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Pharmacokinetics of drugs in pregnancy

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Abstract

Pregnancy is a complex state where changes in maternal physiology have evolved to favor the development and growth of the placenta and the fetus. These adaptations may affect preexisting disease or result in pregnancy-specific disorders. Similarly, variations in physiology may alter the pharmacokinetics or pharmacodynamics that determines drug dosing and effect. It follows that detailed pharmacologic information is required to adjust therapeutic treatment strategies during pregnancy. Understanding both pregnancy physiology and the gestation-specific pharmacology of different agents is necessary to achieve effective treatment and limit maternal and fetal risk. Unfortunately, most drug studies have excluded pregnant women based on often-mistaken concerns regarding fetal risk. Furthermore, over two-thirds of women receive prescription drugs while pregnant, with treatment and dosing strategies based on data from healthy male volunteers and non-pregnant women, and with little adjustment for the complex physiology of pregnancy and its unique disease states. This review will describe basic concepts in pharmacokinetics and their clinical relevance and highlight the variations in pregnancy that may impact the pharmacokinetic properties of medications.

Keywords

Pregnancy; Pharmacology; Pharmacokinetics; Drug transport

Introduction

Various medications are used during pregnancy despite a lack of data in this unique setting.[1,2] Treatment and dosing strategies are based on standard adult doses despite the fact that dosing, safety, and efficacy were determined in healthy, and mostly male, individuals.[3] In some instances, treatment may be withheld from pregnant women due to concerns about maternal or fetal safety. Recent studies in clinical therapeutics in pregnancy suggest a myriad of changes that affect the pharmacologic properties of drugs. A fundamental concept in pharmacology is that a drug must reach the target tissues at sufficient concentration to

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exert its therapeutic effects without causing significant adverse events. Pharmacokinetics (PK) describes the time course of drug concentration in the body. It involves the evaluation of drug absorption, distribution, metabolism, elimination, and transport (Fig.). Various computational models are commonly used to estimate drug PK parameters, but they are beyond the scope of this article. Still, understanding drug-specific PK properties and gestation-specific variations allows for improved treatment and dosing strategies, which can improve treatment efficacy and limit maternal and fetal risks. As such, this review will focus more on the clinical relevance and application of PK parameters and less on the mathematical methods for parameter estimation.

Drug absorption

Drug absorption is the movement of drug from the site of administration into the systemic circulation. Drug absorption is commonly characterized as bioavailability, the fraction or percentage of active drug medication that reaches the systemic circulation intact by any route.[4] Drugs that are administered intravascularly are 100% bioavailable since they are delivered directly into the bloodstream. However, most drugs are administered extravascularly and are expected to act systemically. For this reason, absorption and bioavailability are a prerequisite for pharmacologic action of a drug. Delays or drug loss during absorption may contribute to variation in drug response and side effects and may lead to treatment failure. Intramuscular and subcutaneous administration may lead to a delay in time to reach maximal concentration but has less effect on bioavailability. Increased local blood flow and vasodilation are thought to facilitate drug absorption following intramuscular or subcutaneous drug delivery, although specific drug data are lacking. The greatest variability in drug absorption is seen when a medication is administered orally. For orally administered medications, the bioavailability is affected by the amount absorbed across the intestinal epithelium, as well as first-pass metabolism as the drug crosses the intestine and the liver on its way to the systemic circulation. Stomach pH, food, gut transit time, gut metabolism, uptake, and efflux transport processes may impact oral drug bioavailability.

Nausea and vomiting in early pregnancy may decrease the amount of drug available for absorption following oral administration. Therefore, oral medications should be administered when nausea is minimal. Gastric acid production is also decreased during pregnancy, whereas mucus secretion is increased, leading to an increase in gastric pH.[5,6] These changes can increase ionization of weak acids (e.g., aspirin) and reduce their absorption, and weak bases (e.g., caffeine) will diffuse more readily since they will be primarily unionized. In addition, the slower intestinal motility and decreased gastric acid secretion in pregnancy could alter drug absorption and oral bioavailability. However, no confirmatory evidence validates these assumptions. In fact, studies on β-lactam antibiotics used for asymptomatic bacteruria found no difference in the bioavailability of the drugs (given orally and intravenously) between late pregnancy and postpartum.[7,8] Meanwhile, increased cardiac output and intestinal blood flow may allow for increased drug absorption overall. Taken together, these data suggest that gastrointestinal changes during pregnancy have an overall minimal effect on the bioavailability and therapeutic effect of most oral drugs, especially with repeated dosing. Little information is available on changes in drug absorption for other routes of administration during pregnancy.

Drug distribution

Distribution describes the reversible transfer of a drug between different locations following its entry into the systemic circulation. The volume of distribution (Vd) is used to indicate how extensively a systemic dose of medication is ultimately dispersed throughout the body. It is a theoretical volume that an administered drug would occupy if it were uniformly distributed at a concentration observed in plasma. The Vd is important to determine the loading dose of a drug needed to achieve a certain therapeutic concentration. Drugs that predominantly remain within the vascular system will have a Vd estimate close to plasma volume, whereas drugs that are not bound to any proteins in the body will have a Vd estimate close to total body water. Drugs that are highly bound to tissues, with a small proportion remaining in the intravascular space, will have a very high Vd. By comparison, drugs that are highly bound to plasma proteins and/or have a large molecular weight will tend to concentrate intravascularly and will have a small Vd. A drug's volume of distribution is useful in estimating the dose required to achieve a given plasma concentration. Drug distribution is influenced by various factors including tissue perfusion, tissue binding, lipid solubility, and plasma protein binding. Variations in Vd mainly affect the plasma concentration of the drug, which can directly impact a drug's therapeutic and adverse effects.

Cardiovascular changes during pregnancy include an increase in cardiac output starting in early pregnancy, plateauing by 16 weeks of gestation ~7 L/min and remaining elevated until delivery.[9] A parallel increase is also noted for stroke volume starting at 20 weeks of gestation and a gradual increase occurs with maternal heart rate reaching 90 beats per min at rest in the third trimester.[10] Pregnancy is also marked by ~42% increase in plasma volume, reaching over 3.5 L at 38 weeks of gestation, with parallel increases in total body water and in all body fluid compartments.[9] Expanded extracellular volume and total body water will increase volume of distribution for hydrophilic drugs, leading to lower plasma concentrations. In addition, maternal body fat expands by approximately 4 kg, increasing the volume of distribution for lipophilic drugs. However, little information is available to assess contribution of adipose tissue to altered drug disposition during pregnancy.

On the other hand, plasma protein binding of drugs decreases during pregnancy due to reduced concentrations of both albumin and alpha 1-acid glycoprotein.[11–13] In normal pregnancy, albumin concentrations decrease on average by 1% at 8 weeks, 10% at 20 weeks, and 13% at 32 weeks.[14] Certain pathophysiologic conditions can lead to even lower albumin levels. Decreased protein binding leads to higher concentrations of free drug (for drugs that have limited clearance) and favors more distribution to tissues. These changes can be clinically significant for certain drugs. For example, for phenytoin and tacrolimus, efficacy and toxicity are expected to be related to unbound drug concentration in plasma. During pregnancy, both the drugs exhibit an increased unbound fraction due to lower albumin concentrations and increased clearance.[15,16] A dose titration strategy based on maintaining total blood/plasma concentration in the therapeutic range can lead to increased free drug concentrations and increase the likelihood of drug-related toxicity. In pregnancy, a more thorough approach would be to monitor free drug concentrations and adjust drug dosing to maintain the unbound concentration within its therapeutic range.

Gestation-specific changes also include an increase in uterine perfusion and the addition of the feto-placental compartment. Blood flow to the uterus increases 10-fold from 50 to 500 mL/min at term. In general, small-molecular-weight and lipophilic drugs readily cross the placenta. The fetus and the amniotic fluid can act as additional compartments, leading to increased drug accumulation and an apparent increase in volume of distribution of certain drugs.

Drug metabolism

Drug metabolism involves chemical modification of a drug through specialized enzymatic systems. For some medications, administered as inactive pro-drugs, metabolism is necessary to convert the drug into an active compound. For most drugs, metabolism leads to loss of drug activity. The liver accounts for the metabolism of a vast majority of drugs. Other organs including the intestine and the placenta can also contribute to the clearance of certain drugs. Metabolic enzyme activity is highly variable, affected by ethnicity, gender, age, and enzyme polymorphisms. Certain enzymes are involved in the metabolism of numerous drugs and create a potential for co-administered medications to impact drug clearance.

Clearance is a major pharmacokinetic parameter of a drug; it determines drug exposure as measured by the area under the plasma concentration vs time curve[17] and a body's overall ability to eliminate a drug. Systemic clearance of a drug is the sum of all the clearances by various organs. Clearance is the volume of blood/plasma that is completely cleared off the drug in a unit of time. The clearance of a drug in the liver is determined by hepatic blood flow and the extraction ratio of the drug in the liver. The extraction ratio (ER) refers to the proportion of a drug taken up from the hepatic arterial circulation into hepatocytes, making it available for subsequent metabolism. For high ER drugs (e.g., morphine and propranolol), overall hepatic elimination is limited only by hepatic perfusion (blood flow). In contrast, hepatic clearance of low ER drugs (e.g., diazepam, fluoxetine, or caffeine) is limited by intrinsic metabolic capacity of hepatic cells and the unbound fraction of the drug in plasma, and it would be changed little by changes in hepatic perfusion.

Hepatic drug metabolism includes phase I (oxidation, reduction, or hydrolysis) reactions that introduce more polar or reactive moieties into drug molecules, followed in many cases by phase II (conjugation) reactions to glucuronic acid, sulfate, or other moieties that favor excretion into urine or bile. Oxidative phase I reactions are predominantly carried out by the cytochrome P450 (CYP) family of enzymes that differ in their substrate specificity. The activities of CYP3A4 (50–100%), CYP2A6 (54%), CYP2D6 (50%), and CYP2C9 (20%) are all increased during pregnancy (Table 1).[18–22] Changes in CYP3A4 activity lead to increased metabolism of drugs such as glyburide, nifedipine, and indinavir. By contrast, some CYP isoforms demonstrate decreased activity during pregnancy. CYP1A2 and CYP2C19 appear to undergo a gradual decrease in activity with advancing gestation,[17,23,24] though with uncertain effects on drug therapy. The activity of phase II enzymes, including uridine 5'-diphosphate glucuronosyltransferases (UGTs), is also altered during pregnancy, with a 200% increase in UGT1A4 activity during the first and second trimesters and a 300% increase during the third trimester.[25] This change leads to lower concentrations of UGT1A4 substrates such as lamotrigine, leading directly to poorer seizure control with advancing

gestation in the absence of appropriate dose titration.[26] The effects of pregnancy on enzyme activity can also vary with maternal genotype. A recent study on the PK of nifedipine, used for tocolysis, noted differences in drug clearance due to genetic variability in a specific allele of the CYP3A5 coding gene.[27] Similarly, methadone metabolism varied with the specific genotype of CYP2B6.[28] Enzyme activity varies with ethnicity, gender, age, and certain disease states that are unrelated to pregnancy. Commonly, enzymes have numerous substrates, and different drugs may undergo metabolism by several enzymes. This overlap may lead to changes in metabolic activity when certain medications are co-administered. In primary cultures of human hepatocytes, 17-hydroxyprogesterone caproate (17-OHPC) (a drug used to prevent preterm delivery) modestly increased the activity of CYP2C19. It follows that dosage of CYP2C19 substrates, for example, tricyclic antidepressants, proton pump inhibitors, and propranolol, may have to be increased in patients on 17-OHPC.[29]

Changes in drug metabolism can have implications for drug dosages in pregnancy. For drugs with a narrow therapeutic window, an increased clearance during pregnancy can lead to sub-therapeutic concentrations and worsening disease control. Conversely, to avoid increased toxicity, drug doses may need to be adjusted in the postpartum period, when pregnancy-related metabolic enzyme activity changes resolve.

Drug elimination

Renal drug excretion depends on GFR, tubular secretion, and reabsorption. GFR is 50% higher by the first trimester and continues to increase until the last week of pregnancy.[30] If a drug is solely excreted by glomerular filtration, its renal clearance is expected to parallel changes in GFR during pregnancy. For example, cefazolin and clindamycin exhibit increased renal elimination during pregnancy.[7,31] Despite a uniform increase in GFR during pregnancy, differences in renal tubular transport (secretion or reabsorption) can result in differing effects on renally cleared drugs.[32,33] Specifically, the clearance of lithium is doubled during the third trimester compared to preconception.[34] By comparison, the clearance of digoxin, which is 80% renally-cleared, is merely 20–30% higher during the third trimester compared to postpartum.[35,36] Furthermore, the clearance of atenolol is only 12% higher across pregnancy.[18,37] Such variations in drug clearances limit generalization about the effect of pregnancy on renally eliminated drugs and point to important but less-known gestational changes in renal tubular transporters.

Drug transport

Drug transporters are widely expressed in several organs (Table 2). For example, intestinal luminal transporters can affect drug absorption from the gastrointestinal tract—those in hepatic sinusoids determine drug uptake into hepatocytes where they may undergo biotransformation, transporters in biliary canaliculi govern secretion into bile, and transporters on both the apical and the basolateral surfaces of renal epithelial cells govern tubular secretion and reabsorption. Together, their distribution, substrate specificity, and activities are important determinants governing drug absorption, excretion, and, in many cases, the extent of drug entry into target organs. Knowledge of drug transporter expression and function is necessary for a complete understanding of drug absorption, distribution,

elimination, and effect. In addition, fetal development is dependent upon the transport of nutrients by the placenta toward the fetal side and that of products of fetal metabolism for elimination by the mother.[38] The placenta produces and secretes hormones that affect the maternal physiology and endocrine state.[35,39] The transport role is mediated by the syncytiotrophoblasts, the functional cell of the placenta. These cells have a polarized plasma membrane consisting of a brush border at the maternal side and a border membrane on the fetal side. Compounds transported between the mother and the fetus are carried by the maternal circulation within the uterine vasculature directly through the intervillous spaces and then the syncytiotrophoblasts. Thereafter, blood flows from the fetal side of the placental villi through the fetal capillary endothelium to reach the fetal circulation. Most xenobiotics cross the placental barrier by simple diffusion. Protein binding, degree of ionization, lipid solubility, and molecular weight can affect placental transport. In fact, small, lipid-soluble, ionized, and poorly protein-bound molecules cross the placenta easily. For other substrates, the placenta facilitates maternal to fetal transport through the polarized expression of various transporters.[40] Transporters enable transport of specific endogenous substrates (such as cytokines, nucleoside analogs, and steroid hormones); however, exogenous compounds with similar structures may also interact with them (Table 3).

A number of placental drug transporters have been identified, including the family of multi-drug resistance protein (MRPs). Phosphoglycoprotein (P-gp) and breast cancer resistance protein (BCRP) are the most studied so far and will be discussed in greater detail. P-gp is expressed on the apical microvillous surface, whereas BCRP is mostly identified on the basolateral membrane and fetal blood vessels.[41–44] Their polarized distribution may reflect a difference in their role. Transporters on the apical membrane are thought to allow selective substrates to be transmitted to the fetus and hence may protect the fetus by extruding harmful xenobiotics. Both the transporters have a wide array of substrates. Those of P-gp include endogenous compounds such as cortisol, aldosterone, and bilirubin as well as various drugs such as antibiotics, antiretrovirals, and steroids.[45,46] Substrates of BCRP include antibiotics, antiretrovirals, calcium channel blockers, estrogen, and porphyrins.[45,47,48] These transporters have a number of overlapping substrates for which they have differing affinities.[49,50]

A limited number of studies have examined the gestational changes of placental drug transporters and decrease near term.[51,52] Investigations of BCRP changes have yielded inconsistent results with reported increase, decrease, or unchanged expression with advancing gestation.[53,54] These differences may be related to the variation in tissues used in each study. Furthermore, evidence on the regulation of placental drug transporters expression is scarce. Both estrogen and progesterone appear to increase expression of P-gp and BCRP in trophoblast cell lines.[46,55,56] In vivo studies describe an increase in maternal and fetal glucocorticoids with advancing gestation in parallel with a decrease in P-gp. Surprisingly, studies investigating a possible direct link demonstrate that prolonged exposure to dexamethasone increased P-gp and decreased BCRP expression in mice.[57,58] By comparison, treatment of trophoblast cells with inflammatory cytokines or simulated infection in pregnant rats resulted in decreased P-gp and BCRP expression.[59,60] Also, P-gp and BCRP expression is lower in preterm placentas and placentas from women with

preeclampsia compared to term placentas from uncomplicated pregnancies, suggesting a role for hypoxia in mediating these transporters.[57]

Selective serotonin reuptake inhibitors (SSRIs) including fluoxetine, sertraline, and paroxetine inhibit P-gp in vitro.[61] Along with a decrease in P-gp expression late in gestation, an inhibition of its function may result in fetal and maternal consequences. The most recent guidelines for treatment of depression during pregnancy recommend using the lowest effective dose of SSRIs.[62] Maternal SSRI use in the first and the third trimesters has been linked to congenital anomalies and neonatal complications, respectively.[63] A clear link between inhibition of P-gp, neonatal pulmonary hypertension or tachypnea, and prenatal exposure to SSRIs remains to be determined. Anti-seizure drugs appear to exhibit an inhibitory effect on carnitine placental transport.[64,65] Carnitine deficiency has been linked to apnea, cardiac arrest, and cardiac hypertrophy.[66] Carnitine is mainly actively transported through two transporters.[66–68] One of these transporters—carnitine/organic cation transporter (OCTN2)—is located on the apical membrane of the syncytiotrophoblasts and is inhibited by some anti-seizure drugs such as valproic acid and phenytoin.[69,70]

Pathophysiologic states may also alter transporter expression. P-gp and BCRP expression was lower in placentas from women with preeclampsia compared to term placentas from uncomplicated pregnancies.[57] It is unknown whether transporter expression and activity are altered further in other conditions affecting pregnancy.

Conclusion

Pregnancy involves various changes in maternal physiology and disease. It logically follows that drug disposition and effects are altered in pregnancy. Historically, concerns about fetal safety have limited pharmacotherapy during pregnancy and have hampered drug studies during pregnancy. Although these concerns have validity, pregnant women require medications for medical disorders, and pregnancy does not eliminate the need for therapy. Recent studies on pharmacology in pregnancy highlight the complexity of drug distribution and response in light of the dynamic process of gestation. To extrapolate drug dosage and expected responses from non-pregnant populations is inappropriate and may cause harm for pregnant women. Rather, a structured approach to study the pharmacokinetic and pharmacodynamic properties of drugs used in pregnancy should be followed. In the absence of data specific to a drug, close monitoring of the patient is the most logical step to optimize drug therapy in pregnant subjects.

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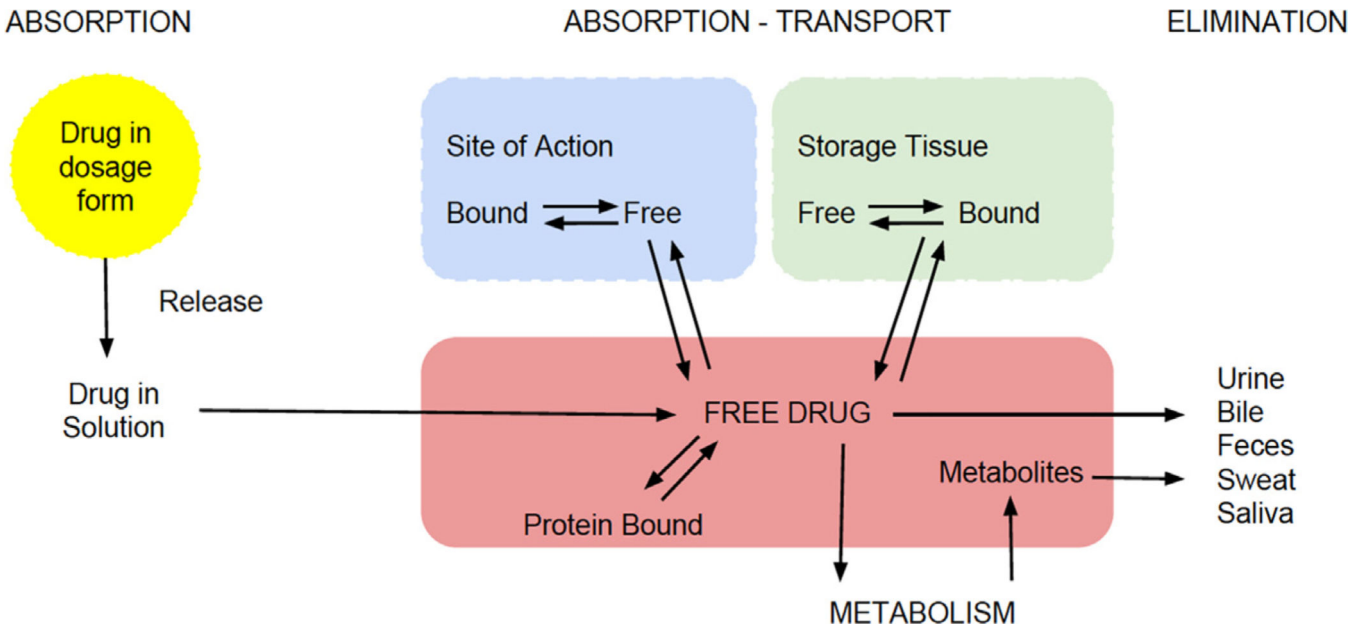

Fig.
The pharmacokinetic process.

Table 1

Pregnancy-induced physiologic changes during near term.

System (reference)	Parameter	Non-pregnant	Pregnant
Cardiovascular[64,71,72]	Cardiac output [L/min]	4.0	6.0
	Heart rate [beats per min]	70	90
	Stroke volume [mL]	65	85
	Plasma volume [L]	2.6	3.5
Respiratory[73,74]	Total lung capacity [mL]	4225	4080
	Residual volume [mL]	965	770
	Tidal volume [mL]	485	680
Liver[75]	Portal vein blood flow [L/min]	1.25	1.92
	Hepatic artery blood flow [L/min]	0.57	1.06[a]
Renal[76]	Glomerular filtration rate [mL/min]	97	144
	Serum creatinine [mg/dL]	0.7	0.5

[a]Not statistically significant.

Table 2

Pregnancy-induced enzyme-specific changes.

Enzyme (references)	Pregnancy-induced change	Potential substrates in obstetrics
CYP3A4[19,20,77,78]	Increased	Glyburide, nifedipine, and indinavir
CYP2D6[77,79]	Increased	Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, and citalopram
CYP2C9[18,80]	Increased	Glyburide, NSAIDs, phenytoin, and fluoxetine
CYP2C19[18,80]	Decreased	Glyburide, citalopram, diazepam, omeprazole, pantoprazole, and propranolol
CYP1A2[17,23,77,81]	Decreased	Theophylline, clozapine, olanzapine, ondansetron, and cyclobenzaprine
UGT1A4[82–84]	Increased	Lamotrigine
UGT1A1/9[25]	Increased	Acetaminophen
NAT2[17,24,85]	Decreased	Caffeine

Table 3

Major drug transporters, their location, and common substrates.

Transporter	Tissues/cells	Selected substrates	Selected inhibitors
P-gp	Intestinal enterocytes, kidney proximal tubule, hepatocytes, brain endothelial cells, and placenta	Glyburide, digoxin, loperamide, ritonavir, and St. John's Wort	Verapamil and cyclosporine
BCRP	Intestinal enterocytes, hepatocytes, kidney proximal tubule, brain endothelial cells, placenta, and mammary glands	Glyburide, statins, porphyrins, and methotrexate	Oestrone and 17 β-estradiol
MRP2	Hepatocytes, kidney proximal tubule, and enterocytes (luminal)	Glutathione and glucuronide conjugates and methotrexate	Cyclosporine and efavirenz
MRP3	Hepatocytes, kidney proximal tubule, and enterocytes (basolateral)	Glyburide, estradiol 17 β-glucuronide, methotrexate, and glucuronate conjugates	Delavirdine and efavirenz
MRP4	Kidney proximal tubule, choroid plexus, hepatocytes, and platelets	Furosemide, adefovir, tenofovir, and methotrexate	Celecoxib and diclofenac
MDR3	Hepatocytes	Digoxin	Verapamil and cyclosporine
OAT1	Kidney proximal tubule and placenta	Acyclovir, zidovudine, lamivudine, adefovir, and cidofovir	Probenecid and novobiocin
OAT3	Kidney proximal tubule, choroid plexus, and blood–brain barrier	NSAIDs, cefaclor, ceftizoxime, and furosemide	Probenecid and novobiocin
OCT1	Hepatocytes and endothelial cells	Metformin, N-methylpyridinium, pindolol, procainamide, ranitidine, and amantadine	Quinine, quinidine, and disopyramide
OCT2	Kidney proximal tubules and peripheral neurons	Metformin and N-methylpyridinium	Cimetidine, cetirizine, and quinidine
OATP2B1	Hepatocytes and endothelial cells	Glyburide, statins, and fexofenadine	Rifampicin and cyclosporine
MATE1	Kidney proximal tubule, liver, and skeletal muscle	Metformin and N-methylpyridinium	Cimetidine, quinidine, and procainamide
MATE2-K	Kidney proximal tubule	Metformin and N-methylpyridinium	Cimetidine, quinidine, and pramipexole
PEPT1	Intestinal enterocytes and kidney proximal tubule	Cephalexin, cefadroxil, valacyclovir, enalapril, and captopril	Glycyl-proline
PEPT2	Kidney proximal tubule, choroid plexus, and lung	Cephalexin, valacyclovir, enalapril, and captopril	Zofenopril and fosinopril