who evaluates the response in the newborns and intervenes if necessary.[11-12]

The newborn nurses should be familiar with the pharmacokinetic and pharmacodynamic effects of the drugs regarding the assessment of clinical effects and the risk factors.[13] Knowing the pharmacokinetics of the drugs is of great importance in the

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prevention of drug administration errors. Ferranti et al[14] specified that drug errors in the pediatric population are three times more than in adult populations. For this reason, the most important responsibility for safe drug use belongs to the nurse.

The aim of this article is to develop a guide regarding the essential principles of pharmacokinetics in newborns and safe drug administration. As a result of the literature review, the newborn pharmacokinetics and nursing approaches are examined under three subheadings: (a) pharmacological definitions-principles, (b) pharmacokinetics in newborns, and (c) responsibilities of the nurse.

Pharmacological Definitions and Principles

It is essential to know the pharmacological principles in order to apply the drugs safely in newborns. *Pharmacokinetics* is the examination of the changing characteristics of absorption, distribution, metabolism, and elimination of the drugs in time. *Pharmacodynamics* is the examination of the biological effects of the drugs on the tissues. It defines the relationship between the pharmacological response and the drug concentration at the site (receptor level) to be affected.[10,15,16]

Pharmacokinetics simply answers the question "What does the body do to the drug?" and pharmacodynamics answers the question "What does the drug do to the body?" While pharmacodynamics focuses on the therapeutic and toxic effects of the drug, in pharmacokinetics the emphasis is on the absorption, distribution, metabolization, and elimination of the drug.[10] Pharmacokinetics-dynamic processes of any drug are presented in Figure 1.

In order to use a drug in the body, it must be absorbed (passing through the body into the bloodstream), disseminated (moving into the influence area via the bloodstream), and transformed into the active form. It is then digested by metabolism and the drug metabolite is excreted from the body.[17] This process prevents the drugs taken at full strength from accumulating in the body and making them toxic. Due to the immaturity of the body systems of the newborns, the absorption, dissemination, metabolism, and excretion of the drugs from the body are different from that in adults. Therefore, the pharmacokinetic processes are also different from adults'. Differences of newborns from the adults in terms of pharmacokinetic processes are outlined in Table 1.

Pharmacokinetics in Newborns

Absorption of Drugs

Drugs administered via non-vascular routes contribute to the systemic circulation through many membranes and go to the area where it will show its effect. These drugs are absorbed depending on the chemical properties of the drug and the personal characteristics of the patient. Developmental changes on the surfaces providing absorption (e.g. gastrointestinal system, skin, pulmonary structure, muscles) are important determinants of bioavailability.[3]

Gastrointestinal Absorption

Acid levels in the stomach and duodenum affect the solubility of drugs, ionization, and gastrointestinal motility. As absorption of acidic drugs occurs at acid pH, basic pH absorbs basic drugs, and the absorption of acidic drugs decreases. As the acid level in the stomach of newborns is 1.5-3.0 at birth, it falls rapidly within a few hours. This decrease is independent of the gestational age and birth weight.[17-19] Basal acid production is associated with postnatal age and reaches the highest level on the 10th postnatal day, reaching the lowest level on the 13th day. The absorption of weak acid drugs such as phenytoin, acetaminophen, and phenobarbital may be reduced in infants due to increased high gastric pH. On the contrary, the absorption of erythromycin and penicillin G increases.[18,20]

In cases when gastric emptying is performed at the fastest, drug absorption from the intestines may be reduced. Gastric emptying is closely related to gestational age, postnatal age, and nutritional pattern. As breast milk and hypocaloric nutrition accelerate gastric emptying, respiratory distress syndrome, gastroesophageal reflux,

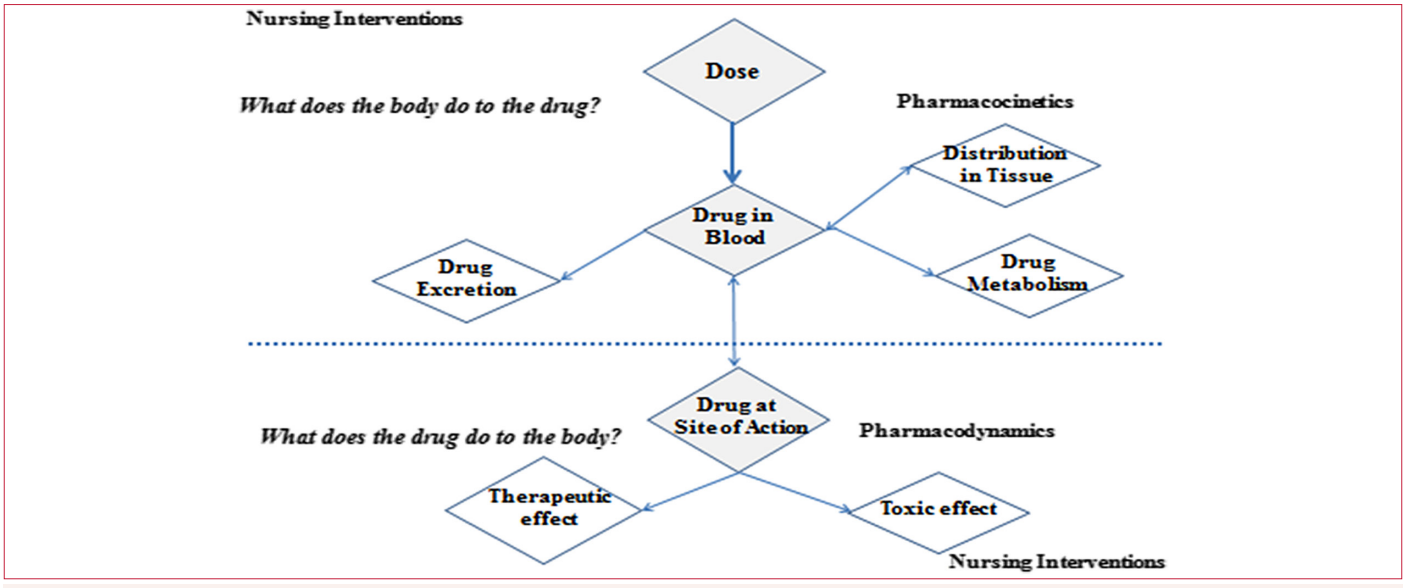

Figure 1. Pharmacokinetics-dynamic processes of a drug. Source: Authors.

Table 1. Differences of Neonates from the Adults in Terms of Pharmacokinetic Feature

Physiologic parameters	Difference compared to adults	Pharmacokinetics implications	Example for drug/s
Absorption			
Oral Absorption			
Gastric pH	↑	Increased bioavailability of acidic drugs Decreased bioavailability of weak acidic drugs	Penicillin G, ampicillin, Phenytoin, phenobarbital,
Gastric emptying time	↑	Delayed absorption	Phenobarbital, digoxin
Gastric and intestinal motility	↓	Unknown bioavailability	Digoxin
Bile acid production	↓	Decreased in bioavailability	Vit E, vit K
Percutaneous absorption			
Body surface area	↑	Increased in bioavability and permeability	Alcohol, iodine
Hydration of epidermis	↑	Inctreased in bioavability	Steroids
Intramuscular absorption			
Skeletal muscle blood flow	Variable	Unknown	N.A.*
Distribution			
Total body fluid and extracelluer fluid	↓	Increase in distribution volume	Aminoglycosides, caffeine, theophylline
Albumin concentration and protein binding	↓	Increase in distribution volume; increase of free fraction; liberation of bilirubin	Phenytoin, sulfonamid
Metabolism			
Enzyme activity	↓	Decrease in hepatic clearance	Kaffeine, morphine
Hepatic maturity	↓	Decrease in hepatic clearance	Phenobarbital
Renal excretion			
Glomerular filtration rate		Decrease in renal clearance	Aminoglycosides
Renal tubular absorption and secretion		Decrease in renal clearance	Beta-lactam antibiotic

*N.A., Not Available
Source: Created by the authors in line with the literature.[3,18,19]

congenital heart disease, and long-chain fatty acids delay gastric emptying.[20,21] Gastric emptying reaches adult rates at approximately 6-8 months of age. Therefore, drug absorption appears to be reduced and delayed after birth, with progressive improvement during the first 3 months.[7]

Another factor affecting the gastrointestinal absorption of the drugs is the quite low bile acid production, amount, and transport in intestines compared to adults.[22,23] The pancreas enzymes in premature infants are notably low. However, the pancreas enzymes in the premature infants in first week are found higher compared to the term infants. Amylase comes out as from pregnancy week 23; however, it remains low for a long time after the delivery. Lipase presents in the weeks 34-36 and increases 5 times within the first week.[22-24] Also, trypsin secretion is low and gradually increases within the first year. Lack of bile and pancreatic enzyme leads the bioavailability of drugs, whose dissolution and intraluminal hydrolization are required for the absorption, to decrease in the newborns.

Colonization of the digestive tract and bile acids affect the metabolism of drugs and bowel motility. It may vary by age, mode of delivery, feeding method, and drugs used. In the infants who were born with vaginal delivery and fed with formula, anaerobe bowel flora forms in the postnatal fourth-sixth days. In cases where bowel surface decreases, the absorption of the drugs also decreases.[22-24] In protein-energy malnutrition, the absorption decreases since there is villous atrophy, gastric emptying is delayed, and bowel emptying extends. In congestive heart failure, the development of mucosal edema, gastric emptying delay, and reduction of bowel circulation affect the absorption of the drug. In the hypo- and hyperthyroid, bowel transition time extends or decreases.[22-25] Comparisons of intestinal factors affecting gastrointestinal drug absorption in infants are outlined in Table 2.

Table 2. Comparisons of Intestinal Factors Affecting Gastrointestinal Drug Absorption in Infants			
Absorption			
Parameters	Full-term neonate	Neonate between 1 day and 1 month	Between 1 month and 2 years
Stomach pH	1-3	> 5	Adult
Time of gastric emptying	Varied/decreased	Varied/decreased	Increasing
Intestinal surface area	Decreased	Decreased	Like an adult
Bacterial flora	Limited	Limited	Developing
Rectal absorption	Very good	Very good	Adult

Source: Created by the authors in line with the literature.[3,21,25]

Intramuscular Absorption

Intramuscular absorption of drugs depends on various factors. The lipophilic nature of the drug allows rapid transition to the capillaries. However, it must also be soluble in a little amount of water in order to prevent it to precipitate at the injection site. The intramuscular drug absorption is inadequate in the newborns since the muscle blood flow is low, the muscle mass contains higher water density, and the muscle contraction is insufficient in such age group.

On the other hand, the circulation of the injection site is very important. In newborns, especially when the cardiac output is low, and circulatory disturbance occurs in the respiratory distress syndrome, the absorption is also low.[5,26] Similarly, in the newborns having less muscular movements, reduced motility, and are seriously ill or in the patients to whom muscular paralysis is applied, contribution of the drugs in the circulation after intramuscular injections is low.[20,27,28]

Percutaneous Drug Absorption

There are many factors affecting percutaneous drug absorption in the newborns. In newborns, the epidermis is thin and the stratum corneum layer has not developed yet. While the stratum corneum layer is in the range of 10-20 folds in a full-term infant, this layer is 2-3 folds in an infant in the 30th gestation week and this layer is not seen in the infants who are smaller than the gestation week 24. Immature vasomotor control and large body surface areas according to their weight affect drug absorption in the skin.[29,30] As long as the gestational age decreases, epidermal permeability increases due to these features. Whereas the permeability is 100-1000 times more than the full-term in the newborns who were born prior to the pregnancy week 30, the absorption is 3-4 times more than the full-term in week 32.[22-24]

Rectal Absorption

The rectal route may be used in cases such as vomiting, convulsion, or in the infants who cannot be fed orally for surgical preparation. However, the absorption may be too irregular because of the form of the drug and duration of stay within the rectum. To know the blood circulation feature of the rectum is important in this respect. While the upper rectum veins open to the portal vein and liver, the lower rectum veins open to the systemic circulation through the inferior vena cava. Thus, since the drugs administered to the upper rectum will first reach the liver, drugs administered to the lower rectum reach the systemic circulation without meeting the liver while it undergoes the first transition effect.[20,27] Those drugs administered to the rectum which dissolve in water or alcohol are absorbed much faster compared with the suppositories.[3,24,30,31]

Distribution of Drugs

After the drugs are absorbed, it is transported to various organs and body tissues via the bloodstream. Factors affecting the distribution are the composition of the body fluids and the level of protein binding of the drug. Drug-protein binding is affected by the physico-chemical properties of the drug, drug concentration, and protein concentrations found in the body. Pathophysiological changes such as blood pH, free fatty acids, diseases (liver diseases, renal diseases, etc.), amount of the binding areas, and affinity between the drug-protein are the other factors affecting the drug-protein binding.[3,15,28]

One of the factors affecting the distribution of drugs in the body is the binding of drugs to plasma proteins. Plasma albumin is the area of primer binding for drugs. This binding limits the amount of free drug in circulation and thus prevents the drug from reaching the toxic level.[22] The albumin and α1-acid glycoprotein plasma concentrations are low in the newborns. For this reason, the concentration of the drug which does not bind to the protein increases in the plasma and poses a risk in terms of toxicity.[5] The amount of binding to plasma proteins can vary from one drug to another. Thus, the density and the amount of the drug that can reach the receptor site is not directly proportional to the dose. The binding capacity of neonatal albumin to certain drugs (such as phenytoin) is low. If the active free drug moiety remains high in the plasma, the possibility of the occurrence of toxic effects increases.[32] The comparison of plasma protein binding percentages of some drugs in newborns and adults is given in Table 3.

Total body fluid and extracelluar fluid are among the most important factors for the distribution of drugs. The amount of fluid in the body is an important variable in determining the highest attainable drug concentration. In preterm neonates, total body fluid is even higher at 80-85% of body weight.[33] This rate is 70-75% in full-terms newborns and reaches the same level (50-60%) as those on reaching 2 years of age.[22,30] Thus, when the same dose given to an adult according to the body weight is given to an infant, the plasma concentration of the fluid-soluble drug in an excessive amount is low.[32] Age-related changes in body composition influence the distribution of lipid-soluble and water-soluble drugs. For example, lipid-soluble drugs such as diazepam have lower volume distribution of drugs in neonates and infants compared with adults. For this reason, appropriate loading

Table 3. Comparison of Plasma Protein Binding Percentages of Some Drugs in Newborns and Adults

Drug	Newborn (%)	Adult (%)
Ampicillin	7-10	18-30
Caffeine	25	30-40
Diazepam	84	99
Digoxin	20	32
Morphine	18-22	33-37
Phenytoin	80	90
Phenobarbital	20-32	45-50
Theophylline	36	56
Vancomycin	36	50-56

Source: Created by the authors in line with the literature.[3,28]

doses are often used in infants to achieve the desired plasma concentration of the drug. Conversely, water-soluble drugs need to be administered at a higher dose per kilogram in the newborn to get adequate plasma and tissue concentrations. Slow bloodstream in the newborn may also affect the distribution of the drug.[30,32,33]

The relative mass of the fat tissue and skeletal muscle tissue in newborns is lower than that of adults. Particularly, the distribution volumes of the drugs whose fat solubility is high are much higher. Therefore, it should be administered in lower doses.[15,20,22]

The blood-brain barrier has not developed yet in the newborns and it is permeable. There is hypersensitivity against the drugs affecting the central nervous system.[20,23,34] Bilirubin competes with the drugs in binding to the albumin. Drugs administered in jaundiced newborns detract the bilirubin from albumin. The increasing bilirubin may cause kernicterus in neonatal whose blood-brain barrier does not develop. This is a condition that occurs in sulfonamide antibiotics administered in the newborns with sepsis.[21] Morphine derivative drugs which do not dissolve in the lipid can pass the blood-brain barrier easily and reach to the central nervous system.[30]

Drug Metabolism (Biotransfer)

Metabolism of the drugs usually takes place in the liver. The blood flow to the liver is necessary for the metabolizing of the drugs. The hepatic blood circulation is slow in newborns. As the cardiac output increases with the development of the newborn, the hepatic blood circulation increases. The liver enzymes start to mature in 2-3 weeks after the delivery.[32] About in the 4th week, the liver functions are fully developed, and an excess amount of drug can be metabolized. If this situation is not taken into account, non-metabolizing drugs in premature infants and newborns may accumulate in the body at toxic levels.[32,35]

Certain drugs can be metabolized faster because the metabolic rate of infants and young infants have a higher metabolic rate than adults. Enzyme system activity is 60-70% at birth when compared to an adult. For this reason, certain drugs are metabolized faster in newborns. The metabolism of many drugs is performed by cytochrome p450 system enzymes in the newborns. The maturation of each enzyme included in the enzyme system differs. For instance; the CYP2D6 enzyme is responsible for transforming the codeine into morphine, an active form. However, the activity of this enzyme is low in newborns, and about a five-year duration is required for reaching the adult level.[30,36,37] The rate of the CYP3A4 enzyme to reach the adult level which provides drugs to be metabolized such as paracetamol, diazepam is faster than the CYP2D6 enzyme. The CYP3A4 enzyme of the newborns reaches the adult level for about 6-12 months.[30]

Another factor that affects drug metabolism is the change in liver size. The fetal liver contains 5% of total body weight and 2% in adults. This explains why most of the drugs in children are excreted faster, and that there is a need for high doses in proportion to this.[20,25] In addition, kidneys play an important role in drug metabolism. Even though the kidney is involved in the biotransformation of drugs, data on the developmental processes of renal microsomal systems are lacking.[7]

Drug Excretion

Excretion is the removal of the drugs or metabolites from the body. There are many different forms of excretion, usually via the liver or renal pathways. These can be sweat, urine, gait, or breast-feeding. Kidneys are important organs providing the elimination of many drugs. Drugs that are not volatile dissolve in the water and have a low molecular weight are generally eliminated through the kidney.[32] Antimicrobial agents frequently used in newborns and caffeine particularly used in premature infants may be given as examples for the elimination of drugs through the kidney. The renal elimination of such drugs varies depending on glomerular filtration rate, renal blood flow, and tubular function (re-absorption and secretion).[28] The renal functions are limited in the newborn due to the fact that kidneys are immature in the delivery. While Glomerular filtration rate (GFH) term is about 2-4 mL/m/1.73 m^2 in newborns, it is 0.6-0.8 mL/m/1.73 m^2 in preterms. Generally, GFH is 30-40% of the adult value. At the end of the third week, GFH reaches 50-60% of adult values. It reaches the adult levels by increasing in a constant way until the infant is 8-12 months of old.[3,20]

Tubular secretion is an active transport process realized in a dependent manner to the renal blood flow. The drug secretion is also dependent on the affinity of carrier proteins in the proximal tubule, secretion area, drug distribution, and transport rate through the tubular membrane. The tubular secretion and re-absorption are immature in the delivery and they are about 20-30% of the adult values. It reaches the adult levels between months of 7-12.[3,15,20] Renal tubular secretion is important for the eliminations of the drugs which are secreted from the kidney such as penicillin and cephalosporin.[38]

The maturation of the tubular re-absorption continues until the adolescent period. Although the lipid-soluble drugs pass through the tubular membrane easily, water-soluble drugs or ionized drugs cannot be reabsorbed. The re-absorption of the acidic or basic drugs varies depending on the pH value of the tubular liquid.[22]

Since the renal functions are not adequately developed in newborns and infants, it may be required to decrease the dose of drugs primarily eliminated through the kidney because renal clearance may be delayed.[39] Dose reduction may be required for preventing toxicity in newborns and premature infants. When this difference is taken into account clinically, the necessity of managing the dose adjustment and follow-up of the drug level carefully in newborns with renal failure become crucial for treatment.

Responsibilities of the Nurses in Drug Administration

Newborns have differences from adults in terms of anatomic, physiological, psychosocial, and cognitive aspects. Knowing these difference is a basis for safe drug administration in newborns. Safe drug administration and preparation of drugs in compliance with the developmental features of the newborn will provide a successful drug administration. The most important responsibility in the safe drug administration in newborns belongs to the nurses. Newborn nurses should calculate the therapeutic levels of the drugs and know the pharmacokinetic-pharmacodynamic properties of the drugs (such as absorption, distribution, metabolism, and elimination) prior to the drug administration. Also, the nurses should monitor the newborns in terms of the expected and adverse effects of drugs by taking these properties into account.[10,40] The responsibilities of the nurses in the safe drug administration in newborns can be listed as[13,25,32,40,41,42]:

1. Vital symptoms and clinical findings should be assessed carefully.
2. Therapeutic and toxic drug effects should be closely monitored.
3. Renal functions should be assessed by monitoring the intake-excreted fluid.
4. Serum levels should be followed for the drugs having narrow therapeutic limits. The volume of the drug administered should be continuously monitored.
5. Precautions should be carefully adapted regarding the drugs that require special safety precautions.
6. Remarkable labels should be affixed on the drugs that are dangerous to be given to newborns and these drugs should be kept away from the preparation area. Care should be taken against the potential side effects of the drugs that have little use in newborns and that have limited experience.
7. The “eight right” principle is important to prevent errors in drug administration and to provide safe medication to newborns.
8. Before giving any drugs to the newborn, the following information should be obtained from the parents: Has the newborn allergy to any drug? How does the newborn react to medication? What are the names of the previously taken drugs, dosage, medication program, and the reason for intake? Based on this information, the effectiveness of the drugs and the tolerance of the newborn are determined. In addition, the level of development of the newborn, drug swallowing status, when and how to prepare is assessed.
9. Determination of safe drug dose: Pediatric drug doses are calculated according to the body surface area or the body weight. In infants, body surface according to the body weight is greater than in adults. For this reason, the drug dose calculated according to the body surface is higher than the amount calculated according to body weight. Safe drug doses are determined by on the age of the newborn and the ability to metabolize the drug. Before giving any medication, the dose of the recommended medication is checked again to see whether it is the right dose for the newborn or the body surface.
10. Before giving any medication, the dose of the recommended medication is checked again to see whether it is the right dose for the newborn or the body surface. Especially in newborns, the decimal units such as milligrams and nanograms in drug dosage calculations should be observed.
11. Body weights of all newborns should be measured and body weight should be followed regularly/daily after the hospital admission.
12. If the mother is breastfeeding the baby, it should be questioned whether the mother is taking medication. The family’s knowledge of the drug to be given should be investigated. Based on this information, the effectiveness of drugs and the child’s tolerance is determined in drug administration.
13. Small elimination of the drugs through the kidneys in the infancy period leads to an increase in the prolongation of the half-life of drugs and drug toxicity risk. For this reason, the dose should be decreased particularly in newborns in the infancy period.
14. Therapeutic and toxic effects of drugs in newborns should be closely monitored due to the physiological characteristics of newborns.
15. Some antibiotics in flacon form have dry powder volume. If the dry powder volume is not taken into account while calculating the doses requested for newborns, the prepared drug dose will be less than the requested dose and thereby lead to dose errors. For this reason, while preparing the antibiotics in flacon form, the dry powder volumes should be considered.
16. The innovations for the pediatric drug information and practices, containing also the use of technological tools, should be closely followed.
17. Relatives of the newborn should be informed of the pediatric doses and adverse effects of the drug verbally and in writing.
18. Pharmacotherapy in newborns and differences from the adults should be included in the undergraduate and postgraduate training of the nurses.

Conclusion

Pharmacokinetics of the drugs in newborns are different from that in older children and adults. Therefore, specific arrangements and considerations are necessary to administer the drugs safely. Further studies are needed in order to determine the knowledge level of nurses about pharmacotherapy in newborns and to examine them in terms of patient safety. This review is thought to be a guide for studies on pharmacotherapy and safe drug administration in newborns.

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