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Gac Med Mex. 2015;151:361-8

GACETA MÉDICA DE MÉXICO **REVIEW ARTICLE**

Pharmacology for the fetus and the newborn

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Abstract

During intrauterine life, the fetus can be exposed to a series of substances ingested by the mother, some of which are necessary for her health but detrimental to fetus. The noxious effects of such exposure could present immediately after exposure in the fetus or be manifested at the time of delivery and sometimes weeks after birth. The passage of drugs or nutrients across the placenta depends on some physicochemicals that have the ability to cross the placenta barrier, and thus get in contact with the fetus and produce harmful effects. Considering the physicochemical properties of the substances, the possibility of such compounds to cross the placenta barrier and thence to the fetus can be predicted. Equally, it is important to consider the characteristics of the newborn as an immature being, different from adults, when carrying out pharmacokinetic and pharmacodynamic processes. Based on the latter, it is important to know the behavior or characteristics of the fetus and the newborn in the face of drug management and above all consider the advantages and disadvantages of the use of such drugs for the care of a being yet in development, as is described in this work. (Gac Med Mex. 2015;151:361-8)

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KEY WORDS: *Pregnancy. Fetal development. Placenta. Drug transference. Newborn.*

Pharmacology during the gestational period

During intrauterine life, the fetus may be exposed to a series of drugs and toxic substances whose effects can be immediate and cause fetal death or produce some damage that may manifest at the moment of birth or even weeks, months or years later[1-2]. Establishing a relationship between intrauterine exposure to drugs and pathologic damage produced in the fetus has been difficult, unless such damage is confirmed after some time[3,4].

The placenta forms a maternal-fetal interface since the moment the blastocyte is implanted in the uterus until the delivery is produced[5]. The primitive trophoblast acts as an anchoring device and satisfies the nutritional needs of the internal cell mass by phagocytosis of the maternal decidual tissue. In this developmental phase, the transport processes between the mother and the inner cell mass are started. When the trophoblast is differentiated and the cell mass is internalized in the embryo, the placenta – which originates in the embryo – adopts the role of the not-yet-developed organs. Hence, its functions include the production of a wide range of substances that are essential to the growth and development of the fetus. The placenta is an organ with immense reserves that operates under a safety factor, which offers a safeguard environment to the fetus. This fact becomes clear by the birth of

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Date of modified versionreception: 09-05-2014
Date of acceptance: 15-05-2014

Table 1. Pathological effects of drugs on the fetus and the newborn

- Fetal emaciation
- Teratogenesis
- Carcinogenesis
- Reproductive system alteration
- Abnormal prenatal growth
- Abnormal postnatal growth
- Inadequacy for delivery process
- Hematological disorders
- Metabolic changes
- Mental retardation
- Neurological sequels

healthy children with a deficient placenta, which demonstrates that the placenta is able to maintain sufficiency of its functions and preserve the child unharmed[6,7].

Several studies indicate that the number of layers separating maternal from fetal circulation conditions the velocity of substance transport across the placenta. The thickness of the human placenta membranes ranges from 25 mm at the beginning of gestation to approximately 2 mm at its termination, which suggests that there are changes in the transference of compounds throughout pregnancy[8]. Some examples are shown in table 1.

Factors regulating mother-fetus substance exchange

Placental transport mechanisms

To be able to cross the placenta, substances follow certain basic transport mechanisms through biological membranes, especially simple diffusion mechanisms. Most drugs cross the placenta through this mechanism. The diffusion rate depends on a concentration gradient between maternal and fetal circulation, as well as on physicochemical properties of the substances, such as their lipid-solubility, degree of ionization and molecular weight[9,10].

Compounds with a high degree of liposolubility are optimally transferred, due to the structural and physicochemical characteristics of membranes; in addition, transference is favored by non-ionyzed or low molecular weight compounds[11]. Athough the capability of some endogenous compounds such as glucose – and possibly iron –, to diffuse across the placenta, it is not adequate to infer that drug transport occurs the same way. An important number of endogenous nutrients, including amino acids, creatinine, sodium, calcium and phosphates, cross the placenta against a concentration gradient, probably by means of active transport mechanisms. Very few drugs or other genobiotic agents cross the placenta in this form[12].

Factors regulating placental drug transport

Lipid solubility

As previously mentioned, highly lipid-soluble drugs rapidly cross the placenta; its passage is only limited by maternal blood flow within the placental lacunae. Drugs such as barbiturates, minor tranquilizers, narcotic analgesics and local anesthetics are transferred by this mechanism and hence they are known as flow-dependent[13]. The high permeability of the placenta to these drugs is reflected by their rapid transference: after the mother is administered an intravenous bolus of a drug with flow-dependence characteristics – such as meperidine –, peak fetal concentration (in the umbilical vein) is reached very quickly[14].

The reduction of the placental blood flow resulting from its decrease in uterine vessels produces, in turn, a decrease in drug transference. This may occur, for example, due to normal uterine contractions during labor by the administration of oxytocic drugs[15].

Highly ionizable or non-lipid soluble drugs can be transferred in a limited way due to low permeability of this biological barrier. The rate this substances cross the placenta at usually is not influenced by flow, as it occurs with lipid-soluble drugs.

Protein binding

As previously mentioned, non-ionized and lipid-soluble drugs transference across the placenta is proportional to the maternal-fetal free drug concentration gradient. Therefore, the passage of drugs with high affinity to maternal plasma proteins will be delayed due to the decrease of the available free drug concentration gradient. After crossing the placenta, they will also be able to bind to fetal plasma proteins, wich act as transporters for some molecules crossing from the maternal circulation. The net effect of this phenomenon is a delay in reaching equilibrium of the drug between both circulations, since a relatively large amount has to be transferred, even with a low concentration gradient, before the free drug is balanced. In addition, there is difference between the drug bound to maternal and

fetal plasma[16]. For example, some drugs, such as antibiotics, local anesthetics, phenytoin and phenobarbital, show a high degree of maternal protein binding, when compared with fetal protein binding; the opposite occurs with salicylates.

Transport of some key substances

Glucose

Glucose is the most important metabolite required by the developing fetus; this is why some of the first investigations on placental transference *in vivo* were conducted to demonstrate the transference of this sugar. Its transport is known to occur by facilitated diffusion, mediated by specific carriers that favor the input of glucose towards the fetus[17].

Vitamins

Different transport systems across the microvillar membrane have been described for water-soluble vitamins, such as choline, ascorbic acid and riboflavin. Studies in human placenta show that choline transport occurs on both directions (maternal and fetal) of the synciotrophoblast[18].

Micronutrients and iron

Fetal requirements of iron – about 300 mg total during pregnancy –, are covered by trans-placental iron transport from maternal transferrin. During pregnancy, in addition to including iron-rich foods in the diet, a doctor-indicated supplement has to be taken. Most iron required during pregnancy is used to increase the hemoglobin mass in the mother. This increase occurs in healthy pregnant women, who have sufficient iron reserves or are adequately supplemented with the mineral[19].

Insulin

Insulin has been shown not to cross the placenta in significant amounts in the human being. Recently, monoclonal antibodies have been used to confirm that placental membranes contain different types of receptors for insulin and insulin-like growth factor (IGF) as an important regulator of fetal growth, and IGF-1 and IGF-2 have been suggested to partially mediate this effect by promoting adequate development and functions of the placenta. For example, IGF-1 plasma levels are significantly decreased on day 21 in gestating rats on low-protein diets. It can be speculated that decreased levels of maternal hormones, such as insulin, leptin and IGF-1, are a signal associating maternal protein malnutrition with the main amino acid-transporters in the placenta.

Table 2. Comparison of the levels of some compounds between the maternal and fetal sides in the equilibrium state

	Equal	Lower in the fetus	Higher in the fetus
Amino acids		+	
Urea	+		
Uric acid	+		
Creatinine	+		
Inorganic phosphorus			+
Free fatty acids		+	
Cholesterol		+	
Glucose		+	
Lactic acid			+
Calcium			+
Magnesium	+		
Chlorine	+		
Sodium	+		
Potassium	+		
Iron			+
Vitamins			
Lipid-soluble	+		
Water-soluble			+
Chorionic gonadotropin		+	
Placental lactogen		+	
Growth hormone			+

Compound-transference tendeencies are driven by the biological requirements of each compartment; some values relating to each side are shown in table 2[20].

Drug placental metabolism

Although the placenta is able to metabolize drugs, its contribution to transform xenobiotic agents is not yet well defined. Due to its reaction capacity, the human placenta

Table 3. Percentage of total weight according to age*

Organ/tissue	Fetus	Full-term newborn	Adult
Skeletal muscle	25	25	40
Skin	13	4	6
Skeleton	22	18	14
Heart	0.6	0.5	0.4
Liver	4	5	2
Kidneys	13	12	2
Brain	12	12	2

*Organs and tissues relative weight according to age, expressed in percentage (%) of total body weight.

is a much less active organ in the biotransformation process than the liver – both maternal and fetal – during the last trimester of gestation. However, its contribution to the synthesis and degradation of endogenous substances, such as steroid hormones, is very important, especially in those where the 1A1 and 2E1 enzymes take part[21,22]

Pharmacology of the newborn

Once the child is born, he is highly vulnerable, since he is exposed to the possibility of suffering complications resulting from the delivery or by contact with his new environment and with micro-organisms capable of infecting and affecting his growth and development and, therefore, sometimes it becomes necessary to resort to drug administration. These medications can have different pharmacokinetics than those in adults, due to immaturity of the newborn's organs, compared to those of an older child.

Pharmacological processes such as absorption, distribution, metabolism and excretion of drugs administered to the newborn are usually decreased[23,24], and this should be considered at the moment of making a prescription, as described below.

Drug distribution

The composition of the newborn's body evolves rapidly. Table 3 shows the relative weight evolution of different organs and tissues according to age. Neonates have a markedly more elevated percentage of water than humans other ages (70% of body weight[25]; in small premature neonates it is 85%). With regard to extracellular water, 40% of the newborn's body weight corresponds to this fluid. Most significantly, many drugs are diffused through extracellular spaces with water as a vehicle to reach the receptor sites; therefore, as the body composition changes throughout the development, drug distribution volumes change as well. This is very important, especially in the case of water-soluble drugs, such as aminoglycosides.

With regard to body fat composition, it is approximately 0.5% in the neonate and it increases after birth to up to 15-20% at six months of age, before starting to gradually decrease by adolescence. Body fat composition is also important for drug distribution and, therefore, organs generally accumulating high concentrations of lipid-soluble drugs have to be considered, since the newborn's organs may accumulate lower concentrations of drugs such as barbiturates and coumarinics, which may delay their clearance, unlike adult persons, in whom this sequestration mandates drug surveillance when these drugs are used[26,27].

Absorption

Drug absorption in children is often similar to that in adults, but there are factors that can alter it.

Blood flow

After an intramuscular or subcutaneous injection, absorption in neonates and adults is known to depend mainly on the blood flow rate to the injected muscles or subcutaneaous area. In case of low muscular mass, if an injection is applied, absorption may be irregular and difficult to predict, since the drug will remain in the muscle and will absorb slower than expected. This aspect can be seriously compromised in neonates, owing to poor peripheral perfusion associated with lower cardiac output, as it occurs in cases of cardiovascular shock, vasoconstriction by sympathomimetic drugs and heart failure, or due to some serious respiratiry disease, as it happens sometimes in adults. If the risk decreases suddenly, there can be an immediate and unpredictable increase in the amount of drug entering the circulation, which can cause for toxic concentrations to appear. Especially dangerous drugs that can cause such situation include cardiac glycosides[28], antibiotics[29,30], aminoglycosides and anticonvulsants[31-33]. Increasing the distribution volume can alter pharmacokinetics and tissue penetration, as well as the clearance of drugs such as indomethacin and van-

comycin. In the presence of these situations, drug monitoring and dose adjustments as needed are recommended to avoid possible toxicity effects or treatment failures.

Gastrointestinal function

Gastrointestinal system in neonates exhibits important biochemical and physiological differences in comparison with older people, especially in gastric acidity, with regard to its production and secretion, which is directly related to weight and gestational age. At birth, pH usually ranges between 6 and 8; while gastric acidity increases within the first 10 days after birth, in premature infants, gastric acid secretion is slower than in full-term infants, which implies the presence of larger amounts of ionizable compounds, which are more difficult to absorb.

During the neonatal period, gastric emptying time is prolonged from 6 to 8 h on the first day of life, and the frequency is directly affected by the presence of food, as well as by its amount or consistency; for example, liquid-consistency and sugary food will delay gastric emptying. Therefore, the absorption of those drugs that are administered by the oral route can be faster in neonates, with peak absorption times of a few minutes, when there is a delay in gastric emptying caused, for example, by some acid food.

Gastrointestinal tract bacterial flora composition

This is another factor that modifies drug absorption, since it influences on intestinal motility, as well as on nutrients' bile salts and drug metabolism. Bacterial flora depends on patient's age (postnatal), type of delivery, type of diet and used pharmacotherapy. Metabolic capability and bacterial microflora function are diminished in the newborn, since optimal degree of maturation has not been achieved, which will not be reached until 4 years of age.

Drugs rhat are absorbed in the small bowel can have its absorption and therapeutic effect delayed because peristalsis in the neonate is irregular and generally slow and, therefore, the amount of drug absorbed in the small bowel can be unpredictable: if peristalsis is slow, a higher amount of the drug may be absorbed, which can cause toxicity in the patient; conversely, an increase in peristalsis, as it happens in diarrheic conditions, may cause lower absorption due to a decrease in intestinal surface area.

Table 4. Oral absorption (bioavailability) of different drugs in the neonate in comparison with older children and adults

Drug	Absorption in the neonate
Penicillin G	Higher
Ampicillin	Higher
Phenylbutazone	Higher
Phenytoin	Lower
Phenobarbital	Lower
Acetaminophen	Lower
Nalidixic acid	Lower
Rifampicin	Lower
Diazepam	Equal
Digoxin	Equal
Sulfonamines	Equal

Vomiting

This is other factor that influences on oral drugs absorption in the newborn; it occurs at this age and can inadvertently impede drugs absorption. Table 4 shows some examples of drugs where oral absorption in the neonate is altered in comparison with older children[25].

Administration route

Due to their physiological characteristics, different routes of drug administration are used in newborns. For example, the most adequate route for chloramphenicol in this age group is intramuscular, since adequate therapeutic serum concentrations are not reached with the oral route. On the other hand, the topical route is frequently used in pediatrics. The skin is an entrance door for different micro-organisms that cause local and systemic infections. In neonates, particularly in prematures, the skin can easily be damaged and injured owing to the large amount of water it contains. These patients are more exposed to suffer infections by bacteria and fungi, which increases the risk of triggering toxic effects due to topical substances application by itself. Total skin surface area ratio of the newborn with regard to weight is, in turn, approximately 3 times higher than in adults. Consequently, bioavailability of drugs' topical dose is approximately 3-fold

higher in newborns than in adults. There are very clear examples of different toxic substances the newborn is exposed to, such as laundry detergents with pentachlorophenol and hydrocortisone in the cases of diaper dermatitis, regardless of their separate use.

Other route by means of which the newborn can receive some drug is breast milk. If during breast feeding the mother is ingesting some medication that is excreted through breast milk, the child will absorbe it[34,35]. The newborn may be exposed to adverse effects of drugs that are excreted through breast milk (> 10%) and therefore, monitoring of the neonate is important when he is being breastfed. For example, doxefin (miconazole/tinidazole) is excreted into breast milk, and even if the mother takes small doses of the drug, it crosses and causes numerous adverse effects in the newborn, such as vomiting, navicular abdomen and muscular hypotonia, which requires hospitalization[36,37].

Plasma protein binding

Albumin is the protein with more drug fixation and transport properties; in neonates, binding to proteins is much lower than in older people. Some studies on plasma albumin and α-1a acid glycoprotein variability in healthy neonates and neonates with renal failure and liver dysfunction show that, as liver dysfunction progresses, albumin concentration decreases, thus resulting in higher amounts of free drug being present, whereas glycoprotein concentration remains unchanged. However, there is no correlation between the levels of albumin and glycoproteins and bilirubin concentrations in patients with liver disease, which, in addition to being a indicator of the hepatic function for drug metabolism, is also an indicator to know any possible interaction at the level of protein binding due to displacement between two or more compounds with high affinity to proteins. The clinician should consider this affinity to proteins before prescribing and avoid as much as possible concurrent use of such compounds at earlier ages.

Table 5 shows the binding degree of some drugs to plasma proteins, which depends on age-related variables, such as absolute amount of available proteins and their binding sites, constant of affinity of the drug to proteins, the pathophysiological condition and presence of endogenous substances competing for proteins[25].

Protein binding is reflected on distribution volume and body clearance of the drug. Some drugs compete with albumin-bound bilirubin. If serum bilirubin increases due to physiological reasons or blood type incompability, it can displace the drug from albumin and increase its free concentration, causing toxicity; an example of this phenomenon is what happens with phenytoin administration used as anticonvulsant[38,39].

Table 5. Plasma protein binding of selected drugs in newborns and adults

	Plasma protein binding	
Drug	**Neonates***	**Adults***
Paracetamol	36.8	47.5
Chloramphenicol	31.0	42.0
Morphine	46.0	66.0
Phenobarbital	32.4	50.7
Phenytoin	74.4	85.8
Promethazine	69.8	82.7

*Average binding values (%)

Acid-natured drugs such as salicylates and sulphonamides are slowly eliminated from the neonate, since they displace bilirubin from its point of fixation to serum albumin[40,41]. This produces an increase of free albumin and causes for a higher concentration of it to cross the blood-brain barrier, which can produce a cerebral lesion.

Interactions by displacement of plasma protein binding sites produce dramatic conditions in the newborn. For example, if plasma protein binding of a drug decreases from 99 to 98%, the result will be a doubling of the drug's concentration from 1 to 2%, which can result in a toxic effect.

Metabolism

Drug metabolism occurs mainly in the liver. In the neonate, the concentration of mixed-function cytochrome P450-dependent oxidase enzymes and conjugation enzymes is 50-70% of that in adults. Glucuronic acid formation does not reach adult values until the third or fourth year of life. Therefore, neonates have little capability to metabolize drugs, many of which have slow clearance and prolonged half-life.

Pharmacokinetics studies of lidocaine show that infants younger than 1 month and low birth weight exhibit elevated distribution values and long half-life, indicating that treatment regimens should be reduced in this group of patients[42].

Table 6. Factors affecting renal excretion of drugs over growth

Physiological variables	Effect on		
	Newborns	**Infancy**	**Childhood**
Renal flow	Increased or decreased	Increased	Present
Urinary circadian rhythm	Absent	Present	Normal
Glomerular filtration	Decreased	Decreased or normal	Normal
Tubular secretion	Decreased	Normal	Normal
Tubular reabsorption	Decreased	Increased, decreased or normal	Normal
Urinary pH	Acid	Variable	Variable

Elimination

Drug excretion or elimination is a very important factor. Glomerular filtration rate (GFR) is much lower in infants born before 34 weeks of gestation than in full-term newborns, and in these it is also lower than in older infants, children or adults (Table 6). The rate is calculated based on the body surface area: in full-term newborns it accounts for only 30 or 40% of the adult value. The function improves in the first week of life, during which GFR and renal plasma flow are increased by 50%; by the third week it increases to 50-60% of the adult value; and by 6 to 12 months, adult-corresponding values are reached.

Therefore, drugs depending on renal function for elimination are slowly cleared from the body during the first weeks of life.

The group of drugs whose clearence is altered includes penicillins, which are cleared in premature newborns at 34% with regard to the rate in adults by body weight. Consequently, the dose of this group of drugs should be reduced at that proportion in this group of infants.A decrease in renal elimination rate has also been observed for aminoglycosides (amikacin, gentamicin, neomycin and streptomycin) in neonates due to immaturity of the organ responsible for this function. Pharmacokinetics studies of the antiviral zidovudine in newborns with AIDS show that elimination is slow at birth and gradually increases within the first week of life, reaching a plateau between the fourth and the eight weeks of age; its bioavailability increases in children younger than 14 days of age due to a decrease of first step metabolism, i.e., the metabolism a drug undergoes before reaching the systemic circulation, understood as the body's capability to clear the drug from blood; hence the agreement of some authors to call it clearance.

Conclusions

Owing to the changing body and physiological evolution of newborns, they have to be considered a particular and high-risk population for the administration of drugs.

There are countless drugs that are useful for adults or older children, but they have not been assessed in pharmacological studies in newborns rationally taking into account the multiple changes that continuously are suffered in this stage of life. It should be pointed out that many drugs are approved and launched into the market without the necessary trials performed in children, and many times they can put the life of the newborn in danger.

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