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Multi-drug resistance (MDR1) gene and P-glycoprotein influence on pharmacokinetic and pharmacodymanic of therapeutic drugs

Influência do gene de resistência múltipla (MDR1) e da P-glicoproteína na farmacocinética e farmacodinâmica de drogas terapêuticas

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- REVIEW -

ABSTRACT

(MDR1) gene expressed in tumor cells and also in several normal tissues, such as intestine, liver, kidney, blood-brain barrier, spinal cord, and placenta. P-gp has been identified in mice, rat, bovine, monkey, rodents, and human beings and has been receiving a particular clinical relevance because this protein expression limits brain access and intestinal absorption of many drugs. This protein plays a role as a protective barrier against a wide variety of substrates, avoiding drug entry into the central nervous system. P-glycoprotein also interferes with drug bioavailability and disposition, including absorption, distribution, metabolization, and excretion, influencing pharmacokinetic and pharmacodynamic of drugs. Modulation of P-gp may help the efficacy of treatment of several diseases and can explain some adverse central nervous system effects induced by drugs after intravenous administration and the poor response of oral administration in patients. Alteration in P-gp expression or function has been associated with several diseases susceptibility in humans and animals. Furthermore, additional studies relating MDR1 and P-gp expression has an important clinical implication also in terms of treatment efficacy.

Key words: *MDR1 gene, P-glycoprotein, therapeutics, pharmacology.*

RESUMO

P-glicoproteína (P-gp) é um transportador de membrana ligado ao gene de resistência múltipla (MDR1), expressado em células tumorais e também em tecidos normais como intestino, fígado, rins, membranas hematoencefálica, hemo-placentária e medula espinhal. A P-gp já foi identificada em camundongos, ratos, bovinos, macacos, roedores e seres humanos e tem ganhado relevância clínica particular em função de sua expressão limitar o acesso de drogas ao cérebro e interferir com a absorção intestinal quando administradas pela via oral. Esta proteína participa da função protetora do organismo contra uma grande variedade de substratos, evitando a entrada de drogas no sistema nervoso central. A P-gp interfere também com a biodisponibilidade dos fármacos, incluindo absorção, distribuição, metabolização e excreção, influenciando assim, a farmacocinética e dinâmica dos mesmos. Desta maneira, a modulação da P-gp pode explicar alguns efeitos adversos no sistema nervoso central, induzidos por alguns fármacos após administração intravenosa, e a pobre resposta após administração oral em pacientes. A alteração na expressão ou função da P-glicoproteína tem sido associada a uma maior susceptibilidade a diversas doenças em humanos e animais. Estudos adicionais relacionados à expressão e à função da P-gp espécie-específica têm implicação clínica importante em termos de eficiência de tratamento.

Palavras-chave: *gene MDR1, P-glicoproteína, terapêutica, farmacologia.*

INTRODUCTION

There is a wide difference of therapy response between species involving several drugs in Veterinary Medicine. Many factors can affect drug disposition such as physicochemical properties of the drug and biological factors including gastric and intestinal time, luminal pH, and mucosal blood flow, when orally administered. Once the drug is in the bloodstream its distribution to diverse cells and tissues, such as the brain, testes, and fetus is also limited by physiologic barriers (MEALEY, 2004). Even with this concept, there are multiple drugs that should cross the barriers, like the blood-brain barrier, but they have

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poorer permeability than expected considering their lipophilicity (TSUJI et al., 1997). This phenomenon can be explained by the presence of drug transporters at the luminal membrane of the endothelial cells lining the brain capillaries which limit drug access to the central nervous system (FROMM, 2004).

Intestinal drug efflux by P-glycoprotein is widely recognized as a major determinant for low or variable oral absorption and bioavailability of several drugs (CUMMINS et al., 2003). A lot of drugs considered P-glycoprotein substrate in the literature are often clinically used also in veterinary medicine.

It has been discovered that due to P-glycoprotein, a drug transporter, plays a role in drug disposition including absorption, distribution, metabolism, and excretion (MIZUNO et al., 2003; SUN et al., 2004) its expression could be an obstacle to adequate drug therapies (CHOO et al., 2000). Besides the drug pharmacokinetics alteration, the presence of this protein is been related with increased susceptibility to diseases in human beings (MEALEY, 2004).

In order to create new strategies for therapies, some authors suggest pharmacological P-glycoprotein inhibition which may offer an advantage to veterinary and human patients (CHOO et al., 2000; MEALEY, 2004).

After these considerations, P-glycoprotein may explain clinical differences of drug response among species and differences in the pharmacokinetics of drugs, including oral absorption, bioavailability, and clinical effect and may also help to understand, avoid, or treat certain diseases. The objective of this review was to collect data from the current literature regarding the influence of the multi-drug resistance gene and P-glycoprotein on the clinical effects of therapeutic drugs in order to establish the ground basis for the manipulation of this gene and its expression for pharmacotherapy use.

Multi-drug resistance gene (MDR1) and P-glycoprotein (P-gp)

Multi-drug resistance (MDR1) gene, also known as ABCB1 gene, is a term that describes the cross-resistance of cells against a range of drugs with different structures and targets. This gene encodes an efflux transporter P-glycoprotein (P-gp) that limits a wide variety of drugs from penetrating cells and depositing them into the extracellular space (XIE et al., 1999; WANG et al., 2004) (Table 1).

P-glycoprotein was first described in 1976, by JULIANO & LING in Chinese hamster ovary cells selected in culture for colchicines resistance (MARZOLINI et al., 2004; MEALEY, 2004). Considered a plasma membrane protein, member of the adenosine triphosphate (ATP)-binding cassette (ABC) super family of energy-dependent efflux protein pumps (SUN et al., 2004), P-gp acts as an active efflux pump leading to lower intracellular accumulation of its substrates (XIE et al., 1999; DAGENAIS et al., 2004; RODRIGUEZ et al., 2004). Due to the difficulty to precisely characterize the substrate molecular requirements, previously reported data are controversial about P-gp substrates and inhibitors (SUN et al., 2004). However, there are studies that correlate some drugs as P-gp substrates such as anticancer or chemotherapy agents, βAdrenoceptor antagonists, Ca^{++} channel blockers, cardiac drugs, steroids, opioids; immunosuppressant, Human Immunodeficiency Virus (HIV) protease inhibitors, antiemetic, antibiotics, lipid-lowering agents, and histamine H1 receptor antagonists (FROMM, 2004; IERI et al., 2004; MARZOLINI et al., 2004; MEALEY, 2004). Experiments are showing that several drugs determined substrates for murine P-gp are also substrates for human and canine P-gp (MEALEY et al., 1998/2001).

P-glycoprotein is expressed at relatively high levels not only in tumor cells, where confers multiple drug resistance, but also in many normal tissues, such as intestine, liver, kidney, blood-brain-barrier, and placenta (THIEBAUT et al., 1987; LOTSCH, 2001; MIZUNO et al., 2003; SUN et al., 2004). In normal tissues, P-gp is present in the apical membranes of intestinal epithelial cells of the gastrointestinal tract, in the biliary canalicular membranes of hepatocytes in the liver, in the luminal membranes of proximal tubular epithelial cells in the kidney, and in the luminal membranes of brain capillary endothelial cells of the blood-brain-barrier (CORDON-CARDO et al., 1989; THIEBAUT et al., 1987; WANG et al., 2004). P-gp is also expressed in the spinal cord (CORDON-CARDO et al., 1989) and choroids plexus and although data are limited, this protein may modulate substrate penetration also at these sites (DAGENAIS et al., 2004).

Normal physiological function of P-gp in healthy gastrointestinal tract remains under investigation (HO et al., 2003). Although under normal laboratory conditions P-gp has shown not essential for the basic physiologic functioning, assuming primarily only a protective capacity for the organism by decreasing drug disposition (MEALEY, 2004). Some authors relate that based on anatomical localization, the presence of P-gp limits the oral bioavailability of a wide class of drugs (BOUER et al., 1999; MIZUNO et al., 2003; FROMM, 2004; GEYER et al., 2005), pumping drugs back into the lumen once they are absorbed across the intestinal mucosa (BOUER et al., 1999;

Table 1 - Therapeutic agents that are P-glycoprotein substrates or inhibitors

Substrates			Inhibitors
Antiacids	**β-Adrenoceptor antagonists**	**Immunosuppressants**	**Diverse Inhibitors**
Cimetidine	Bunitrolol	Cyclosporine A	Agents
Ranitidine	Carvedilol	Sirolimus	Verapamil
	Celiprolol	Tacrolimus	Quinidine
Antibiotics	Talinolol		Valspodar (PSC)
Erytromycin	Reserpine	**Opioids**	Cyclosporine
Tetracycline		Loperamide	Ketoconazole
Rifampin	**Ca^{++} Chanel Blockers**	Domperidone	
Levofloxacin	Ditiazem	Morphine	
	Mibefradil	Pentazocine	
Antiemetic		Methadone	
Ondansetron	**Cardiac drugs/Antiarrhythmics**	Asimadoline	
	Digotoxin	Fentanyl	
Antitumor Agents	Digoxin		
Paclitaxel		**Steroids**	
Doxorubicin	**Histamine H1, receptor antagonists**	Dexametasone	
Daunorubicin	Fexofenadine	Methulprednisolone	
Vinblastine	Terfenadine	Aldosterone	
Vincristine		Progesterone	
Actinomycin D	**HIV Proteases Inhibitors**	Hydrocortisone	
Docetaxel	Amprenavir	Cortisol	
Etoposide	Indinavir	Corticosterone	
Imatinib	Nelfinavir		
Teniposide	Saquinavir	**Others**	
	Ritonavir	Colchicine	
		Itraconazole	
		Phenothiazines	
		Ivermectin	

FROMM, 2004). It suggests that P-gp in the epithelium of the gut wall determines the plasma concentration of orally administered drugs (MIZUNO et al., 2003). According to JONKER et al. (1999), besides diminishes the oral bioavailability in the intestine, MDR1 P-gp increases drug elimination into bile and urine. In dogs, the role of P-gp related with oral drug administration still under investigation (MEALEY, 2004; FROMM, 2004).

Nowadays, P-gp is also recognized as an important component of the blood-brain barrier limiting entry and accumulation of many compounds into the brain (LOTSCH, 2001; DAGENAIS et al., 2004; SCHINCKEL et al., 1994) and contributing to the protective function of the central nervous system (XIE et al., 1999; MIZUNO et al., 2003).

Maternal fetal interface (placenta) is another important blood-tissue barrier that expresses P-gp among multiple drug transporters, which also contributes to protecting the fetus from unintentional exposure of the mother to xenobiotics or a required drug therapy during pregnancy (FROMM, 2004).

P-glycoprotein encoded in MDR1 gene has already been identified in mouse, rat, bovine, dogs, monkeys, rodents, dogs, and human genomes (THOMPSON, 2000; BRADY et al., 2002).

The extensive overlap in the substrate specificities and tissue localization of P-gp and the major oxidative drug metabolizing enzyme in the intestine cytochrome P450 3A4 (CYP3A4) has lead to the hypothesis that these two proteins work together to protect the body from absorption of harmful xenobiotics, acting synergistically in the small intestine (BOUER et al., 1999; CUMMINS et al., 2003; MIZUNO et al., 2003; MARZOLINI et al., 2004; MEALEY, 2004). There are clearly evidences that within small intestine, this P-gp is maximally expressed in the epithelial cells of the ileum (HO et al., 2003). P-gp controls the access of drugs to the metabolizing enzyme and results in increased metabolism from prolonged exposure to the enzyme through repeated cycles of absorption and efflux (CUMMINS et al., 2003).

In human beings, the main limiting factor to oral bioavailability is the metabolism by CYP3A4 in the

small intestine accompanied by P-gp mediated efflux (MIZUNO et al., 2003).

Reports relate that pharmacological inhibition of P-gp function in mice, people, and dogs drastically improves oral bioavailability of P-gp substrate drugs. The inhibition of P-gp/CYP3A4 system was shown using ketoconazole to increase oral bioavailability of cyclosporine (MEALEY, 2004).

Clinical and therapeutic implications and relevance

Since the MDR1 gene and P-gp were proved to induce drug resistance in certain tumors, pharmacogenetics concepts has had a significant impact on individual response of drugs treatment and genotyping has been considered a new tool for predicting individual drug-metabolizing capabilities and therapeutic establishment (IERI et al., 2004).

Although different factors may influence inter-individual variability in pharmacokinetics and pharmacodynamics of drugs, the expression and influence of MDR1 gene and P-gp as a principal determinant are supported by *in vitro* and *in vivo* studies to explain interspecies variability in certain drug dose-effect relationship.

Several studies with mice disruption demonstrated the relevance of P-gp on pharmacokinetic and drug disposition of drugs as verapamil, vinblastine, cyclosporine A, digoxin, opioids, and dopamine antagonists (COLLAGHAN & RIORDAN, 1993; SPARREBOOM, et al., 1997; BOUER et al., 1999; SCHINKEL et al., 1994/1996). Despite of the absence or lack of P-gp had been correlated with no phenotypic abnormalities and remained fertile in mice (SCHINKEL et al., 1996), MDR1 (-/-) knockout mice had increased blood-brain barrier penetration and increased intestinal absorption or reduced drug elimination through the liver, kidney for a large variety of drugs tested (SPARREBOOM et al., 1997; GEYER et al., 2005), becoming MDR1 (-/-) and (+/+) mice, a good model system to evaluate the P-gp function (SCHINKEL et al., 1994, 1996).

Since PULLIAM et al. (1985) discovered the particular increased penetration of ivermectin through the blood-brain barrier resulting in 31-fold higher concentration of the drug in the brain than in the plasma, it has been established in the literature that Collie is an "ivermectin-sensitive" breed leading to the hypothesis that this subpopulation has altered MDR1 gene expression compared with unaffected dogs. In 1997, LANKAS et al. demonstrated that mouse strain naturally deficient in MDR1 gene was also extremely sensitive to the neurotoxic effects of ivermectin, resulting in higher brain accumulation of this drug.

MDR1 gene and P-gp studies have been developed to show the P-gp-drugs interaction (THOMPSON et al., 2000; WANDEL et al., 2002) and also to find a way to modulate these gene and protein and improve the treatment efficacy (MICKISCH et al., 1991; LIGHT et al., 1996; PLEBAN & ECLER, 2005). P-glycoprotein over expression is considered the predominant mechanism responsible for development of multi-drug resistance in tumor therapy (MICKISCH et al., 1991; LIGHT et al., 1996; PLEBAN & ECLER, 2005). P-glycoprotein inhibition cyclosporine induced showed to enhance paclitaxel (Taxol) oral bioavailability, an excellent P-gp substrate and a drug for treatment of cancer, in MDR1 (-/-) mice and humans (SPARREBOOM et al., 1997; MARZOLINI et al., 2004). The non-competitive digoxin-verapamil interaction was reported to increase digoxin plasma concentration by 40% in humans due to verapamil interacts with P-gp as a modulator, resulting in intestinal, liver, and kidney P-gp inhibition (VERSCHRAAGEN et al., 1999).

According to SADEQUE et al. (2000), loperamide was the first opioid evidenced to be a P-gp substrate in humans. Usually, this drug does not induce central nervous system effects when administered at anti-diarrhea doses because it is efficiently excluded from the brain by P-gp. Increased entry of loperamide into the central nervous system was demonstrated after inhibition of P-gp using quinidine. Quinidine also increased the absorption and plasma concentrations of oral morphine with concomitant increase on clinical effects in humans (KHARASCH et al., 2003). Methadone is another opiate drug suggested to be a substrate of the efflux pump P-gp (BOUER et al., 1999). In rat model, it was related the oral methadone potency increased three fold with the presence of P-gp inhibitor (RODRIGUEZ et al., 2004).

Differently from human beings, there is no information available on the literature regarding the effect of P-gp on oral drug bioavailability, especially in horses.

Several studies aimed to modulate MDR1 gene and P-gp expression to improve the effects of some drugs, increasing the efficacy of treatments of certain diseases (MICKISCH et al., 1991). For example, cyclosporine A, a P-gp modulator, has shown clinical efficacy in acute myeloid leukemia (QUADIR, et al., 2005).

Modulation of P-gp can affect drug bioavailability, increase or decrease penetration of its substrates into the central nervous system, and affect the therapeutic efficacy (MIZUNO et al., 2003; DAGENAIS et al., 2004; WANG et al., 2004). Some researchers have been used foods besides drugs, to

inhibit P-gp and subsequently enhance drug intestinal absorption (HO et al., 2003). Flavonoids and coumarins of naturally occurrence in fruits, vegetables, and herbs have been implicated in significant drug-food interactions due to appear to modulate P-gp activity (SUN et al., 2004).

Recently P-gp expression or inhibition has been related with certain diseases in human and animals increasing the susceptibility for them. An important disease greatly discussed is the viral immunodeficiency syndrome (HIV) and seems that the expression of P-gp limits the intestinal absorption of HIV protease inhibitors and the access to the brain, contributing to virus persistence (CHOO et al., 2000).

However, some MDR1 gene polymorphisms described in human beings have been related with drug pharmacokinetics alteration and also with increased susceptibility to diseases such as Parkinson's disease, inflammatory bowel disease, multi-drug resistant epilepsy, and renal carcinoma (MEALEY, 2004). Recent literature relates links between MDR1 gene polymorphisms and Crohn's Disease, and Ulcerative Colitis in humans (WILK et al., 2005). The development of spontaneous colitis in genetically engineered MDR1a (-/-) mice at around 12 weeks of age reported in a study suggested that reduced MDR1 gene expression or activity in intestinal epithelial cells may be a factor in the pathogenesis of inflammatory bowel disease (HO et al., 2003; WILK et al., 2005). It is hypothesized that P-gp deficient increase the exposure of tissues and organs to potentially toxic xenobiotics. According to several studies in herding breeds dogs including Collies and Australian shepherds, MDR1 gene polymorphism is the cause of their ivermectin sensitivity. In rodent models data suggest that P-gp may also play a role in regulating the hypothalamic-pituitary-adrenal axis (MEALEY, 2004).

Further studies are needed to understand and determine the influence of P-glycoprotein and drug interactions on oral drug disposition and brain access, besides to explain the relation between P-gp and certain diseases. The knowledge about P-gp functionality is important for the success of several clinical treatments (HENDRIKSE & VAALBURG, 2002).

CONCLUSION

P-glycoprotein (P-gp) is encoded by the multi-drug resistance (MDR1) gene that influences drug pharmacokinetic and pharmacodynamic. The presence of P-gp in the blood-brain barrier and intestine actively pumps drugs out of the central nervous system and the intestinal tract, and also limits gastrointestinal absorption of substrate drugs. Blockage of P-gp allows for enhancing central nervous system entry of some drugs and increases oral bioavailability offering new possibilities to explain the efficacy of some drugs, and the pathophysiology of several diseases related to the absence of the MDR1 gene expression. The authors suggest that the MDR1 gene and the P-gp should be studied in different species and a relationship between the protein presence or absence and the pharmacology of therapeutic drugs should be determined.

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