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Open Access Journal of Pharmaceutical Research
ISSN: 2574-7797

Mini Review: Pharmacokinetics Changes During Childhood, Old Age and Pregnancy

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Mini Review

Volume 3 Issue 4

Received Date: November 13, 2019

Published Date: November 27, 2019

DOI: 10.23880/oajpr-16000189

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Abstract

In the different stages of life, various anatomical and physiological changes occur and can influence the responses to drugs, due to pharmacokinetic processes also change with age. In this context, it is important to analyze how the anatomical and physiological changes influence the absorption, distribution, metabolism, and elimination of drugs during childhood, old age and pregnancy with to obtain the best pharmacological response without effects adverse when drugs are prescribed in these populations. Therefore, this review shows general aspects of each pharmacokinetic parameter, as well as special considerations on the absorption, distribution, metabolism and elimination process of drugs in the child, in the elderly and in the pregnant woman to obtain therapeutic success and prevent both therapeutic failure and the toxicity.

Keywords: Pharmacokinetics parameters; Child; Elderly people; Pregnancy

Introduction

Pharmacokinetic is a branch of pharmacology that studies the processes of absorption, distribution, metabolism, and elimination that suffered by drugs in the body [1]. These pharmacokinetic processes are different in the child, in the elderly and in the pregnant woman, which is why a review of the most relevant pharmacokinetic aspects to consider during the prescription of medications in these populations is briefly described below.

In this context, from the site of administration, the drug begins to release from the pharmaceutical form, and cross the membranes biologicals to the bloodstream [2]. When the drug enters the bloodstream it begins to distribute to organs or tissues. For example, the water-soluble drugs are mainly distributed to body water and fat-soluble drugs are distributed to organs or tissues that have a high amount of fat such as liver, brain, and adipose tissue [3]. The principal objective of the metabolism process is to modify the original drug molecule to a molecule that is more easily excretable and finally, drugs

or their metabolites are eliminated from the body by different pathways, the renal is the most common [3,4].

General Aspects of the Drug Absorption Process

As for the drug absorption process, it is important to know the pKa of the drug, the pH of the medium surrounding the drug, the thickness, the irrigation, the contact area and integrity of the biological membrane; as well as the contact time of the drug with said membrane, since these variables positively or negatively influence its bioavailability [5,6]. The drugs are chemically weak acids or bases, and depending on their pKa and the pH of the surrounding environment, the drugs can be dissociated in varying amounts; that is, of the administered amount of the drug, one percentage will remain in its undissociated form and another percentage will be in its dissociated form [7]. In this regard, for the absorption process the form that is of particular interest is that which is not dissociated, because it can more easily pass through the biological membranes because it is liposoluble [1]. Based on the above and according to the Henderson-Hasselbalch equation, when the pH value of the medium surrounding the drug is equal to the pKa value of the drug, then 50% of the amount of the drug in its form will be taken not dissociated and the other 50% will be in its dissociated form [3,4]. In summary, we can say that acidic drugs are better absorbed in acidic media, such as diazepam, acetylsalicylic acid, and indomethacin, are better absorbed in the stomach and basic drugs such as propanolol, atropine, and allopurinol, are better absorbed in basic media such as the small intestine [1].

In relation to the thickness of the membrane, the absorption of the drugs is inversely proportional to the thickness, that is, the thinner the biological membrane that has to pass the drug, the faster and greater its absorption; on the other hand, the irrigation or blood flow that has the membrane or the site where the drug is administered is directly proportional to the absorption of a drug, that is, the greater the blood supply, the greater and faster the absorption; The lower the blood flow, the lower or slower the absorption of a drug [1,3]. The longer the contact time has the drug with the biological membrane, the greater and faster its absorption; finally, as regards the integrity of the biological membrane, it is essential that said membrane, where the drug is applied, must be fine so that it acts as a semipermeable barrier; that is to say, it should not have wounds or injuries, if this occurs, there is a risk that a greater quantity of drug will enter the bloodstream and thus toxicity can occur [1,3].

The main anatomical and physiological changes that modify the process of drug absorption in the child, in the elderly and the pregnant woman are described below.

Absorption of Drugs in Children and the Elderly

From birth to old age, anatomical and physiological changes occur that influence the rate of absorption of drugs, this causes fluctuations in plasma concentrations according to the age of the patient and the route of administration used [8]. For this reason, it is essential to choose the right drug and the best route of administration at the different stages of life to obtain the best bioavailability and guarantee therapeutic success and avoid toxicity or therapeutic failure.

In this regard, the functional maturity of the organs of a young adult with an average weight of 70 kg is compared with the functionality of the organs of a full-term or premature newborn, can be observed functional immaturity of the organs in the children [9]. For example, at the gastrointestinal level in pediatric patients, it is observed that the secretion of gastric acid is lower than in the young adult, this decreases the bioavailability of drugs that are weak acids such as phenobarbital. The biliary function is immature, and the enterohepatic circulation is diminished too and with it, the bioavailability of liposoluble drugs such as diazepam is reduced [10]. On the other hand, intestinal motility and gastric emptying time are also reduced, so the contact time of drugs administered orally with the gastrointestinal mucosa increases and this favors the absorption rate increase [11]. The same occurs in the elderly but the cause is different, that is, during ageing, the organs decrease in size because they have fewer functional cells, so there is a lower functional surface area of absorption in the gastrointestinal tract and also decreases their blood flow [12].

In relation to the administration of drugs intramuscularly or subcutaneously in young children, it is important to consider that there are fluctuations in the absorption rate, due to the variability of muscle mass and subcutaneous adipose tissue; as well as the poor local blood flow of the muscles and the depth in the injection site, the same occurs in the elderly [11,12].

As for transdermal absorption in term newborns and the elderly, absorption by this route of administration is greater than in the young adult, because the stratum corneum is thinner. If medications are to be applied through this route of administration, the skin dont be have wounds, skin rash or eczema, burns, etc., because

this causes the membrane permeability to be lost, which increases considerably the absorption of the drugs and getting to produce systemic effects [1,13,14]. In the elderly, cases of salicylate poisoning applied topically into the skin have been reported; Therefore, in addition to the thickness of the skin, for this route of administration, the quantity of drug applied, the size of the area or body surface where the medicine is applied and the way of applying it must also be considered; that is to say, if only put into the skin or this area is massaged since the massages cause heat and vasodilation so that the blood flow in this area increases and this favors a greater absorption of the drug applied to the skin [14,15].

Absorption of Drugs in Pregnancy

During pregnancy, various anatomical and physiological changes influence the absorption of drugs. For example, at the gastrointestinal level the pH of saliva decreases mainly in hyperemesis, this can affect the absorption of drugs administered sublingually [16]. On the other hand, there are also changes in the pH of the gastric content due to the increase in gastrin, generally, the pH becomes less acidic, this decreases the absorption mainly of drugs that are weak acids [17]. Intestinal motility also decreases due to the effect of progesterone and, on the other hand, as the pregnancy progresses the growth of the uterus decrease the intestinal movement and gastric emptying, and the drugs remain more in contact with the surface of absorption, and this favors a greater absorption of the drugs [16]. As for the route of inhalation administration, particularly during pregnancy, the absorption rate of the drugs is increased because of the cardiac output increase during pregnancy, also, hyperventilation causes a faster speed in pregnant women diffusion through the alveolar membrane than in a woman who is not pregnant [18].

Table 1 shows the main physiological changes that occur in the child, in the elderly and the pregnant woman and how they influence the process of drug absorption according to the route of administration.

Route of administration	Physiological change	Clinical relevance	References
Oral	Decrease the production of gastric acid (There is a slight decrease in pH)	In most older adults, these changes lack clinical significance. Except with calcium carbonate, since it requires very acidic means for its optimal absorption and accumulation of calcium in the intestinal lumen can produce constipation, for this reason in these patients calcium citrate is recommended, which dissolves more easily in a less acidic environment.	[8-12]
	Decrease the speed in gastric emptying. (The drug stays longer in this site).	The drugs absorption may increase.	
	Reduces gastrointestinal motility (The drug stays longer in this site).	In the third trimester of pregnancy, drug absorption may increase.	
	Decrease blood flow in the gastrointestinal tract and enterohepatic circuit.	In premature infants and neonates, it is important to consider the low bioavailability for fat-soluble drugs.	
	Decrease the absorption surface (The drug is absorbed more slowly and erratic).	Is important in premature infants and older adults.	
Transdermal	Decrease blood flow (The drug stays longer on this site).	Toxicity may occur due to excessive topical administration of medications in both the child and the elderly. In pregnancy, this route of administration also represents a risk if there are skin lesions	[13-15]
	The thickness of the skin decreases, it is thinner (More drug is absorbed)		
Intramuscular	Decrease blood flow (The drug stays longer on this site).	Although absorption in children and older adults can be erratic, no significant changes are observed in the magnitude of the response.	[11,12]
Pulmonary	Cardiac output is increase and the capacity respiratory too	In pregnancy the absorption of drugs by inhalation is increase.	[18]

Table 1: Physiological changes in children, the elderly and pregnancy and their clinical importance in drug absorption.

General aspects of the Drug Distribution Process

When the administered drugs reach systemic circulation, the distribution process begins immediately, during this process the drugs first reach the most irrigated organs such as the liver, and then reach the less vascularized tissues or organs such as adipose tissue and joints Likewise, the water-soluble drugs are mainly distributed to total body water and fat-soluble drugs to adipose tissue [1]. On the other hand, when the drug enters the bloodstream an amount will be dissociated and another quantity will be not dissociated; the dissociated fraction will bind albumin if the drug is acidic or acid 1-alpha-glycoprotein if the drug is basic; subsequently the drug will be transported together with these proteins invariable quantity [3,4]. The amount of the drug that does not bind to the plasma proteins is the one that produces a pharmacological response. Therefore, the greater the amount of free drug, the greater the response and the greater the risk of toxicity. There are drugs and components of food and medicinal plants that compete for the binding sites of plasma proteins and this effect can produce toxicity in the patient [1,3]. Finally, the volume of distribution refers to the amount of liquid in which a drug is diluted.

Distribution of Drugs in Children and the Elderly

The volume of distribution of the drugs is modified in children and the elderly, due to changes in body composition and the binding of drugs to plasma proteins. In relation to body composition at different stages of life, changes in the content of total body water, adipose tissue and muscle are observed. In term newborns the body water content is 70%, and in the older adult it decreases to 54%, while adipose tissue is 13.4% in the term newborn while in the older adult increases up to 30% and finally the muscle mass is found in 13.4% in the term newborn and in the older adult decreases up to 12% [19]. These changes are very important to consider because children will have a greater volume of distribution for water-soluble drugs so the dose should be increased to achieve the desired pharmacological effect. However, in clinical practice, the children don't receive, high drug's doses because the metabolism and elimination processes are diminished and their liver and kidney are still immature and on the other hand, in the term newborns the concentration of albumin and total proteins is low, this may favors toxicity by increasing the free fraction of the drug [20]. In the elderly, the volume of distribution is reduced for water-soluble drugs but increased for fat-soluble drugs, which favors increasing their elimination half-life, so that dose adjustment should be made considering your liver and kidney function. It also decreases the synthesis of albumin either due to malnutrition or because de *novo* synthesis decreases as there is less number of hepatocytes and less blood flow in this organ, this results in the increase of the drug-free fraction with the consequent risk of toxicity, mainly this it happens with drugs such as phenytoin, warfarin, digoxin, and acetylsalicylic acid [20,21].

Distribution of Drugs in Pregnancy

In pregnancy, the body composition changes, the total body water increases considerably from 25 L at the beginning of pregnancy to 33 L at the end of the pregnancy and the extracellular fluid increases by approximately 25% [22]. This influences that the volume of distribution of water-soluble drugs during pregnancy increases, that is, the pregnant woman will require a higher dose of the drug to obtain an effective pharmacological response compared to a woman who is not pregnant. However, this is not done in clinical practice because the cardiac output is increased because the organs and tissues need to be more irrigated during pregnancy, and this favors high concentrations of the drugs taken by the mother to the product through of the placenta [23].

The binding of drugs to plasma proteins is also diminished in pregnancy because there is less plasma protein [17]. However, it is very important to consider that concentrations of free fatty acids increase considerably as pregnancy progresses, so the risk of a competitive drug interaction of albumin binding sites between free fatty acids with the drugs administered to the pregnant woman, they will favor the increase in the free fraction of the drug, since fatty acids have a high affinity for plasma albumin [22, 23].

General Aspects of the Drug Metabolism Process

In the metabolism process, the drug original molecule is modified by various chemical reactions to a molecule that is more polar and more easily excretable. The main organ that participates in this process is the liver [1,3]. During this process, the drugs can be transformed into an inactive, active (prodrug) or toxic molecule. It is important to mention that there are drugs that do not biotransform, that is, their chemical structure is not modified and eliminated unchanged. In general, the reactions of the metabolism suffered by drugs are divided into phase I and phase II reactions. Phase I reactions are very simple chemical reactions such as oxidation,

reduction, hydrolysis, etc. Of these chemical reactions, the most important and most occurring are the oxidation reactions carried out by cytochrome P450 enzymes (CYP450) [24]. CYP450 is a very large family of enzymes that are responsible for metabolizing or bio transforming many substances in the body including drugs. Of all the cytochromes, the most abundant isoform that participates in the metabolism of most drugs is CYP3A4 and CYP3A5 [1,25]. There are drugs and substances present in food, medicinal plants, as well as environmental toxins that can inhibit or induce CYP450 [26,27]. If these enzymes are inhibited there will be less CYP450 that perform the metabolism and therefore the concentrations of the drug in the blood will increase, which can cause an increase in the pharmacological effects and with it an intoxication. Instead, if these enzymes are induced there will be more CYP450 that perform the metabolism and therefore the concentrations of the drug in the blood will decrease, which can cause a decrease in the pharmacological effects and thus therapeutic failure [28]. On the other hand, phase II reactions are also called conjugation reactions (glucuronide acid), because it is conjugated with the drug molecule or metabolite previously formed in phase I reactions [3].

Drug Metabolism in Children and the Elderly

In the child, the pharmacokinetic process of metabolism is diminished because his organs are immature and hepatic blood flow is limited. In general, in the term newborn, the phase I reactions of drug metabolism, mainly the oxidation reactions measured by CYP450 enzymes are reduced, however, as the child grows the metabolic rate for these reactions already increases that these enzymes are expressed and induced as the child is exposed to various xenobiotics, including drugs [1,4]. Phase II metabolism reactions vary according to the maturation of the enzymes responsible for conjugation. For example, in newborns up to 3 months, the sulphotransferase activity is more developed than glucuronidation [10]. In the same way, in the older adult, the hepatic metabolic rate is decreased since there is a lower number of hepatocytes and therefore a smaller amount of CYP450 enzymes and on the other hand, the hepatic blood flow is decreased. These factors favor that in the older adult the elimination half-life of drugs increases in comparison to the elimination half-life of a healthy young adult. Another aspect to consider in the metabolism of drugs in the elderly is the pharmacological interaction through induction and enzymatic inhibition, derived from polypharmacy in the elderly and the concomitant consumption of herbal products. Phase II reactions are not affected or modified by increasing age [27,28].

Drug Metabolism in Pregnancy

In pregnancy, cardiac output is increased, however, hepatic blood flow does not seem to change. About the metabolism of drugs during pregnancy, the most important aspect to consider is the effect of the increase in progesterone levels on liver metabolism, since progesterone acts as an inducer of the hepatic microsomal system [29]. This may decrease plasma concentrations of drugs specifically metabolized by the CYP3A4 isoform and produce therapeutic failure. However, in clinical practice, the ideal is not to prescribe drugs during pregnancy or only use them if the expected benefits in the mother and the product overcome the risks [30].

General Aspects of the Drug Elimination Process

Finally, the elimination process explains how drugs are eliminated from the body. The main organ that participates in this process is the kidney [1,2]; at the renal level, the drugs can be removed by filtration and/or tubular secretion but also at the tubular level they can be reabsorbed. Therefore, for the elimination process, it is important to know the pH of the urine and the pKa of the drug [3]. Unlike the absorption process, acidic drugs are better eliminated in basic media and basic drugs are better eliminated in acidic media [1]. However, when the drugs are acidic and the pH of the urine is acidic or when the drugs are basic and the pH of the urine is basic, then the drugs are reabsorbed at the tubular level (They enter the general circulation again), this is due, under these conditions of pKa and PH, the undissociated fraction of the drug predominates, which is highly liposoluble and can easily cross biological membranas [1,3]. Most drugs are eliminated through first-order kinetics (the elimination rate is proportional to plasma concentration). Ethanol, for example, is eliminated by zero-order kinetics (the elimination rate is fixed and independent of plasma concentration). Both kinetics indicates the time of permanence of drugs in the body [4].

The routes by which drugs can be eliminated from the body are, urine, bile, faeces, breast milk, respiratory (volatile substances such as alcohol), saliva, sweat, tears, semen, vaginal discharge, skin, nails, and hair [3]. Drugs can be eliminated in varying amounts by different routes. For example, rifampicin which is a red antibiotic, this drug is mainly eliminated by bile and undergoes enterohepatic circulation, but it is also eliminated in a

smaller amount by urine, sweat, saliva, tears, and faeces [31,32]

Elimination of Drugs in Children and the Elderly

In children, renal function is diminished, glomerular filtration rate and renal blood flow are lower in the newborn and reach adult values between 6 months and one year of life [8,33]. For this reason, the renal elimination capacity of medications is related to glomerular filtration capacity, and tubular secretion, which is why this aspect must be considered in the dosing of neonates and especially in premature infants [10,34]. The renal elimination rate decreases during the elderly, because the number of nephrons and the blood flow that reaches the kidney decreases [12]. In this population it is important to perform dose adjustment when there is kidney damage [35,36].

Elimination of Drugs in Pregnancy

In pregnancy, the renal blood flow and glomerular filtration rate are increased, so that the drugs whose elimination depends on their renal excretion will be clarified much more rapidly with the consequent decrease in their plasma and therapeutic concentrations [37]. On the other hand, during pregnancy, the urinary pH approaches basic values, so there will be a marked excretion of acidic medications such as barbiturates, penicillins, acetylsalicylic acid, sulfonamides, etc [38].

Conclusion

Changes in the pharmacokinetic processes related to childhood, ageing and pregnancy should always be considered in the prescription of medications, since they influence the responses to drugs since they determine the time of onset, intensity, and duration of pharmacological effects. The participation of a multidisciplinary team in the area of health is essential to guarantee in these patients an appropriate prescription, identify and avoid the development of pharmacological interactions and ensure adherence or compliance with pharmacological treatment.

Acknowledgement

The authors would like to acknowledge the University of Guanajuato for the grant of this publication.

Conflict of Interest

The authors declare no conflict of interest.

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