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DIPLOMOVÁ PRÁCE

Principy transportu léčiv přes placentu: nové aspekty pro farmakoterapii v těhotenství

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DIPLOMA THESIS

Principles of drug transport across placenta: new aspects for pharmacotherapy in pregnancy

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Poděkování

Na tomto místě bych ráda poděkovala PharmDr. Martině Čečkové-Novotné, Ph.D. za její pomoc a trpělivost při vypracování této diplomové práce.

Fig. 1. Placenta. Adapted from internet source www.pattiramos.com/Placenta.html

Prohlášení

„Prohlašuji, že tato práce je mým původním autorským dílem, které jsem vypracovala samostatně. Veškerá literatura a další zdroje, z nichž jsem při zpracování čerpala, jsou uvedeny v seznamu použité literatury a v práci řádně citovány.“

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1. LIST OF ABBREVIATIONS

ABCG2/ BCRP	breast cancer resistance protein
AF	atrial flutter
ATP	adenosintriphosphate
AED	antiepileptic drugs
ABC	ATP-binding cassette
Da	Dalton
ECG	electrocardiography
GDM	gestational diabetes mellitus
HIV	humanimunodeficiecyvirus
MDR	multidrug resistance
M-mode	motion-mode
MRP	multidrug resistance-associated protein
MXR	mitoxantrone resistance protein
NBF	nucleotide-binding fold
P-gp	P-glycoprotein
PI	protease inhibitors
OCT3	extraneuronal monoamine transporter
hENT	human equilibrative nucleoside transporters
OCTN2	carnitine transporter
SVT	supraventricular tachycerdia

2. INTRODUCTION

For more than half a century, scientists and physicians have recognized pregnant women as a unique population from the point of view of drug therapy.

Until the thalidomide-induced birth defects occurred in the early 1960s, physicians generally believed that the uterus provided a protective environment for the fetus.

Subsequently, it has become accepted that any chemical substance, including any therapeutic agent, administered to a mother is able to permeate across the placental barrier and fetus(Yaffe, 1998).

When managing a pregnant patient with medication, the treatment of mother and fetus, two individual patients, should be considered independently, and the decision must be based on the risk/benefit assessment of both (Gedeon and Koren, 2005). It must be evaluated in association with other treatment modalities like direct injection of drug to the fetal compartment or delivery, which is an option when the fetus is mature enough.

Different clinical situations can occur with the demand for the treatment focused on mother or fetus, or the therapy of the same disease of both of them.

The first group is represented by either chronic illnesses (diabetes mellitus, hypertension, asthma, epilepsy etc.) or newly arisen problems like gastrointestinal disturbances and infections of the mother. Although there is a continuing need to receive chronic medications during pregnancy, drug therapy is still often without a specific rationale (Yaffe, 1998).

Modern pediatrics defined situations like fetal tachycardia, pulmonary immaturity which confer great morbidity and mortality numbers. These numbers support the preference of transplacental treatment over an expectance approach when clinicians wait to treat the disease state after delivery.

The third group constitutes a drug administration to mother for the same purpose for both, mother and child. This is the case of HIV infection when the pharmacotherapy aims to manage the active infection of mother and reduce the probability of vertical transmission to the child during labour.

For optimization of pharmacotherapy during pregnancy it is necessary to understand the mechanisms involved in the transported of drugs from mother to fetus across the placenta.

3. AIMS OF THE STUDY

The aim of this work was to summarize recent information on the principles of transplacental passage of drugs and to review current approaches in the pharmacotherapeutic treatment of selected deseases in pregnancy in context with the transplacental drug transfer. The review is based on scientific information gained from the internet databases, such as Science Direct, Medline etc.

4. GENERAL ASPECTS OF DRUG TRANSFER FROM MOTHER TO FETUS

4.1. Structure of placenta

The primary function of all placentas is to act as an interface between the mother and fetus that allows appropriate metabolic exchanges of gases and selective transport of different molecules including nutrients and waste products. This function is accomplished by bringing maternal and fetal blood into close apposition while maintaining both separation of the two circulatory systems and the integrity of maternal and fetal organisms.

Human placenta is a discoid organ formed by both fetal and maternal tissues. Maternal part gives rise to septa that mark out functional units – cotyledons. Each cotyledon comprises an arbour of villi, branching from large stem villi containing the major fetal vessels to free villi that extend into the intervillous space (containing maternal blood) (Kaufmann et al., 1988).

The trophoblast and mesoderm overlying the intervillous space is called the chorionic plate. Those villi that spread along the maternal endometrium are called anchoring villi, and in the combination with the adjacent compact decidualized endometrium they form the basal plate. Maternal blood enters and leaves the intervillous space via the basal plate, whereas fetal vessels enter and leave the villi via the chorionic plate of the placenta.

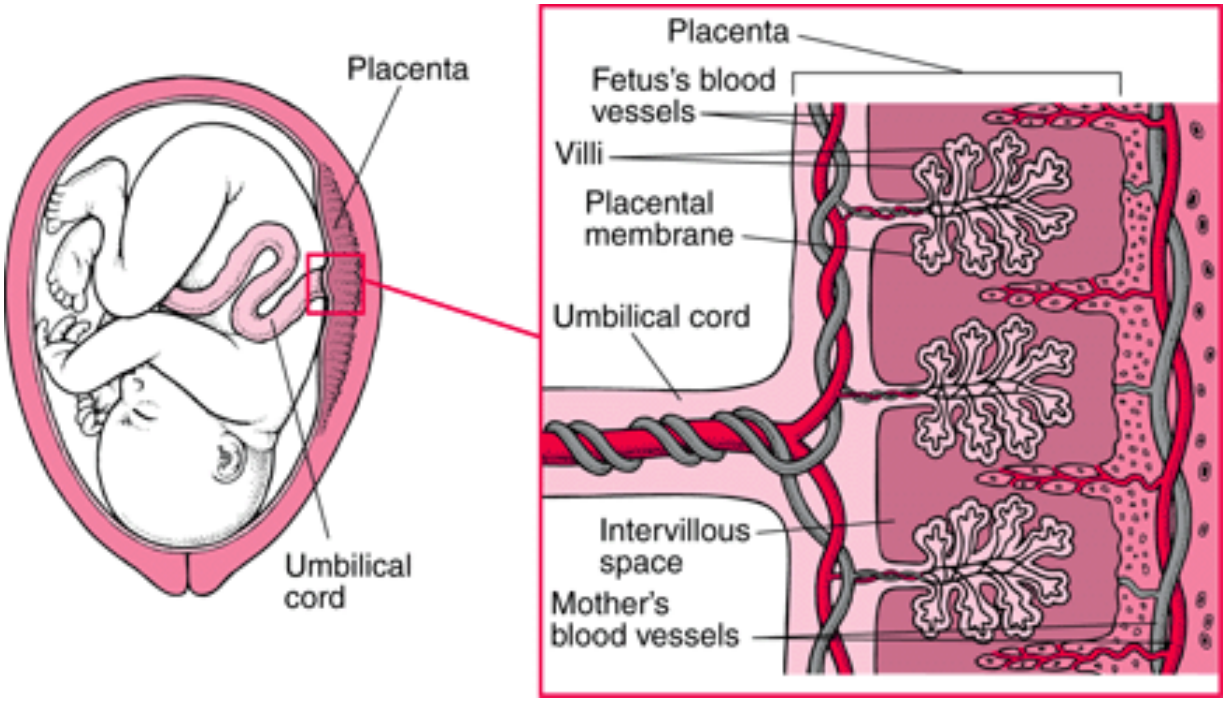

Fig. 2. A schematic representation of the human placenta. Modified from internet source: www.merck.com

Despite variation in the arrangement of layers, trophoblast always forms the external epithelium of the fetal component of the placenta. Trophoblast cells are found as large multinucleate cells layer, called syncytial trophoblast, which emerges by recruiting cytotrophoblast cells (Ringler and Strauss, 1990). The villi have a nearly complete cytotrophoblast layer underlying the surface layer of syncytial trophoblast during most of the first trimester, but as the gestation proceeds the cytotrophoblast cells become stelete and the layer discontinuous.

Finally syncytial trophoblast develops thick and thin regions, with many of the thin regions closely apposed to fetal vessels, where the basement membrane is shared with the endothelial cells of the fetal capillary. Although the endothelium may be quite thin in these fetal vessels, it is continuous and does not contain fenestrations, so the role of the endothelium in the 'barrier' should not be ignored (Firth and Leach, 1996). However, the rate-limiting barrier for permeation across the human placenta is the syncytiotrophoblast layer (Ala-Kokko et al., 1993; Sibley, 1994; Enders and Blankenship, 1999).

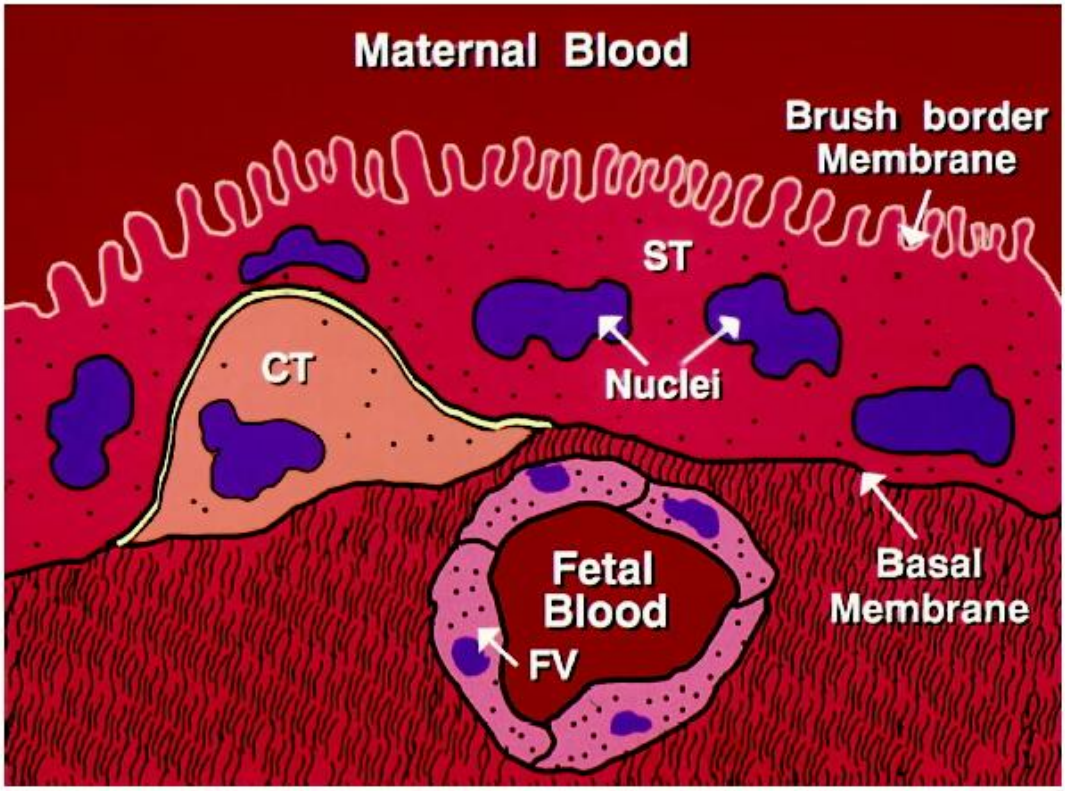

Fig. 3. Schematic representation of the maternal-fetal interface in the placenta.
ST - syncytiotrophoblast; CT - cytotrophoblast; FV - fetal blood vessel. Adapted from Moe, 1995.

Although the syncytial trophoblast appears to be continuous, it is sometimes

argued that the combination of basal bays and surface invaginations or a separate tubular system results in pathways through the syncytium (Kertschanska et al., 1997).

Thus the layer of syncytiotrophoblast is histologically and functionally polarized with apical surface of maternal facing brush border membrane and fetal-facing basal membrane.

Nomenclature of placental morphology is based on the contributions by different extraembryonic membranes and on the tissue layers intervening between maternal and fetal blood, separating them into three groups: hemochorial, endoteliochorial, epiteliochorial. Human placenta belongs to the group of hemochorial placentas, in which maternal blood directly bathes the trophoblast. These placentas can be referred to as being hemomono- (human), di- (rabbit), or trichorial (mouse, rat) depending on the number of layers of trophoblast cells present in the thinnest portions of the definitive placenta (Enders, 1965). For this reason, the information gained about the structure and function of placenta should be extrapolated from one species to another with caution (Finn, 1994).

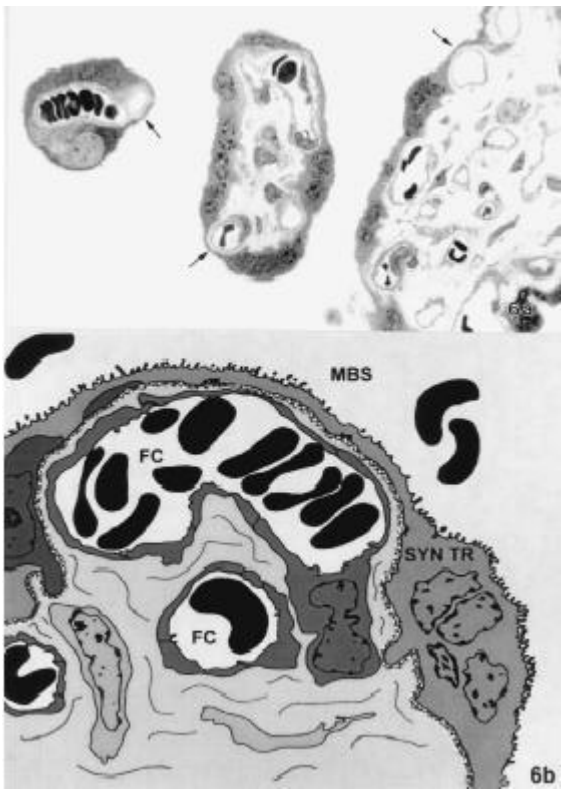

Fig. 4. Light micrograph of the villous hemomonochorial chorioallantoic placenta of the human. Fetal capillary (FC), maternal blood space (MBS). Adapted from Enders and Blankenship, 1999.

4.2. Models for investigation of placental barrier

A variety of in vitro systems currently exists to evaluate the transport and metabolism processes of many of the significant endothelial and epithelial tissue barriers to drug delivery. The emergence of in vitro models for the human placenta within past decades opened the door for investigations of drug transport and metabolism mechanisms and apply that knowledge to developing drugs that more selectively target either the mother or the fetus in drug therapy (Dancis and Liebes, 1995).

Human trophoblast culture systems, both primary cultures and cell lines, also exist, including those that form monolayers, and have been used to study uptake and transport mechanisms at the cellular and molecular levels (Ringler and Strauss, 1990; Yui et al., 1994; Bloxam et al., 1997; Liu et al., 1997; Sastry, 1999).

The obvious importance of the syncytial trophoblast in pregnancy and its ready availability from term placentas has resulted in extensive study of this tissue in relationship to maternal–fetal transfer (Sibley and Boyd, 1988; Smith et al., 1992). Modern cell biological methods have even permitted dissection of this layer by separate isolation of apical (microvillus) and basal cell membranes of syncytial trophoblast, as used in studies of glucose transporter protein (Jansson et al., 1993) and chloride transport (Powell et al., 1998).

The single cotyledon model is used extensively to characterize the transport and the metabolism of numerous pharmacologic agents and nutrients. It is well established as a safe in vitro surrogate for human placental transfer. The major attribute that makes this a desirable model is that it demonstrates placental transport independent of fetal metabolism. Another advantage of this model is the ability to validate each experiment individually with the addition of antipyrine (Shenker et al., 1989; Shenker et al., 1987; Dancis et al., 1988). The ex vivo technique of dual perfusion of placental lobule (DPPL) has proved to be a powerful tool in the prediction of the extent of term placental transfer of drugs in vivo (Schneider et al., 1985). However, these data represent 1 time point in placental transfer of the drug, namely at delivery, and consequently do not reflect the dynamic changes in its concentration.

One of the traditional in vitro model is BeWo cell line, originally derived from a human choriocarcinoma (Patillo and Gey, 1968), quite similar in morphological and biochemical features to normal trofoblast cells.

In vivo techniques to study placental transfer of drugs involve animal studies for

measurement of maternal-fetal and fetal maternal clearance, thus studies with chronically catheterized macaque (Tuntland et al., 1998), baboon (Garland et al., 1998) and sheep (Kumar et al., 1999) have been developped to determine ther mechanism of placental drug transfer.

Recently an imaging methodology providing a means of studying material transfers in the placenta at a much higher level of topographic and functional precision than previously possible was described. The use of an affinity-based tracer with a fluorescent tag, requiring a confocal scanning laser microscope, offers high detection sensitivity with high spatial and temporal resolution of processes within five compartments (maternal and fetal blood, syncytiotrophoblast, fetal endothelium, extracellular matrix). The methodology should set a new standard for studies of drug transfer to the fetus (Sölder et al., 2009).

4.3. Drug transport across placenta

Although the placenta was viewed as a protective barrier, the transmission to the fetus, of drugs administered to the mother is now widely demonstrated (Pacifici and Nottoli, 1995). With the exception of drugs with large molecular weights, such as heparin or insulin, most drugs appear to cross the placenta and are associated with varying degrees of fetal exposure.

The predominant mechanism by which substances cross the human placental barrier is simple passive diffusion either transcellularly or paracellularly (Robinson et al., 1988; Ala-Kokko et al., 1993; Sibley, 1994) and depends upon the transmembrane concentration gradient. An inverse relationship generally exists between placental transport rates and molecular weight of substances that cross by passive diffusion (Schneider, 1991). The physicochemical properties of drugs play a significant role in determining transtrophoblast permeation. Molecules that are relatively lipophilic, with low protein binding, short elimination half-life, a low degree of ionization (pKa), and have molecular weights of less than 600 Da, permeate readily across the syncytiotrophoblast layer (Ala-Kokko et al., 1993).

Several additional factors influence the overall placental permeation. These factors include the developmental changes in the placental barrier, such as pH and protein gradients, thickness and surface area of the barrier, volume of distribution, rate of metabolism and excretion by the placenta and placental blood flow, and specific placental transport systems (Elliott et al., 1991; Koren, 2001; Hardmons et al., 2006). The placenta expresses a number of carrier mechanisms that are well-characterized in other tissues and are yet of unknown physiological significance in placental function (Ganapathy et al., 1999).

Other mechanisms including active transport and facilitated diffusion also operate in the placenta (Audus, 1999). Although most transporters at the placenta probably exist for the purpose of aiding transport of physiologically important substrates to the fetus, some transporters appear to prevent transport of chemicals (including toxins, xenobiotics) to the fetus (Unadkat et al., 2004).

4.3.1. Pharmacokinetic aspects

Absorption phase can be altered by maternal changes in gastric secretion and motility, disturbing the degree of ionization and solubility. Once absorbed, maternal drug metabolism may be influenced due to elevation of endogenous hormones such as progesterone, which can stimulate the hepatic microsomal oxidase system and result in increased transformation of drugs such as phenytoin (Langer et al., 2000; Lobstein et al., 2001). Conversely, theophyline and caffeine experience reduced hepatic elimination as a consequence of elevated estradiol.

Total body water expansion, including plasma volume (Bournissen et al., 2003) and generally increase in extracellular fluid space (Langer et al., 2000; Lobstein et al., 2001) contributes to an increase in volume of distribution and may lower the concentration of drugs and increase their elimination half-life.

Protein binding alterations may also occur as a result of changes in both the concentration of specific proteins and changes in protein binding affinity. Decrease in maternal serum albumin may lead to corresponding increase in the free fraction of drug (Beck, 1981; Boyd and Hamilton, 1970). Increased levels of free fatty acids and total lipids due to hormonal changes in pregnancy partially saturate the protein binding capacity for drugs. There is a markedly lower concentration of specific binding proteins and altered binding affinity of drugs in the fetus (Holcberg et al., 2003a) and there is a 3 fold lower level of a1-acid glycoprotein in the fetus compared to the mother (Bournissen et al., 2003).

Lipid solubility, the pH of the maternal and fetal fluids, the ionization constant of the drug (pKa) and the molecular weight also influence the passage of the drug across the placenta. In general, uncharged, un-ionized molecules with high lipid solubility and lower molecular weight penetrate the cell membranes more readily than hydrophilic ionized drug molecules (Heikkila et al., 1992).

The pH gradient between the maternal and fetal circulations and the pKa of the drug also influence transfer of weak acids and bases. Since fetal plasma is 0.1 lower than maternal plasma pH, for weak bases the un-ionized free drug crossing the placenta becomes ionized and is trapped in the more acidic fetal circulation (Holcberg et al., 2003a; Langer et al., 2000), resulting in fetal drug concentrations that may eventually exceed maternal plasma concentrations and lead to toxicity. The pH of the amniotic fluid is also lower than that of maternal plasma.

4.3.2. ABC family transporters

The ABC transporters are one of the largest families of active transport molecules (Higgins, 1992; Dean et al., 2001). There are 48 ABC genes in the human genome and they are dispersed mostly on different chromosomes, with a few clusters of 2–5 genes (Dean et al., 2001).

The structure of ABC transporters consists of two sets of hydrophobic segments that span the membrane and are thought to confer all or most of the specificity of the transporter, and a pair of ATP-binding domains or nucleotide-binding folds (NBFs). ABC genes either encode a full transporter encoding all four domains, or a half-transporter with a single TM domain and a single NBF. Half-transporter proteins must dimerize as either homo- or heterodimers to form a complete transporter complex. All the transporters posses to a greater or leader extent extracellular *N*-glycosylation branches. Based on in vitro studies on P-gp (Shinkel et al., 1993) it appears that this *N*-glycosylation is not necessary for the basic transport function of these transporters. However, *N*-glycosylation probably has an important cell-biological role for these proteins, helping in stabilizing membrane insertion and possibly routing to, and stability in the plasma membrane.

The group of efflux transporters in the ABC superfamily have been identified in the placenta, where they are involved in detoxification processes and multidrug resistence, forming an essential part of the barrier (Young et al., 2003; Utoguchi et al., 2000; Atkinson et al., 2003; Audus et al., 2002; Pascolo et al., 2003; Tanabe at al., 2001; St-Pierre et al., 2000; Ushigome et al., 2003).

The generally accepted mechanism of multidrug resistance is that the efflux transporters expel a variety of structurally diverse drugs, drug conjugates and metabolites from cells against considerable concentration gradients in an ATP-dependent manner, usually from the apical membrane surface of polarized epithelial cells (Bodo et al., 2003). These efflux transporters include P-glycoprotein (P-gp), which is encoded by the *MDR1* gene, multidrug resistance-associated proteins (MRP-1through-6 and 10-12), and breast cancer-resistance protein (ABCG2) (Ozben, 2006). Other ABC transporters have been implicated in drug resistance, but these other transporters play highly specialized roles in normal physiology and are less likely to be usurped to play a role in drug resistance.

4.3.2.1. P – glycoprotein

Juliano and Ling in 1976 were the first to note that a particular 170 kD glycoprotein was associated with this resistance (Juliano and Ling, 1976) and over a decade later the gene encoding P-gp, then termed mdr1 (and later called MDR-1), was cloned (Roninson et al., 1986). P-glycoprotein polypeptide consists of two very similar halves, each containing 6 putative transmembrane segments, and an intracellular ATP binding site, with the first extracellular loop being *N*-glycosylated.

P-gp is mainly present in epithelial cells of adrenals, kidneys (brush border cells of proximal tubules), liver (biliary canalicular surface of hepatocytes), colon (apical surface of columnar epithelial cells), small intestine (epithelial cells), brain (capillary endothelial cells), peripheral nerves (capillary endothelial cells), heart, placenta and testes (Fojo et al., 1987; Thiebaut et al., 1987; Saito et al., 1997), where it localizes to the apical membrane (Thiebaut et al., 1987; Higgins, 1992).

In the human placenta there is abundant expression of the MDR1 gene throughout pregnancy (Mylona et al., 1996; Allikmets et al., 1998) with significant levels of P-gp, demonstrated by immunohistochemistry (MacFarland et al., 1994). Studies with human microvillar membranes of term human trophoblasts have indicated an active MDR1 (Nakamura et al., 1997). Although P-gp is found in the placentas of gravid mice and tends to increase during pregnancy (Novotna et al., 2004), Gil et al. (2005) showed a significant decrease of its level in human placenta from the 13-14th to the 38-41st week of gestation, suggesting that the ability of the placenta to protect the fetus from xenobiotics is greater in early pregnancy than at term. The possibility that different cell types within the placenta express P-gp at different stages of gestation really exists (Gil et al., 2005).

It confers a chemoresistance to cells for numerous xenobiotics by actively pumping molecules outside cells, in fact translocating its substrates from the basolateral to the apical side of the epithelium and consequently decreasing their intracellular concentrations (Kartner et al., 1983). This ability to extrude xenobiotics gives this protein some physiological properties of protection and detoxification. This principle has been directly demonstrated using P-gp deficient mutant or knockout mice for at least four different P-gp substrates: an analogue of the pesticide avermectin, the cardiac glycoside digoxin, the HIV protease inhibitor saquinavir, and the anticancer drug paclitaxel (Lankas et al.,1998; Sugawara et al., 1988; Huisman et al., 2001). However,

P-gp is also implicated in the transport and regulation of endogenous molecules such as hormones (Wolf and Horwitz, 1992; Ueda et al., 1992) or phospholipids (Oude Elferink et al., 1996; Pohl et al., 2002).

P-gp is involved in the pharmacokinetics of numerous drugs, participated in the absorption, distribution and elimination phases, on contrary to cytochrome P450 enzymes that are only involved in drug metabolism.

Different types of P-gp interaction exist. First a direct interaction with the binding sites on P-gp blocking transport of substrates (e.g. verapamil, cyclosporin A) in competitive or non-competitive manner, and secondly an inhibition of ATP binding (e.g. vanadate), ATP hydrolysis (e.g. cyclosporin A) or coupling of ATP hydrolysis to the translocation of the substrate (Ambudkar et al., 1999). But the mechanisms of P-gp inhibition are rather complicated and depend on both substrates and inhibitors, and do not always follow simple kinetics (Lin, 2003). Thus it can be supposed that compounds able to interact with P-gp activity could induce important modifications of bioavailability for numerous concomitantly administered drugs.

The transplacental transfer of several drugs such as saquinavir, paclitaxel, and digoxin in P-gp knockout mice has been shown to be 2–16 times greater as compared with mice with functional P-gp (Smith et al., 1999). Therefore, one might propose that the use of drugs that are P-gp substrates would reduce fetal drug exposure (Lankas et al., 1998). Their most striking property is the diversity with few common structural denominators. They are usually organic molecules ranging in size from less than 200 Da to almost 1900. Most of the efficiently transported molecules are uncharged or (weakly) basic in nature, but some acidit compounds can also be transported, albeit at a low rate. As most P-gp substrates are quite hydrophobic, in principle they can diffuse passively across biological membranes at a reasonable rate.

In the case of desirable increase of penetration of P-gp substrates beyond placental barrier, as with the therapy of fetus, inhibition of P-gp would allow substrates of P-gp to cross in considerable amount. Studies evaluating human placental transfer of P-gP substrates such as saquinavir have demonstrated that inhibition of P-gp can markedly impair its protective efflux function (Mölsä et al., 2005). Thus the uptake of P-gp substrates drugs into the fetus can be increased by P-gp inhibitors such as cyclosporin A, verapamil and progesterone (Ushigome et al., 2000).

Tab. 1. Selected clinically significant substrates of P-gp. Adapted from (Čečková-Novotná et al., 2006).

Cytotoxic drugs: vinca akaloids, taxanes, antracyclines, actinomycin D, epipodophyllotoxins
HIV protease inhibitors: amprenavir, saquinavir, ritonavir, nelfinavir, indinavir
Antibiotics: erythromycin, levofloxacin, gramicidin B
Cardiac drugs: digoxin, quinidine, carvedilol, celiprolol, talinolol
Antiemetics: domperidone, ondasetrone
Others: ivermectine, colchicine, losartan, phenytoin, morphine

However, different results have been found in perfused human placenta, in which neither quinidine nor verapamil were able to enhance digoxin concentration in the foetal compartment (Holcberg et al., 2003b). The main hypothesis was related by authors to the placenta's age. Effectively, progesterone is a potent inhibitor of P-gp activity and its levels increase with pregnancy age. Thus P-gp activity is probably strongly down-modulated in mature placentas, explaining the lack of inhibitor effect.

The interaction between quinidine and digoxin is directly linked to P-gp inhibition, confirmed by the fact that in knock out mice (mdr1a-/-), digoxin plasma levels are not modified by quinidine, whereas in wild-type mice, quinidine significantly increases plasma digoxin levels by 73% (Fromm et al., 1999).

In the case of proton pump inhibitors, which are known to interact with drug metabolising enzymes, a recent in vitro study has clearly demonstrated that omeprazole, lansoprazole and pantoprazole are are able to down-modulate digoxin efflux (Pauli-Magnus et al., 2001).

Many of the initially identifies inhibitors, like the calcium channel blocker verapamil or the immunosupressive agent cyclosporin A, turned out to be themselves transported substrates of P-gp, suggesting that they act as competitive inhibitors. For other inhibitors no significant transport by P-gp could be demonstrated, indicating that they probably work through other mechanisms. Still, it may be that some of the latter compounds are just diffusing so quickly across membranes that transport by P-gp, although it does occur, is not detectable (Litman et al., 2001).

Actually, the P-gp inhibitors that were initially recognized, such as verapamil,

are actually relatively poor P-gp inhibitors in vivo, because of their own pharmacodynamic effects that severely restrict the plasma levels that can be achieved. By now there are many P-gp inhibitors with increasingly suitable properties for clinical use.

Tab. 2. P-gp inhibitors. Adapted from Čečková-Novotná et al., 2006.

First generation chemosensitizers: verapamil, quinidine, cyclosporin A, progesterone, tamoxifen, trifluoperazine trifluopromazine, flupentixol
Second generation chemosensitizers: dexverapamil, PSC833, biricodar, GF120918, MS-209
Third generation chemosensitizers: LY335979, OC144093, XR9576
Herbal extracts: St.John's, Rosemary, Rhei Rhizoma, Ephedrae herba
Antibodies: MRK16

Food can also interact with P-gp. For example, grapefruit juice, a well-known enzymatic inhibitor of cytochrome P450 that leads to increased bioavailability of co-administered drugs, is implicated in interactions with P-gp, although with rather contradictory results. Three studies made evident an inhibition of P-gp activity by grapefruit juice on P-gp expressing cell cultures, that increased vinblastine and talinolol cell levels (Wang et al., 2001; Takanaga et al., 1998; Spahn-Langguth and Langguth, 2001). But studies in humus failed to prove an significant effect of grapefruit juice on human P-gp activity (Becquemont et al., 2001). Piperine, a major component of black pepper, is also known to down-modulate efflux activity of P-gp and inhibit digoxin and cyclosporin A transport in P-gp overexpressing cells (Bhardwaj et al., 2002).

4.3.2.2. MRPs

Multidrug resistance-associated proteins (MRPs) constitute another member family of ABC transporters. Currently there are nine known MRPs, six of them fully sequenced. Recent findings show that human placenta at term expresses at least free members of MRP family: MRP 1, MRP 2 and MRP 3. MRP 2 is expressed on the apical membrane of syncitiotrophoblast, while MRP 1 and MRP 3 are expressed on the basolateral membrane and the blood vessel endothelia (Borst et al., 2000).

Their size and function vary greatly. In contrast P-gp, MRPs appeal to efflux polar compounds (Borst et al., 2000) and function mainly as a (co-)tranporter of amphipathic organic anions. It can transport hydrophobic drugs and other compounds (for example inflammatory mediator leukotriene C4), as proved Mrp1 knockout mouse who were viable and fertile but showed deficiencies in LTC4-mediated inflammatory reactions (Robbiani et al., 2000), that are conjugated or complexed to glutathione, to glucuronic acid, or to sulfate (Leier et al., 1994; Müller et al., 1994; Evers et al., 1996; Loe et al., 1996).

The role of MRPs in the placenta has not been fully explained, but it is likely to bear (besides possible pharmacological role) important physiological activity. For more detalied review of numerous members of this group please see the review article (Schinkel and Jonker, 2003).

4.3.2.3. ABCG2

The most recently discovered ABC drug efflux transporter is BCRP, named for breast cancer resistance protein since it was cloned from a breast cancer subline, or mitoxantrone resistance protein, since it appeared to be responsible for the high levels of resistance to mitoxantrone observed in cell lines expressing the gene (Dietel et al., 1990; Nakagawa et al., 1992). Later it was placed in the "G" subfamily of ABC transporters and called ABCG2. Unlike the discussed transporters, this is a half-transporter, like the whole "G" subfamily, consisting of only a single N-terminal, intracellular ATP binding site, followed by 6 putative transmembrane segments. The last extracellular loop is in all likelihood *N*-glycosylated (Maliepaard et al., 2001a).

ABCG2 is a 72-kDa protein composed of 665 amino acids. The transmembrane domain of ABCG2 (residues 361 to 655) is predicted to have six transmembrane segments and an extracellular loop between segments five and six. Since ABCG2 is a half-transporter, it is believed to homodimerize, or possibly oligomerize in order to function (Ozvegy et al., 2001), in contrast to other members of the G subfamily of transporters ABCG5 and ABCG8, which heterodimerize to form a functional transporter (Graf et al., 2002). A tetrameric structure made up of four homodimer complexes was suggested (McDevitt et al., 2006). Building a phylogenetic tree using protein sequences of primates suggests that the function of ABCG2 has remained relatively conserved across vertebrate evolution (Robey et al., 2009).

By northern blot analysis, high levels of ABCG2 expression in placenta were reported (Doyle et al., 1998), specifically in the syncytiotrophoblasts as examined by immunohistochemistry (Maliepaard et al., 2001a). ABCG2 is believed to protect the developing fetus from the possible transmission of toxins as well as remove toxins from the fetal space (Jonker et al., 2000), as demonstrated for example in studies of transport of cimetidine from the fetal to maternal space against a concentration gradient (Staud et al., 2006), ABCG2 mediated transfer of 14C-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (Myllynen et al., 2008) and fetal penetration of glyburide (Pollex et al., 2008; Zhou et al., 2008; Gedeon et al., 2006; Gedeon et al., 2008).

The list of substrates and inhibitors of ABCG2 has been steadily expanding since its discovery, but yet no clear structure–function relationship has been identified that would explain the definitive requirements for a substrate or for an inhibitor. It is hoped that closer insights into the structure of ABCG2 could translate into a better understanding of the function of the protein, yielding potent and specific inhibitors (Robey et al., 2009).

Tab. 3. Selected non-chemotherapy substrates of ABCG2. Adapted from Robey et al., 2009.

Antivirals: zidovudine (AZT), lamivudine, abacavir
HMG-CoA reductase inhibitors: rosuvastatin, pitavastatin, cerivastatin
Antibiotics: ciprofloxacin, ofloxacin, norfloxacin, erythromycin, nitrofurantoin
Calcium channel blockers: Azidopine, dipyridamole, nitrendipene
Other compounds: sulfasalazine, cimetidine, riboflavin, vitamin K3, glyburide, d-Luciferin

4.3.3. Other transporters

Transporters that are facilitative (or equilibrative) can function both as influx or efflux transporters depending on directionality of the concentration gradient (Unadkat et al., 2004). It comprises groups of extraneuronal monoamine transporter (OCT3), human equilibrative nucleoside transporters 1 and 2 (hENT1 and hENT2), carnitine transporter (OCTN2)

Extraneuronal Monoamine Transporter (OCT3) is a Na^+ and Cl^--independent monoamine transporter and belongs to the family of organic cation transporters. This transporter is responsible for importing dopamine and norepinephrine into the fetal compartment, and is sensitive to inhibition by steroids. The physiological substrates of OCT3 include serotonin, dopamine, norepinephrine and histamine, OCT3 also interacts with the antidepressant desipramine (Shang et al., 2003). Transport defects in *Orct3*-deficient mice have been observed in embryonic development, indicating the importace of OCT3 function during pregnancy (Zwart et al., 2001).

Although hENT1 is throught to be situated on the brush-border membrane of the placental syncytiotrophoblasts (Barros et al., 1995), the placental localization of hENT2 is currently unknown. hENT1 and hENT2 have a broad specificity for nucleosides and nukleoside drugs, both transport purine and pirimidine nucleosides but with different affinities (Ward et al., 2000). hENT1 transports cytidine, guanosine, thymidine and adenosine with a higher affinity, while hENT2 transports inosine with a higher affinity than hENT1. The two transporters also differ significantly in their sensitivity to inhibition by the inosine analog, nitrobenzylthioinosine (NBMPR) (Ward et al., 2000; Yao et al., 2002; Griffith and Jarvis, 1996). hENT1 and hENT2 efficiently transport drugs (Lum et al., 2000) such as gemcitabine (Mackey et al., 1998) and ribavirin (Jarvis et al., 1998).

Carnitine Transporter (OCTN2) is localized at the placental brush-border membrane (Wu et al., 2000) as well as in the blood-brain barrier (Friedrich et al., 2003), OCTN2 transports carnitine into these privileged sites. The transport of cations by OCTN2 occurs in a Na^+-independent manner, whereas the transport of zwitterions occurs in a Na^+-dependent manner (Wu et al., 2000).

Because OCTN2 transports organic cations, its activity can be inhibited by cationic drug substrates. Ohashi et al. (1999) showed that many zwitterionic and cationic drugs inhibit OCTN2 in human embryonic kidney cells, including

tetraethylammonium, pyrilamine, quinidine, verapamil and valproate.

4.3.4. Placental metabolism

Apart of the active efflux transporters placenta itself can serve as a metabolic shield, as it is known to express a wide range of enzymes involved in phase I as well as in phase II of biotransformation reactions (Pasanen, 1999) possibly reducing fetal exposure.

In the case of CYP enzymes, there has been confirmed functional activity in the placenta for isoforms CYP1A and CYP2E1. The CYP1A1/1A2 isoform is the dominant CYP variant present in the placenta and is inducible by exposures to xenobiotics including polycyclic aromatic hydrocarbons, components of tobacco smoke. Additional isoforms, CYP19 (aromatase) and CYP11B (cholesterol side chain-cleaving enzyme) are also known to be present in the placenta throughout pregnancy. Placenta has the potential to express other CYP isoforms depending on the length of gestation and the health of the mother (Pasanen, 1999).

Activity of several phase II enzymes (e.g. sulphotransferases, glutathione-*S*-transferases, uridine diphosphate glucuronosyltransferases or *N*-acetyltransferase) was also revealed in placental tissue. However, none of these enzymes has been proven to play an important role in detoxication of xenobiotics (Pasanen, 1999; Syme et al., 2004). Therefore, proper placental metabolism of drugs and xenobiotics seems to be of relatively minor importance in limiting drug passage across the placenta (Syme et al., 2004).

5. PHARMACOTHERAPY OF DISEASES IN PREGNANCY

There is a strong evidence for many conditions that the immediate management during gestation decreases morbidity and mortality rates. In many cases results advise to prefer transplacental drug treatment over other modalities and encourage clinicians to treat mother and her child during pregnancy. Maternal DM, treatment of HIV infected pregnant women in order to prevent vertical transmission of the virus and fetal tachycardia belong to the most challenging situations.

5.1. Diabetes mellitus

Gestational diabetes mellitus affects 3-10% of pregnancies, and the incidence continues to rise with the rising rates of obesity. Approximately 50% of the women require medication. The intervention demonstrated a 67% lower risk for a serious perinatal outcome (Crowther et al., 2005).

Insulin is the preferred pharmacological treatment in pregnancy because it is unable to cross the placenta due to its large molecular weight (6000 Da), but pain, discomfort as well as the increased cost and training required to administer injections make compliance with the therapy a critical issue.

Oral hypoglycemic agents exemplify a group of medications that has been excluded from use in obstetrics for many years, mostly because of the little information about their transplacental passage available. Metaanalysis failed to show increased teratogenic risk among women treated with oral hypoglycemic agents (OHAs) during the first trimester (Gutzin et al, 2003).

5.1.1. Glyburide

Several studies that compared insulin with glyburide, a second-generation sulfonylurea, demonstrated similar efficacy in achieving glycemic control (Langer et al., 2000; Fines et al., 2003; Jacobson et al., 2005; Langer et al., 2005; Ogunyemi et al., 2007). Neonatal outcomes after glyburide are similar to insulin (Langer et al., 2000; Fines et al., 2003), so it appears to be safe by measures of obstetric and neonatal outcomes (Moretti et al., 2008), or by an evalution of neonatal body composition which precisely reflects individual effects of the maternal environment on fetal growth and better estimates fetal effects of various methods of maternal glycemic control (Lain,

2009).

The use of glyburide during pregnancy has potential advantages including decreased

cost, ease of administration, fewer side effects, and patient satisfaction.

Glyburide has been shown to exhibit marginal placental transfer (Robidoux et al, 1998). A randomized control trial (Langer et al., 2000) found no detectable levels of glibenclamide in cord serum. Glibenclamide's exceptionally high protein binding, above 99.8%, allows for less than 0.2% of free drug to circulate and cross the placenta. Additionally, its high protein binding is coupled to a short elimination half-life made possible by its low volume of distribution (0.2 l/kg) and rapid clearance (1.3 ml/kg/min). In short, glibenclamide has only a brief opportunity to cross the placenta (Feig et al., 2004; Koren, 2001).

Elliott et al.'s (1991) dually perfused human placental model showed virtually no appearance of glibenclamide in the fetal circulation. Even when maternal concentrations were 8 fold greater than therapeutic peak levels, suggesting glibenclamide may be actively pumped back to maternal circulation, and can both maintain maternal steady state concentrations and normoglycemia while decreasing fetal exposure and risk of hypoglycemia.

Recent research, using the ex vivo human placental perfusion model, has revealed that glyburide is effluxed by an active mechanism against a concentration gradient from the fetal to the maternal compartment and that this mechanism is not affected by the P-glycoprotein inhibitor verapamil (Kraemer et al, 2006).

Further investigation carried out on P-gp, MRP1-3 and ABCG2 overexpressing cell lines indicated that glyburide is preferentially transported by ABCG2 and MRP3 (Gedeon et al, 2006). Additional research using placental brush border membrane vesicles revealed a significant increase in the vesicular uptake of glyburide in the presence of novobiocin, a ABCG2 inhibitor, while MRP3 inhibition did not demonstrate a similar effect (Gedeon et al, 2008). Hence, this study provides the first evidence for ABCG2 as the specific transporter responsible for the active efflux of glyburide in the human placenta.

In addition, the possible involvement of other placental transporters, such as MRP5, remains to be established (Meyer Zu Schwabedissen et al, 2005). Likely the involvement of MRP transporters in the transport of glyburide, if any, is not clinically significant.

The data on the kinetics of the formation of glyburide metabolites by the microsomal preparations from human and baboon livers and placentas strongly suggest that several cytochrome P450 isozymes are involved (Zharikova et al., 2007).However, the activity of placental enzymes changes with gestation (Hakkola et al., 1998) and its metabolism of glyburide cannot be determined at the different preterm gestational ages.

Moreover, the metabolites formed in the presence of human placental and hepatic microsomes were identical. The major metabolite formed by human placenta is M5 (ethyl-hydroxy glyburide), which contributes 87% of the total (Zharikova et al., 2007). But it is not clear whether they pharmacologically active and what are their effects on peri- and neonatal outcome.

It can be concluded that the CYP isozymes metabolizing glyburide in human placenta might be similar to those in the liver, and the lower activity is due to decreased expression (Hakkola et al., 1998).

As mentioned above we can consider glibenclamide and insulin equally effective in achieving good glycemic control and in the influence on perinatal outcomes, so the published data is robust enough to recommend glibenclamide to GDM women who are reluctant to accept insulin.

5.1.2. Metformin

Recently, metformin, currently the only used biguanide, was compared with insulin treatment in gestational diabetes mellitus (GDM) patients, and found to be similarly as effective as insulin for maternal blood glucose control and neonatal outcome (Moor et al, 2005).

Only scarce data exist explaining the mechanism by which metformin crosses biological membranes (Wang et al, 2003; Kimura et al, 2005a; Kimura et al, 2005b) and the exact mechanism of the transplacental transfer of metformin is unknown.

Metformin is a weak base, highly polar, positively charged hydrophilic compound, with a small molecular weight, a low binding capacity to plasma proteins, and is not known to freely diffuse through cell membranes. The exact mechanism by which metformin crosses the biological membranes is not completely understood. Metformin has been shown to act as a substrate for three organic cation transporters OCT1, OCT2, and OCT3, which are the only transporters known to be involved in

metformin transport to date. There are no current data indicating the presence of OCT1 presence in human placenta, OCT2 is only moderately expressed and OCT3 has considerable expression in human placental tissue (Unadkat et al., 2004). Therefore, it can be speculated that OCT3, and to some extent OCT2, are responsible for the transport of metformin across the human placenta.

Additional studies are needed to assess the exact mechanism of metformin transport across the human placenta, and possible accumulation in the fetal compartment.

The risk to the fetus could be either direct (ie, dependent on the amount of the drug transferred from the maternal to fetal circulation) or indirect (ie, because of the effects of the
drug on placental functions).

The transfer and distribution of metformin in placentas that were obtained from uncomplicated pregnancies was not different from diabetic placentas and indicates that GDM does not affect the transfer or distribution of metformin, no accumulation of the drug in the placental tissue occured. Metformin does not affect placental glucose uptake or transport (Elliot et al., 1997).

Based on the results of ex vivo metformin transfer model (Kovo et al., 2008), it could be assumed that fetal exposure to this medication is low, suggesting the safety of its use during pregnancy. However, this assumption contradicts recently published data that reveals that metformin concentrations in both umbilical artery and vein are roughly the same as in maternal serum (Vanky et al, 2005). In the same report (Vanky et al., 2005), the concentration of metformin in the umbilical vein exceeded that in the maternal serum, and the authors suggested that the fetus can excrete metformin to the amniotic fluid and reabsorb it into the fetal circulation by swallowing.

Metformin transferred to the fetal circulation will remain as a free/active drug because of its lack of binding to plasma and tissue proteins. Because metformin is a hydrophilic drug, the increased total body water volume during pregnancy and enhanced renal elimination could reduce its concentration in maternal plasma and require dose adjustment.

We can conclude that metformin is able to cross the mature human placenta, thus, fetal exposure must be considered when treating pregnant women with metformin.

5.1.3. Rosiglitazone

Rosiglitazone is a member of thiazolidinediones, potent oral antihyperglycemic agents (Patel et al., 1998; Cox et al., 2000) that reduces insulin resistence (Matthews et al., 1999) exerting its glucose-lowering effect by binding to peroxisome proliferator-activated receptor γ (Lehmann et al., 1995; Berger et al.,, 1996). Rosiglitazone improves sensitivity to insulin in muscle and adipose tissues and inhibited hepatic gluconeogenesis.

Both glyburide (Elliott et al., 1994) and rosiglitazone (Cox et al., 2000) have similar molecular weights and cross placenta by simple diffusion. In addition, rosiglitazone is similar to glyburide in that it is extensively (99.8%) bound to plasma proteins, particularly albumin. This property of rosiglitazone may explain why the drug did not cross into the fetal circulation. Clearance indices of rosiglitazone in the placental perfusion studies now reported are comparable with those previously reported for glyburide (Elliott et al., 1991; Elliott et al., 1994; Koren, 2001).

Rosiglitazone, like other drugs of this class, contains a thiazolidinedione core but differs from pioglitazone, englitazone, and troglitazone in the presence of an aminopyridyl side chain (Perry and Petrie, 1998; Young et al., 1998). It is believed that these side chain substitutions are responsible for differences in disposition, metabolism, and antidiabetic efficacy (Berger et al., 1996).

Rosiglitazone has fewer side effects than other thiazolidinediones, importantly though, rosiglitazone has been associated with less hypoglycemia and decreased C-peptide, insulin, and proinsulin levels when compared with glyburide.

Rosiglitazone has been classified as a pregnancy category C drug. No ill effects on implantation or teratogenicity have been observed in animal studies, however, the use of rosiglitazone in rat and rabbit models has been associated with fetal growth restriction.

Although demonstrated, there is also negligible transfer of rosiglitazone across the placenta with minimal fetal accumulation, further human studies are needed with regard to the safety and efficacy of rosiglitazone before it can be considered for the management of pregnancies complicated by diabetes.

5.2. HIV infection

About 6000 HIV-infected women were delivered of live-born infants in 1989 in USA (Oxtoby, 1990). With an infection rate of about 30%, about 1800 children were HIV-infected.

About 90% of HIV-infected children is due to vertical transmission from the infected mother. This perinatal transmission of HIV occurs as a result of transplacental dissemination of the virus and intrapartum exposure to infected blood and genital tract (Duff, 1996; Bryson, 1996; John and Kreiss, 1996).

As HIV crosses the placenta and infects the fetus (Connor et al., 1994; Sperling et al., 1996), the treatment of pregnant women with antivirals has two purposes: to protect the mother against HIV and to avoid vertical transmission of this virus. HIV therapy usually consists of nucleosidic analogue inhibitors of reverse transcriptase in combination with one HIV protease inhibitor.

5.2.1. Reverse transcriptase inhibitors

In vitro and in vivo results are consistent with the view that the nucleoside reverse transcriptase inhibitors cross the human placenta and produce significant pharmacological concentrations in the fetal circulation. Nevirapine, the only studied non-nucleoside reverse transcriptase inhibitor, reach the equilibrium between the fetal and maternal concentration.

The nucleoside reverse transcriptase inhibitors, and probably the non-nucleoside reverse transcriptase inhibitors, but more information is necessary for these latter drugs, cross the human placenta and reach pharmacological significant concentrations in the fetal blood.

With the exception of didanosine, the nucleoside reverse transcriptase inhibitors and nelfinavir, a non-nucleoside reverse transcriptase inhibitor, cross the placenta and the cord, and maternal plasma concentrations equilibrate (Pacifici, 2005).

Cord blood concentrations of zidovudine and lamivudine tend to equal maternal concentrations at the time of delivery, whereas cord blood concentrations of didanosine and zalcitabine are approximately 50% that of maternal concentrations (Rogers et al., 1990; Sanberg and Slikker, 1995). Non-nucleotide reverse transcriptase inhibitors, such as nevirapine, have also been shown to cross the placenta (Mirochnick, 2000; Rogers et al., 1990). Several factors may account for their passage including the drug’s lower

protein binding (60%), low molecular weights, favorable degree of lipophilicity (Voit et al., 1985). As well, the majority are not P-gp substrates. Hence, these drugs passively diffuse across the placenta and are administered in sufficient doses to cross the placenta and prevent maternal-fetal transmission of HIV during labor (Gedeon and Koren, 2006).

According to the data by Bawdon et al. (1992), didanosine has the lowest clearance index (0.13) among the nucleoside reverse transcriptase inhibitors and the cord to maternal plasma ratio is lower than the unity (Pons et al., 1991; Chappuy et al., 2004b). Among the nucleoside reverse transcriptase inhibitors, abacavir has the highest clearance index (0.47) and the cord and maternal plasma concentrations of this drug equilibrate (Chappuy et al., 2004b). The second and third clearance index is that of zidovudine (0.28—0.54) and lamivudine (0.25), and the concentrations of these drugs equilibrate in the cord and maternal blood. The highest clearance index was obtained with bisheteroypiperazine (0.75), a non-nucleoside reverse transcriptase inhibitor, and this antiviral should cross the placenta well but little is known about this drug (Pacifici, 2005).

5.2.2. Protease inhibitors

Both the results obtained in vitro and in vivo show that the protease inhibitors poorly transfer the placenta because of their great molecular weight. When the molecular weight is greater than 500Da, the clearance index is lower than 0.1 and the in vivo placental transfer is incomplete as it is in the case for ritonavir and saquinavir. The molecular weight of these compounds ranges from 506Da (amprenavir) to 721Da (ritonavir) (Pacifici, 2005).

The transfer rates of the protease inhibitors ritonavir and saquinavir have been extremely low (Casey and Bawdon, 1998; Forestier et al., 2001). Chappuy et al. (2004a) have recently shown that the protease inhibitors have a poor transfer across the human placenta.

A recent in vivo study also suggested low placental transfer of both drugs (Marzolini et al., 2002). Both saquinavir and ritonavir are known P-gp substrates and a possible reason for low transfer is P-gp mediated efflux (Pacifici and Nottoli, 1995). Protease inhibitors are substrates of P-gp and few human data are available to evaluate their effect in utero (Lee at al., 1998).

Protease inhibitors (PI) do not cross the placenta to a clinically appreciable

extent (Maarten et al., 2001). Nelfinavir, ritonavir, saquinavir and lopinavir undergo incomplete transplacental transfer (Owen et al., 2005). Low PI placental transfer can be attributed to high protein binding (98%) and that these drugs are substrates for placental P-gP transporter (Huisman et al., 2000). For example, Saquinavir is a P-gP substrate with a high molecular weight (767 g/mol), high protein binding (98%) and partition coefficient which may contribute to the small amount that crosses the placenta (Forestier et al., 2001).

The protease inhibitors reduce the mother's viral load but cannot be used to protect the fetus against HIV (Pacifici, 2005).

However, if certain protease inhibitors are effluxed by the placenta, and do not reach the fetus, future use of the appropriate ABC inhibitor may allow for greater concentrations in the fetal compartment and the prevention of materno-fetal HIV transmission (Gedeon and Koren, 2006).

5.2.3. Fusion inhibitors

Enfuvirtide, is the first member of a novel class of antiretroviral agents, the fusion inhibitors, which interfere with the entry of HIV-1 into the human immune cell (Williams, 2003).

It seems not to be transferred across the placental barrier. Even at maternal concentrations twice above therapeutic levels, no placental transfer of enfuvirtide was observed (Ceccaldi et al., 2008).

The high molecular weight of the molecule (4492 kDa) and its ionized state may account for the lack of placental transfer (Gavard et al., 2006; Ghosn et al., 2004). First, it is unlikely to lead to any toxicity to the fetus, suggesting that enfuvirtide could be used in HIV-infected pregnant women without causing fetal exposure, on the other hand, it would not have any benefit as direct in utero postexposure prophylaxis to protect the fetus from vertical HIV transmission (Ceccaldi et al., 2008).

5.3. Fetal tachycardia

Fetal tachycardia, defined as a heart rate greater than 180 beats/min regardless of gestational age, is a condition that occurs in approximately 0.4% to 0.6% of all pregnancies (Bergmans et al., 1985). The subset of these cases with more sustained periods of tachycardia and higher heart rates is associated with congestive heart failure, fetal hydrops, neurologic morbidity, and intrauterine death (Naheed et al., 1996; Sonesson et al., 1996; Donn and Bowerman, 1993). Most centers have therefore opted for prenatal intervention in the form of maternal pharmacologic treatment (Allan et al., 1991; Kleinman et al., 1985; Simpson and Sharland, 1998; Cuneo and Strasburger, 2000; Van Engelen et al., 1994; Frohn-Mulder et al., 1995; Jaeggi et al., 1998; Sonesson et al., 1998; Ebenroth et al., 2001; Krapp et al., 2002; Strasburger, 2000; Oudijk et al., 2000; Oudijk et al., 2002).

Sustained tachycardias are indications for therapy because of their potential to produce fetal hydrops, which is characterized by masive anasarca, cardiomegaly, hepatosplenomegaly, and polyhydramnios. The mortality reaches as high as 50% to 98% (Iliff et al., 1983; Kleinman et al., 1982; Etches and Lemons, 1979; Hutchison et al., 1982).

In the case of persistent tachycardia, established by M-mode fetal echocardiography, it is strongly recommended to initiate transplacental treatment, as it can improve prognosis dramatically (Pézard et al., 2008). Before initiation of therapy, preexisting maternal arrhythmias and/or a prolonged QT segment should be excluded by a thorough examination of medical history and a maternal ECG (Oudijk et al., 2004).

After 20 years of accumulated experience, the therapeutic protocol consists of the use of four main agents and a three-stage strategy.

Digoxin is administered as first choice, and if it fails it is followed by flecainide (Allan et al., 1991; Frohn-Mulder et al., 1995) or sotalol (Oudijk et al., 2000) either on their own or with digoxin as second-line therapy. In this scheme, amiodarone remains on reserve for refractory cases and is only used as a third-line agent (Strasburger , 2005).

5.3.1. Digoxin

The cardiac glycoside digoxin is clinically used to treat fetal tachyarrhythmias

and fetal congestive heart failure (Holcberg et al., 2003b). Digoxin is the most commonly used drug (Ito et al., 1994). A steady-state serum digoxin concentration is low in pregnancy, compared to nongravid state (Rogers et al., 1972). Pharmacokinetics of digoxin during pregnancy is characterized by increased clearance and shorter elimination half-life (Azancot-Benisty et al., 1992). Therefore, a dose to maintain therapeutic concentrations of digoxin tends to be higher during pregnancy than usual. There are no specific data on pharmacokinetics of the other drugs in pregnancy (Ito, 2001).

Digoxin has been the drug of first choice in many centers, it is a well-known drug with a good evidence-based in neonates and children (Pézard et al., 2008). The presence of hydrops is associated with a lower success rate of digoxin monotherapy (Van Engelen et al., 1994). This is ascribed to poor placental diffusion of digoxin in hydropic placenta (Younis and Granat, 1987).

Clinically significant interactions between digoxin and P-glycoprotein inhibitors have been well recognized.

Verapamil increases digoxin serum concentrations by inhibiting P-glycoprotein-mediated digoxin excretion. Similarly in the treatment of fetal tachyarrhythmia, coadministered verapamil may enhance digoxin transfer into fetus by blocking placental P-glycoprotein.

Pharmacological manipulation of placental P-glycoprotein and/or other transporters has become a potential new option to optimize pharmacotherapy for fetal tachyarrhythmias (Ito, 2001).

In conclusion, digoxin is a safe drug in the treatment of fetal tachycardia, however, its use results in relatively low conversion rates, and frequently second line drugs are required to achieve sinus rhythm (Oudijk et al., 2004).

5.3.2. Flecainide

It has been proposed as an effective drug in the treatment of SVT, especially SVT associated with hydrops, either as drug of first choice or in combination with digoxin. The transplacental transfer is good (Wagner et al., 1990; Bourget et al., 1994; Barjot et al., 1998).

It has been used as drug of second choice in nonhydropic SVT, and drug of

first choice in hydropic SVT resulting in conversion rates ranging from 75 – 92 % (Allan et al., 1991; Ebenroth et al., 2001; Krapp et al., 2002).

Its use in fetal tachycardia therefore is mainly concentrated on SVT complicated by hydrops. It has been associated with intra-uterine deaths, however, the occurrence of an intrauterine death is a well known complication in fetal hydrops, and we can only speculate on the exact relationship with flecainide (Oudijk et al., 2004).

5.3.3. Sotalol

The placental transfer is excellent (Oudijk et al., 2003), as sotalol passes the placenta easily and completly (O´Hare et al., 1980). Apparently sotalol does not accumulate in the fetus, which implies that the excretion of sotalol by the fetal kidney is efficient close to term. The adequate renal excretion may explain the relatively high concentration of sotalol in amniotic fluid. Statistically a strong relationship between the maternal blood level and the success of therapy was not shown. The therapy-resistant cases required either electrical cardioversion or multiple drug therapy, which suggests that the success of therapy may be more related to the type of arrhythmia (Oudijk et al., 2003).

Sotalol seems to be more efficacious than other drugs in fetal AF. The success rate of sotalol as a single therapy in the treatment of atrial flutter in the reported studies was approximately 65 %, and reached 80 % after the addition of digoxin (Oudijk, 2003).

Sotalol has been associated with intrauterine deaths, mainly in hydropic cases with SVT (Oudijk et al., 2000), we opted for a different strategy (Oudijk et al., 2002). The success rate in fetal SVT was approximately 55 % with sotalol as a single drug and reached 75 % after the addition of digoxin (Oudijk et al., 2004).

As proarrhythmia effect of sotalol is known to be dose-related (Hohnloser and Woosley, 1994), low initiation doses are preferable and dosage increases should be stepwise.

Some beta-blockers, such as propranolol, have been associated with intrauterine growth retardation (Pruyn at al., 1979), but sotalol is not associated with fetal growth restriction (Oudijk et al., 2003).

In conclusion, sotalol is a very potent drug in the treatment of fetal AF, with or

without hydrops, and is recommended as drug of first choice. Sotalol seems contraindicated in SVT complicated by hydrops (Oudijk et al., 2004).

5.3.4. Amiodarone

The transplacental transfer is relatively low (Oudijk et al., 2003). Recently, a large study by Strasburger et al. (2004) was published in which amiodarone was initiated in drug-refractory fetal tachycardia complicated by hydrops. A high success rate of 93 % in SVT was accomplished, and a lower conversion rate of 33 % in AF (Strasburger et al., 2004).

Traditioinally, amiodarone was used as third-line therapy and reserved for refractory cases, although amiodarone was shown to be effective for all fetuses, whether they were hydropic or not, and whether the agent was used alone or in association with digoxin, with the exception of two cases. It confirms observations made by Kositeth et al. (Khositseth et al., 2003), Jouannic et al. (2003) and Strasburger et al. (2004).

Amiodarone is equally so after maternal oral administration (even in hydropic cases), with a relatively rapid onset of action despite its mediocre transplacental passage (Pézard et al., 2008). Maternal tolerance to amiodarone was also good. No maternal thyroid complications were observed. Two patients given the amiodarone-digoxin combination showed elevated levels of serum digoxin and clinical signs of digitalis intolerance. Amiodarone is known to raise the plasma levels of digoxin, which therefore necessitates careful dosage adjustments (Marcus, 1983). Fetal cardiac tolerance was also acceptable. To our knowledge, pulmonary and ocular complications linked to the use of amiodarone in fetuses have not been reported. Nevertheless, we must attempt to keep the duration of amiodarone administration during fetal life as short as possible (Pézard et al., 2008).

In conclusion, amiodarone is efficient in the treatment of fetal tachycardias after oral maternal administration. When amiodarone is used as first-line monotherapy in hydropic fetuses, its benefits seem to outweigh the risks, both for the fetus and mother. The study also suggests that amiodarone may be a valuable first-line choice for the treatment of less severe forms of fetal STV (Pézard et al., 2008).

6. CONCLUSION

The expanding knowledge concerning transplacental drug transfer was enabled by the development of models in vivo and ex vivo. The layer of syncytiotrophoblast was shown as a rate-limiting for drug permeation and pharmacokinetic studies revealed that substance penetration is greatly influenced by the activity of efflux transporters. Their interactions with inhibiting substances and their own substrates can modulate transplacental distribution.

Detailed investigation of interactions of these substances can offer a framework for sophisticated therapy with minimized fetal exposure, or on the contrary, learn to give preference to the passage of drugs towards the fetus and target it as the object of therapy.

According to current level of knowledge, appropriate drug candidates, which respond by their physical-chemical features to be optimal gestational medications (for example glyburide), have been designated. But continued research and sorting information will help to achieve more safety for both mother and child.

7. SUMMARY

After thalidomide-induced birth defects affair, the view of uterus as pharmacologically unconquerable site dramatically changed. Subsequently it was accepted that any chemical substance permeates across the placenta. As there was a continuing need for many mothers to continue to receive medications for chronic disease states, extensive research was launched to gain an appropriate rationale.

Progressive investigation of placental barrier compounds allowed the emergence of in vitro and in vivo models, which enabled particularly drug transport studies. Syncytiotrophoblast plays an important role as a rate-limiting component of the barrier.

Detailed understanding of pharmacokinetic changes that occur during gestation offered a rationale for pharmacotherapy in pregnancy (large charged molecule, excessive protein-binding, short elimination half-life, volume of distribution, fetal-maternal serum pH gradient). The mechanism of passive diffusion is most important way of drug transport.

Perfusion studies clarified the crucial role of active efflux transporters, members of ABC protein family, namely P-glycoprotein, multidrug resistence-associated proteins a ABCG2. As P-gp was first to be discovered, is the most studied until now. Its substrates and inhibitors are well defined and their interactions are cardinal for rational pharmacotherapy in pregnancy. Although, many metabolizing enzymes have been identified within placental tissue, including CYP450 isoforms, they seem not to be a limiting factor in transplacental passage of drugs.

Pharmacotherapy can be targeted to mother, fetus or both as in the case HIV infection.

Similar efficacy and safety in the treatment of GDM was proved for insulin and oral hypoglycemic agents. The molecule of glyburide was shown as a prototype of an optimal agent for the therapy of mother.

There are marked differences in two concomitantly administered groupes of anti HIV drugs: reverse transcriptase inhibitors readily cross the placenta and efficiently suppress the activity of virus within the fetus, while protease inhibitors in fact don´t penetrate and their effect is restricted to the maternal compartment, where they decrease the viral load.

The most used and successful drugs in fetal tachycardia are digoxin, sotalol, flecainide and amiodarone, which are indicated according to the natural of arrythmia and clinical status (presence of fetal hydrops).

Further exploration of efflux transporters modulation will contribute to safer and

much more effective treatment.

8. SOUHRN

Po thalidomidové aféře se náhled na farmakologickou nedostupnost placenty významně změnil. Následně byl přijat názor, že placentu prostupuje v podstatě jakákoliv chemická látka. Jelikož je potřeba léčit chronické choroby matky i během těhotenství, strhla se vlna výzkumů, která měla dát této léčbě racionální podklad.

Postupné získávání informací o jednotlivých složkách placentární bariéry umožnilo vznik in vitro a in vivo modelů, které podpořily studium léčiv. Syncytiotrofoblast hraje důležitou roli v rychlosti přestupu léčiv přes bariéru.

Pro distribuci léčiv je nezbytné uvažovat změny ve farmakokinetice během těhotenství (vazba na bílkoviny, distribuční objem, krátký eliminační poločas, polarizace, pH gradient mezi sérem matky a plodu). Pro většinu léčiv je nejdůležitějším mechanismem transportu pasivní difuze.

Klíčovou roli v definitivním prostupu do fetálního kompartmentu má skupina ABC proteinů, v placentě zastoupena především P-glykoproteinem, skupinou MRP transportních proteinů a ABCG2 transportérem. P-gp byl objeven jako první a je nejlépe prozkoumán. Bylo definováno mnoho jeho substrátů a inhibitorů, jejichž vzájemné interakce jsou stěžejní pro racionální farmakoterapie v těhotenství. I když byla v rámci vlastní placentární tkáně definována celá řada enzymů (včetně izoforem CYP450), zdá se, že nejsou limitujícím faktorem pro transplacentární přestup léčiv.

Cílem farmakoterapie může být jak primárně matka nebo plod, tak v případě HIV infekce oba.

V terapii gestačního diabetu mellitu byla prokázána srovnatelná účinnost a bezpečnost insulinu i perorálních antidiabetik. Na modelu glyburidu byl definován prototyp léku s optimálními vlastnostmi pro terapii matky.

Mezi základními skupinami společně podávaných látek v terapii HIV infekce jsou významné rozdíly: inhibitory reverzní transkriptázy snadno prostupují a působí na virus i v rámci plodu, zatímco inhibitory proteázy v podstatě neprostupují a jejich účinek je omezen na organismus matky, tudíž na snížení virové nálože.

Nejužívanější a nejúspěšnější léčiva používaná v léčbě fetální tachykardie jsou digoxin, sotalol, flekainid a amiodaron. Jsou indikovány dle podstaty arytmie a klinického stavu (přítomnost fetálního hydropsu).

Další výzkum modulace funkce lékových transportérů přispěje k bezpečnější a efektivnější léčbě.

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