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Cardiovascular Ion Channel Inhibitor Drug-Drug Interactions with P-glycoprotein

Kaitlyn V. Ledwitch[1] and **Arthur G. Roberts**[1,2,3]

[1]University of Georgia, Department of Pharmaceutical and Biomedical Sciences, 240 W. Green St., Athens, GA 30602

Abstract

P-glycoprotein (Pgp) is an ATP-binding cassette (ABC) transporter that plays a major role in cardiovascular drug disposition by effluxing a chemically and structurally diverse range of cardiovascular therapeutics. Unfortunately, drug-drug interactions (DDIs) with the transporter have become a major roadblock to effective cardiovascular drug administration because they can cause adverse drug reactions (ADRs) or reduce the efficacy of drugs. Cardiovascular ion channel inhibitors are particularly susceptible to DDIs and ADRs with Pgp because they often have low therapeutic indexes and are commonly coadministered with other drugs that are also Pgp substrates. DDIs from cardiovascular ion channel inhibitors with the transporter occur because of inhibition or induction of the transporter and the transporter's tissue and cellular localization. Inhibiting Pgp can increase absorption and reduce excretion of drugs, leading to elevated drug plasma concentrations and drug toxicity. In contrast, inducing Pgp can have the opposite effect by reducing the drug plasma concentration and its efficacy. A number of *in vitro* and *in vivo* studies have already demonstrated DDIs from several cardiovascular ion channel inhibitors with human Pgp and its animal analogs, including verapamil, digoxin and amiodarone. In this review, Pgp-mediated DDIs and their effects on pharmacokinetics for different categories of cardiovascular ion channel inhibitors are discussed. This information is essential for improving pharmacokinetic predictions of cardiovascular therapeutics, for safer cardiovascular drug administration and for mitigating ADRs emanating from Pgp.

Keywords

P-glycoprotein; drug-drug interactions; cardiovascular drugs; ion channel inhibitors; pharmacokinetics

INTRODUCTION

Cardiovascular drug prescriptions have significantly increased over the past decade with over 15% of patients on multidrug regimens (a.k.a. polypharmacy) (1). Of hospitalized patients on cardiovascular medications, ~4% exhibited serious adverse drug reactions

[3]To whom correspondence should be addressed. audie@uga.edu.

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(ADRs) (2). Cardiovascular ion channel inhibitors, which are used to treat cardiac arrhythmia and hypertension, represent a major contributor of cardiovascular drug ADRs (3, 4). These drugs target channels and enzymes that control the flow of ions in vascular smooth muscle cells and the cardiomyocytes (3). This serves to regulate cardiac inotropy, maintain the resting potential of cardiovascular cells and control blood pressure (3). Unfortunately, many of these drugs such as digoxin have a low therapeutic index, so any changes to their plasma concentration can potentially lead to ADRs (3). Many cardiovascular drug fatalities from ADRs are the result of drug-drug interactions (DDIs) with cardiovascular ion channel inhibitors (5–7). In one study the cardiovascular ion channel inhibitor digoxin was implicated in a majority of preventable DDIs (6). In another study, the cardiovascular ion channel inhibitor amiodarone, which is known to have several significant DDIs, had the second highest frequency of ADRs (7).

One of the main contributors to cardiovascular ion channel inhibitor DDIs and ADRs is the ATP-binding cassette (ABC) P-glycoprotein (Pgp) transporter (8). In general, Pgp is a promiscuous drug transporter that can bind multiple drugs simultaneously (9), which includes interactions with a chemically and structurally diverse range of cardiovascular drugs (10, 11). These interactions in combination with the narrow therapeutic indexes makes Pgp particularly susceptible to cardiovascular DDIs. The transporter is also prone to DDIs because of its function in absorption, elimination and distribution of drugs (11). This function leads to changes in cardiovascular ion inhibitor drug plasma concentrations and results in ADRs or reduced drug efficacy (9).

A general overview of cardiovascular drugs and Pgp was published (11), but no recent comprehensive review has been published that discusses Pgp-mediated DDIs from cardiovascular ion channel inhibitors and their clinical consequences. This review discusses a wider range of cardiovascular ion channel inhibitors and provides a more detailed analysis of the observed pharmacokinetics than (11). This review also describes the pharmacodynamics of cardiovascular ion channel inhibitors including their targets and mechanisms of action. Then we discuss Pgp-mediated transport of the cardiovascular ion channel inhibitor and DDIs observed with the drug. This is followed by a discussion and comments on the observed pharmacokinetics of coadministering the drug.

1. CARDIOVASCULAR DISEASES (CVD) AND CURRENT TREATMENTS

Cardiovascular disease (CVD) is a leading cause of death worldwide (12). CVD represents a class of diseases of the vascular system that can involve blood vessels such as coronary artery disease and stroke, or the heart, which includes congestive heart failure and hypertension (12). A number of treatments have been developed to treat CVD that target receptors, channels and enzymes of the cardiovascular system (13–19). Since hypertension represents a major risk factor for several diseases within CVD (20), several drug classes have been developed to lower blood pressure (e.g. 13). Some of the most effective treatments for hypertension have targeted the angiotensin-renin-aldosterone system, which is the signaling pathway for regulating blood pressure and fluid balance (13). There are also antihypertensive drugs that target the α and β adrenergic receptors that affect the action of catecholamines, norepinephrine and epinephrine (14–16). Loop diuretics represent a third

class of antihypertensive drug that reduce blood pressure by decreasing fluid volume as a result of inhibiting the Na^+-K^+-$2Cl^-$ symporter in the kidneys (21). To treat strokes, cardiovascular drugs have been designed to reduce blood clotting by targeting proteins within the coagulation cascade or involved in platelet aggregation (17). High cholesterol, which represents a major risk factor for CVD, is most often treated with statin drugs (18). These drugs lower high cholesterol by targeting 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase, which is the rate-limiting enzyme in cholesterol biosynthesis (18). The cardiovascular drugs that are the focus of this review are cardiovascular ion channel inhibitors. These drugs are used to treat a range of diseases within CVD, including hypertension, cardiac dysrhythmias and atrial fibrillation (19). These drugs affect vascular physiology by directly inhibiting the flow of ions through Ca^{2+}, K^+ or Na^+ channels or indirectly by increasing intracellular Ca^{2+} concentration through inhibition of the Na^+/K^+ ATPase (19). In addition to the reviewed drugs, there are emerging therapies for CVD that target chemokines, high density lipoproteins and microRNA and there has been some progress towards the actual regeneration of cardiomyocytes (22).

2. CARDIOVASCULAR ION CHANNELS

Cardiovascular ion channels control the flow of ions and function to regulate the heart rhythm and blood pressure (23, 24). They are found in cardiomyocytes of the heart and vascular smooth muscle cells of the arteries and veins where heterogeneous expression of these channels promotes proper heart rhythms and blood pressure (23, 24). Mutations in genes that code for the ion channels or alterations in their expression level leads to inherited or acquired cardiac arrhythmia (23). Table 1 shows several types of cardiovascular ion channels, including Ca^{2+}, Na^+ and K^+ channels. The table also shows the channel isoforms, their general functions and cardiovascular diseases associated with them.

Calcium Channels

Cardiovascular Ca^{2+} channels are voltage-dependent channels that control the flux of Ca^{2+} into vascular smooth muscle cells and cardiomyocytes (25). Inward flux of Ca^{2+} ions by the channel triggers additional Ca^{2+} release from the sarcoplasmic reticulum (25). Calcium binds and induces a conformational change in the troponin-tropomyosin complex that facilitates interaction between the actin filament and myosin, and leads to a muscle contraction (25). There are two types of cardiovascular Ca^{2+} channels, long-lasting (L)-type and transient (T)-type Ca^{2+} channels, that activate the inward flux of Ca^{2+} ions through relatively high and low voltage potentials, respectively (25). The L-type Ca^{2+} channels function to excite and contract muscle cells, while T-type Ca^{2+} channels serve a cardiac pacemaking function and regulate arterial resistance (25). Defects in the ion channel have been associated with various cardiovascular disorders, including arrhythmias and hypertension (26)

Potassium Channels

Potassium ion transport by these proteins is accomplished by several mechanisms including Ca^{2+} activation, voltage and ATP (27). These channels are a major regulator of vascular smooth muscle cell voltage and resting potential (27). The channels also function to regulate

the duration of the action potential in the cardiac muscle (27). Abnormal functioning of this channel has been associated with hypertension and Brugada syndrome, which leads to increased risk of cardiac death (26, 27).

Sodium Channels

Voltage-gated sodium channels (Na_V) control the Na^+ ion flux through Na^+– induced conformational changes (28). In the heart, influx by these channels is responsible for the initial fast upstroke of the cardiac action potential (28). There is also recent evidence that these channels contribute to the contractile response of vascular smooth muscle cells (29). Defects in this channel are associated with a number of cardiomyopathies including long QT syndrome (26, 28).

Na^+/K^+ ATPase

This ATP-dependent enzyme effluxes Na^+ ions out, while pumping K^+ ions into cardiovascular cells (30). The enzymes help maintain the resting potential and cell volume through osmosis, and indirectly decrease intracellular Ca^{2+} concentration through the Na^+/Ca^{2+} exchanger (30). Defects in the energy-dependent transporter are associated with heart failure and atrial fibrillation (30).

3. ION CHANNEL INHIBITORS AND THEIR MECHANISMS OF ACTION

Ion channel inhibitors are used to redistribute ions and restore the natural rhythm of the heart by inhibiting specific channels and transporters of the cardiovascular system (23). These inhibitors can be classified as calcium, sodium, or potassium channel inhibitors and cardiac glycosides, but may fit into multiple ion channel inhibitor categories and may have an array of electrophysiological actions (31). For example, the antiarrhythmic drug quinidine is a well-known sodium channel blocker, but it also exerts action against potassium channels and α-adrenergic receptors (31). For simplicity, ion channel inhibitors in this review will be discussed according to their main site of action. Table 2 summarizes the general categories of cardiovascular inhibitors, their mechanism of action, clinical uses and ADRs.

Calcium Channel Inhibitors

These drugs are used to treat a range of cardiovascular disorders including hypertension and arrhythmias (32, 33). Calcium channel inhibitors (or blockers) disrupt the flow of L- and/or T-type Ca^{2+} channels (19, 32, 33). This disruption increases the intracellular Ca^{2+} concentration in vascular smooth muscle cells and cardiomyocytes, which leads to vasodilation and promotes a regular heart rhythm (32, 33). ADRs from toxic concentrations of calcium channel inhibitors result in bradycardia (abnormally slow heart rate) and hypotension that can lead to serious complications including death (32, 33).

Potassium Channel Inhibitors

Potassium channel inhibitors prolong repolarization and the action potential duration in cardiomyocytes by interfering with conduction through potassium channels (19, 34). In general, these inhibitors are used to treat cardiomyopathy and atrial fibrillation (19, 34). They have also been used to treat ventricular and tachycardia during cardiac arrest (34).

These drugs exhibit a range of ADRs including worsening arrhythmias, blue-gray hyperpigmentation and sudden cardiac arrest (35).

Sodium Channel Inhibitors

Sodium channel blockers are used to suppress heart tachycardias and atrial flutter by decreasing the flow of Na^+ ions through the sodium channel and reducing the action potential duration (31). Reduction of Na^+ ion flow by these inhibitors is accomplished by stabilizing the inactivated state of the Na^+ channel through fast and slow mechanisms (31). ADRs from these inhibitors include bradyarrhythmias (slowed heart rate) and slow atrial flutter (31).

Cardiac Glycosides

Cardiac glycosides are a special type of ion channel inhibitor and include digitalis glycosides such as digoxin, digitoxin and ouabain (36). Clinically, these drugs are used to treat atrial fibrillation and flutter, and some cases of heart failure (37, 38). These drugs target the Na^+/K^+ ATPase in the heart, which indirectly increases intracellular Ca^{2+} concentration by the effect of decreasing intracellular Na^+ levels on the sodium-calcium exchanger (36). The increase in intracellular Ca^{2+} corresponds with an increase in inotropy or force of contraction of the heart (36). In addition to cardiovascular ADRs, gastrointestinal and neuropsychological disorders are commonly observed with this class of drug (37, 38).

4. CHARACTERISTICS OF PGP AND ITS EFFECTS ON ION CHANNEL INHIBITOR DISPOSITION

Pgp is a member of the ATP-binding cassette (ABC) transporter superfamily and can efflux a chemically and structurally diverse range of molecules (10, 11). Fig. 1A shows the X-ray crystal structure of mouse Pgp, which consists of two nucleotide-binding domains (NBDs), 12 transmembrane (TM) helices and a large 6000 $Å^3$ drug binding cavity (8). Fig. 1B shows the generally accepted model for ATP-driven drug efflux by Pgp. The left side of the panel depicts drugs binding to Pgp from the cell membrane or the cytosol within the TM region of Pgp with the NBDs separated (8, 39). The binding of two ATP molecules shifts the NBDs together (right side of Fig. 1B) and releases the drug to the extracellular side of the membrane (8, 39). ATP is hydrolyzed into ADP and inorganic phosphate (P_i) resetting the NBDs back to their initial conformation for another round of drug binding and transport (left side of Fig. 1B) (8, 39).

Pgp plays a key role in cardiovascular ion channel inhibitor DDIs by altering drug plasma concentrations and distribution, and by its cellular localization and expression levels. The transporter is found at relatively high concentrations on the lumenal side of enterocytes and reduces oral absorption and bioavailability by effluxing drugs back into the intestinal lumen (Fig. 2A) (40). The transporter is also found at relatively high concentrations on the lumenal side of kidney proximal tubule cells and the bile canalicular surface of hepatocytes decreasing drug plasma concentrations by excretion (Fig. 2B and 2C) (40). Pgp also affects drug distribution. Pgp is found on the blood side of epithelial cells located at the blood brain barrier (BBB) and reduces brain penetration of cardiovascular drugs (Fig. 2D) (40). Pgp is

also present on the maternal side of placental trophoblasts preventing entry of cardiovascular drugs and protecting the unborn fetus (Fig. 2E) (41). Although there is Pgp present in the heart, it has little effect on drug disposition because of its relatively low concentration (42). Moreover, Pgp expression levels in all of these tissues can be influenced by genetic polymorphisms of Pgp, cardiomyopathy and different stages of pregnancy (43–45).

Pgp-mediated DDIs result in significant changes in the drug pharmacokinetics by the inhibition or induction of the transporter. Inhibition of intestinal Pgp is saturable and will lead to an increase in oral absorption of Pgp substrates, while inhibition of excretory cells in the kidneys and the liver will reduce the clearance and increase the terminal elimination half-life ($t_{1/2}$) of Pgp substrates (46). The combined inhibition will result in a net increase in the drug plasma concentration, and will lead to an increase in the peak drug plasma concentration (C_{max}) and the individual's exposure as reflected by the area under the curve (AUC) in the pharmacokinetics profile (46). This is particularly problematic for several cardiovascular ion channel inhibitors because of their relatively low therapeutic indexes and because elevated drug plasma concentration can lead to toxic drug plasma concentrations and serious ADRs (47). Inhibition of Pgp at the BBB or in the placental trophoblasts potentially increases penetration and toxic exposure to the brain and fetus, respectively (46). Pgp inhibition there can lead to changes in the drug's distribution, which is reflected in the apparent volume of distribution (V_D) (46). Induction of Pgp will have the opposite effect of Pgp inhibition by decreasing the drug plasma concentration and exposure, but might also significantly reduce a drugs' efficacy. This will lead to a decrease in the C_{max} and AUC in the pharmacokinetics profile (46). Pregnancy, age, sex and disease can also contribute to the pharmacokinetics and the clinically-observed DDIs (48).

5. *IN VITRO* ION CHANNEL INHIBITOR DDIs WITH PGP AND THE CORRESPONDING CLINICAL OBSERVATIONS

A number of *in vitro* studies have demonstrated that several cardiovascular ion channel inhibitors are substrates of and exhibit DDIs with Pgp. In some cases, the observed pharmacokinetics with the cardiovascular ion channel inhibitors seem to correlate with *in vitro* studies implying the involvement of Pgp. In other cases, the *in vitro* Pgp and the pharmacokinetics seem to contradict. In this section, *in vitro* DDI studies with Pgp and specific ion channel inhibitors are discussed and compared to the observed pharmacokinetics. The pharmacokinetic details associated with each DDI are summarized in Table 3.

Amiodarone and Dronedarone

Amiodarone and dronedarone are potassium channel blockers used to treat cardiac dysrhythmias (49). Amiodarone is converted into the active metabolite monodesethyl-amiodarone (DEA) by cytochromes P450 in the liver (50). There is currently no evidence that amiodarone or dronedarone are actually transported by Pgp, but DEA was weakly transported by human Pgp in Caco-2 cells with an efflux ratio of 1.6 (51). These drugs are particularly prone to Pgp-mediated DDIs because of their unusually long elimination $t_{1/2}$ (52, 53). While dronedarone has a $t_{1/2}$ of ~24 hours (53), which is long by most standards,

amiodarone and DEA have $t_{1/2}$ of several days to over a month due to accumulation in adipose tissue (52, 54).

In vitro cell studies with porcine kidney epithelial cells overexpressing human Pgp have shown that both amiodarone and DEA inhibit transport of digoxin and the anticancer drug daunorubicin (55, 56). Amiodarone also inhibited transport of the sodium channel inhibitor flecainide in porcine kidney epithelial cells overexpressing human Pgp and in human intestinal epithelial LS180 cells (57).

These potassium channel inhibitors are also known to exhibit a number of DDIs in the clinic (e.g. 58, 59, 60). The pharmacokinetic consequences of amiodarone-digoxin DDIs have been the most thoroughly evaluated (e.g. 58, 61). Amiodarone causes ~70% increases in the C_{max} and AUC of digoxin, while there were very little changes in V_D of digoxin and surprisingly no significant decrease in the renal clearance (e.g. 58, 61). The authors explained the lack of renal clearance to an increase in intestinal absorption and a decrease in extrarenal clearance (58) implying the preferential inhibition of Pgp in the intestines and liver. Amiodarone also showed very strong DDIs with the related cardiac glycoside digitoxin leading to drug toxicity in several cases (62). Amiodarone was also found to increase the oral bioavailability of the anticoagulants, dabigatran, rivaroxaban and apixaban by ~10% through inhibition of intestinal Pgp (60, 63). In contrast, dronedarone showed even stronger DDIs with digoxin than amiodarone (59). The AUC of digoxin was almost 2-fold higher with dronedarone and there was a 60% decrease in renal clearance (59).

Amlodipine, Nicardipine and Nifedipine

The dihydropyridine drugs amlodipine, nicardipine and nifedipine are typically used in the treatment of hypertension and target the L-type Ca^{2+} channels (32). At pH 7.4, the drugs were Pgp ligands, but were not transported by Pgp (64, 65). At pH 6.5, amlodipine was efficiently transported by Pgp with an efflux ratio of ~10 (65), but it is unknown if nicardipine or nifedipine are also transported under these conditions. Digoxin transport by Pgp was inhibited by submicromolar concentrations of nifedipine and nicardipine (61). In the clinic, coadministration of nifedipine and digoxin lead to an increases in the C_{max} and AUC in patients of 5% and 21%, respectively (61). DDIs from the coadministration of digoxin and nicardipine had a similar increase in C_{max}, but the increase in the AUC was only ~6% (61). In contrast, despite its molecular similarity to nicardipine and amlodipine, amlodipine did not show significant clinical DDIs with digoxin (66). However, amlodipine did show clinical DDIs with simvastatin, which is a recognized Pgp substrate (67), with significant increases in the C_{max} and AUC of simvastatin from 9.6 to 13.7 ng/ml and 34.3 to 43.9 ng • h/ml, respectively (68).

Digoxin

Digoxin is the most commonly prescribed cardiac glycoside and inhibits the Na^+/K^+ ATPase (47). The drug is primarily eliminated through the kidneys unmetabolized (38). Several *in vitro* studies with cells that express human Pgp have shown that digoxin is a good substrate for the transporter (e.g. 69, 70, 71). Because of digoxin's low therapeutic index, the drug is administered at doses that it is unlikely to affect pharmacokinetic parameters of other drugs

in the clinic (38). For example, digoxin only had minimal effects on the exposure of oral anticoagulant edoxaban (72). However, one study did find that the drug did increase the elimination $t_{1/2}$ by ~20% and decreased renal clearance of quinidine at elevated doses, although digoxin's affect on the *AUC* of quinidine was not statistically significant (73).

Therefore, most *in vitro* and *in vivo* studies have focused on inhibition of digoxin transport, which are known to occur with a number of Pgp ligands (61). *In vivo*, Pgp transport inhibition typically leads to significant increases in the *AUC*, C_{max}, $t_{1/2}$ and decreases in renal and extrarenal clearance of digoxin (61). Inhibition of intestinal Pgp often leads to increased oral absorption and bioavailability of the drug (61). Because Pgp is found at relatively high concentrations at the BBB (40), one might expect the V_D of digoxin would increase significantly as well. In knockout mice lacking mouse Pgp, digoxin concentrations in the brain increased almost 30-fold versus wild type mice (74). Instead, the V_D of digoxin often decreases in the presence of another drug (e.g. 75). One possibility is that Pgp inhibition at the BBB can be compensated by alternate efflux transporters including several isoforms of the multidrug resistance-associated protein (MRP) and the breast cancer resistance protein (BCRP) (76). This hypothesis is supported by that fact that digoxin is also a substrate for MRP2 (77). To complicate the digoxin pharmacokinetics further, digoxin can induce Pgp (78), which explains why Pgp-mediated DDIs between verapamil and digoxin were reduced after long-term coadministration (79).

Digitalis-related molecules

Digitalis-related molecules are functionally and structurally similar to digoxin (36), and include digitoxin, bufalin and strophanthidin. These molecules are generally good substrates of human Pgp like digoxin (80, 81). Digitoxin and bufalin both inhibited digoxin transport in Caco-2 cells containing human Pgp (71). Digitoxin also inhibited Pgp-mediated secretion of quinidine in the rat small intestine (82).

Diltiazem

Diltiazem is a benzothiazepine drug that targets L-type Ca^{2+} channels and is used in the treatment of hypertension and certain types of arrhythmia (32). The drug is known to be a relatively weak substrate of the transporter with an efflux ratio of 1.64 (64). Studies showed that diltiazem inhibited both quinidine and digoxin transport (61, 82). In the clinic, coadministration of diltiazem and digoxin to patients moderately increased the C_{max} and *AUC* by about 30% (61).

Flecainide

Flecainide is an antiarrhythmic agent that specifically inhibits the $Na_V1.5$ Na^+ channel, which affect the fast depolarization phase of the cardiac action potential (31, 83). *In vitro* studies have shown that it is transported by Pgp with an efflux ratio of ~2 (57) and a clinical study showed that it increased blood plasma concentrations of digoxin by ~20% (84).

Mibefradil

Mibefradil is a non-specific inhibitor of both L- and T-type voltage-gated Ca^{2+} channels (85). The drug was weakly transported by Pgp in porcine kidney epithelial cells

overexpressing the human and mouse Pgp (86). The drug appears to inhibit digoxin transport in human Pgp containing Caco-2 cells with low micromolar potency (61). In the clinic, the drug increases the C_{max} and AUC of digoxin by 41 and 31%, respectively (61). The drug also shows strong Pgp-mediated DDIs with the cholesterol-lowering drug atorvastatin with a 4-fold increase in the AUC from 134 to 594 ng • h/ml when coadministered with mibefradil (87, 88).

Ouabain

Ouabain functions like other digitalis drugs (36) and is similar in structure to it, but only has a single sugar functional group rather than three. No Pgp-mediated transport of ouabain has been observed with mammalian cells expressing human Pgp (80, 81). Ouabain also did not inhibit digoxin in human epithelial Caco-2 cells (71). However, Pgp-mediated DDIs with this drug may occur indirectly through induction of the transporter (78).

Phenytoin

Phenytoin a sodium channel inhibitor that is used to treat abnormal heart rhythms and used as an alternative to digoxin (89). *In vitro* studies with human Pgp overexpressing cell lines and the drug have shown that it ranges from being a non-substrate to a substrate (c.f. 90, 91). *In vivo*, the drug has been shown to be a Pgp substrate with rats using Pgp-specific inhibitors (92). The drug inhibits transport of the anti-cancer drug paclitaxel in bovine retinal endothelial cells (93). However, in the clinic, phenytoin-paclitaxel interactions do not appear to result from Pgp-mediated DDIs, but from cytochrome P450-mediated DDIs due to cytochrome P450 induction (94, 95). Coadministration of this drug with digoxin in patients decreased the AUC and increased in the total clearance of digoxin around 20–30%, but no significant effects on the volume distribution or the renal clearance of digoxin was observed (96). This pharmacokinetic outcome is also consistent with cytochrome P450-mediated DDIs.

Quinidine

The sodium channel inhibitor quinidine is a stereoisomer of the anti-malarial drug quinine (31). *In vitro* and *in vivo* studies have demonstrated that this drug is a good substrate for Pgp (97). Quinidine is known to inhibit transport of several Pgp substrates (e.g. 57, 69). Several *in vitro* studies with cells expressing human Pgp have demonstrated that quinidine inhibits digoxin transport (61). In the clinic, coadministration of digoxin with quinidine decreased the terminal elimination $t_{1/2}$, total and renal clearance, and the V_D of digoxin in patients, while increasing its absorption and bioavailability (61, 98, 99). In mammalian cells expressing Pgp, quinidine inhibited transport of the sodium channel inhibitor flecainide (57). In the clinic, quinidine reduced the renal clearance of flecainide from 10.6 to 8.1 ml/min/kg (100). Quinidine also increased the AUC and C_{max} of the oral anticoagulant edoxaban from 1577 to 2575 ng • h/ml and 223 to 390 ng/ml, respectively (72), and increased the oral bioavailability of methadone and fentanyl (101, 102). In addition to Pgp inhibition, quinidine also exhibits DDIs through Pgp induction (70).

6. CURRENT STRATEGIES FOR OVERCOMING PGP-MEDIATED DDIs IN THE CLINIC

In the clinic, finding alternative drug combinations to avoid DDIs all together is the most preferable strategy. For example, one can administer mibefradil and pravastatin, which does not elicit Pgp-mediated DDIs, instead of mibefradil and atorvastatin (87, 103). In many cases, this approach may not always be feasible, so methods have been developed to minimize ADR from DDIs.

The first step to minimize Pgp-mediated DDIs is to identify drugs that are known to exhibit DDIs (48, 104). For drugs that are coadministered, low therapeutic index drugs can be administered at subtherapeutic doses and the pharmacodynamic response monitored to minimize the risk of ADRs from DDIs (48, 104). Therapeutic drug monitoring (TDM) is another method to minimize ADRs from DDIs (104). In the method, the drug plasma concentration is measured directly in the blood or indirectly through biological fluids and correlated to a pharmacodynamic endpoint such as blood pressure (104). Although less common, another approach is to give a digitalizing dose, which is a series of small doses to control and achieve a therapeutic concentration and avoid ADRs (48).

Cardiovascular ion channel inhibitor DDIs and their observed pharmacokinetics discussed in the review are summarized in Table 3. The first column shows the name of the drug, while the next columns identify substrates, inhibitors and inducers of Pgp. Since many ion channel inhibitors have DDIs with digoxin (e.g. 61), their effects on digoxin PK parameters are shown in the next column. The penultimate column shows other observed DDIs and the last column are the corresponding references.

Table 3 shows that cardiovascular ion channel inhibitors range from being non-ligands to good substrates for Pgp. Although digoxin is often considered the gold standard for measuring Pgp-mediated DDIs (40), drugs with very similar molecular structures can have dramatically different inhibitory potency to digoxin transport such as nifedipine and amlodipine (61, 64, 66). Some of the drugs are also Pgp inducers (70, 78). In the clinic, cardiovascular ion channel inhibitors show a large range of effects on digoxin pharmacokinetics. Large increases in digoxin exposure and drug plasma concentration are observed in the presence of dronedarone (59), while decreases in digoxin plasma concentration are observed in the presence of phenytoin (96). Unfortunately, *in vitro* Pgp-mediated inhibition of digoxin transport and the observed pharmacokinetics are not well correlated. For example, despite being potent inhibitors of digoxin *in vitro*, nicardipine and nifedipine had relatively modest effects of digoxin pharmacokinetics *in vivo* (61, 64). The most studied cardiovascular ion channel inhibitors, digoxin, amiodarone and verapamil, are known to exhibit DDIs with several Pgp ligands. On the other hand, only a few Pgp-mediated DDIs have been noted in the literature with the other drugs, and this reflects a significant gap in our understanding of Pgp-mediated DDIs. Bridging this knowledge gap will require additional Pgp DDI studies in the future.

7. CONCLUSIONS AND FUTURE PERSPECTIVES

This review was focused on DDIs-mediated by Pgp, but, in reality, clinically-observed DDIs are multifactorial and reflects the complex interplay between drug metabolizing enzymes and transporters (105). For example, the pharmacokinetics profile from verapamil-quinidine DDIs reflects the combined inhibition of Pgp-mediated transport and drug metabolism by cytochromes P450 (106). Drug metabolites can also contribute significant Pgp-mediated DDIs (105) such as is the case with amiodarone and its metabolite DEA (55, 56). Alternative transporters such as MRP2 can potentially mitigate Pgp-mediated DDIs at the BBB and the placenta by effluxing the same drugs (76, 77, 107, 108). Influx transporters that actively transport Pgp inhibitors, and are found in specific tissues can potentially increase Pgp's sensitivity to inhibitors skewing the pharmacokinetics. For example, amiodarone is a substrate of the organic anionic transporting polypeptide 2B1 (OAT2B1) influx transporter that is found in relatively high concentrations in hepatocytes and intestinal cells, but relatively low concentrations in the kidneys (109, 110). Under these conditions, Pgp will be more sensitive to amiodarone inhibition in hepatocytes and intestinal cells than kidney cells because of the higher intracellular amiodarone concentration mediated by OAT2B1. Under these conditions, we anticipate relatively high intestinal absorption and decreased extrarenal clearance as a result of Pgp inhibition and relatively little effect on renal clearance of Pgp substrates. This is exactly what we observe pharmacokinetically with amiodarone and digoxin (58).

Because of the involvement of alternate transporters and drug metabolizing enzymes in cardiovascular ion channel inhibitor disposition, extrapolating clinically observed DDIs to Pgp-mediated DDIs observed *in vitro* remains a significant challenge (111). To overcome this challenge, future *in vitro* studies with cardiovascular ion channel inhibitors will need to consider contributions from alternate transporters and drug metabolizing enzymes in addition to Pgp.

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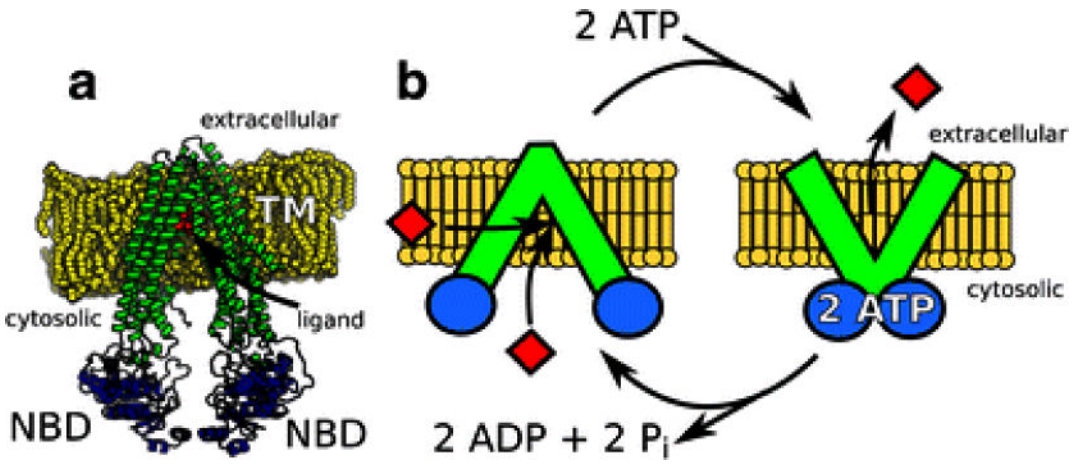

Fig. 1.

Structure and ATP-driven transport mechanism of Pgp. A) The X-ray crystal structure of mouse Pgp showing the transmembrane (TM, green), nucleotide-binding domains (NBDs, blue) and the position of QZ59-RRR, which is labeled “ligand” (red) in a phosphatidylcholine lipid bilayer (yellow) (8). B) Conformationally and ATP-driven model of efflux by Pgp. On the left of the panel, drug binding (red diamonds) occurs with the NBDs of Pgp separated. Binding of 2 ATP causes the NBDs to come together and leads to the release of drug (red diamonds) to the extracellular space. The extracellular and cytosolic sides of the cell membrane (yellow) are shown on the top and bottom of the membrane, respectively.

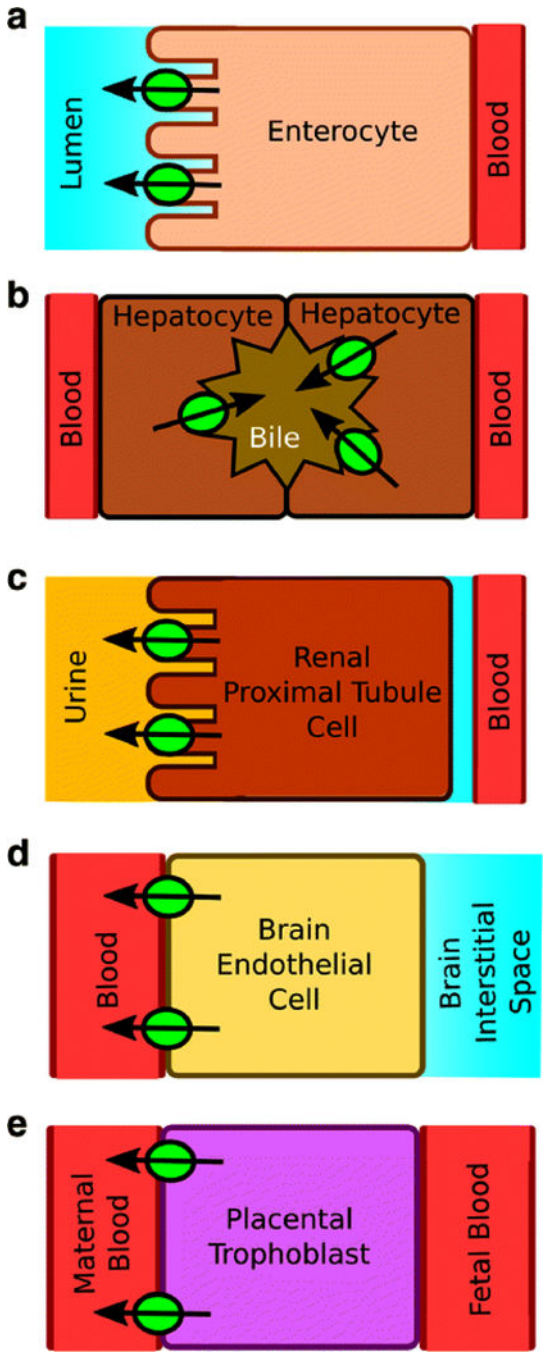

Fig. 2.

Pgp localization in A) an enterocyte, B) a hepatocyte, C) a kidney proximal tubule cell, D) a brain endothelial cell and E) a placental trophoblast. The green circles are Pgp and the arrows denote the direction of efflux.

Table 1

Types and function of cardiovascular ion channels

Ion Channel	Relevant Types	Physiological Function	Associated Cardiovascular Diseases	References
Ca^{2+} channels	• Long-lasting (L-type) • Transient (T-type)	• L-type: excite and contract muscle cells • T-type: cardiac pacemaking function and regulate arterial resistance	arrhythmias, Brugada syndrome, hypertension	(25, 26)
K^+ channels	• Calcium-activated (BK_{Ca}) • Voltage-gated (K_V) • ATP-dependent (K_{ATP}) • Inwardly rectifying (K_{IR})	• Mediate membrane and resting potential • Regulate cardiac action potential	atrial fibrillation, Brugada syndrome, hypertension, long and short QT syndrome	(26, 27)
Na^+ channels	• Voltage-gated (Na_V)	• Initial fast upstroke of the cardiac action potential • Contractile response of vascular smooth muscle cells	atrial standstill, Brugada syndrome, cardiac conduction disorders, dilated cardiomyopathy, erthromelalgia, long QT syndrome, nonprogressive familial heart block	26, 28, 29)
Na^+/K^+ ATPases	• α and β isoforms	• Resting potential, cell volume and $[Ca^{2+}]$	atrial fibrillation, heart failure	(30)

Table 2

Characteristics of cardiovascular ion channel inhibitors

Inhibitor Class	Examples	Mechanism	Clinical Uses	ADRs	References
Ca^{2+} channel inhibitors	amlodipine diltiazem mibefradil nicardipine nifedipine verapamil	Inhibit or interfere with Ca^{2+} influx by binding to specific sites on the channel	angina, arrhythmias, hypertension, coronary artery disease	bradycardia, hypotension	(19, 32, 33)
K^+ channel inhibitors	amiodarone dronedarone	Interfere with K^+ ion flow	cardiomyopathy, atrial fibrillation and flutter	arrhythmias, blue-gray hyperpigmentation, hepatotoxicity, pulmonary fibrosis	(19, 34, 35)
Na^+ channel inhibitors	flecainide phenytoin quinidine	Stabilize the inactivated channel conformation through fast and slow mechanisms	atrial flutter, tachycardias	bradyarrhythmias, slow atrial flutter, proarrhythmia	(31)
Cardiac Glycosides	digitoxin digoxin ouabain	Inhibit Na^+/K^+ ATPase and indirectly increase intracellular $[Ca^{2+}]$	atrial fibrillation and heart failure	atrioventricular block, bradycardia, gastrointestinal and neurological disorders, ventricular arrhythmias,	(36–38)

Table 3

Pgp-mediated DDIs of commonly prescribed cardiovascular ion channel inhibitors

Drug	Sub.[a]	Inh.[b]	Ind.	Digoxin PK	Other	References
amiodarone	non	6 μM	NA	*AUC*: increases 66%[c] CL_R: no change C_{max}: increases 78%[c] V_D: no change or decreases	apixaban[d] dabigatran[d] digitoxin[e] daunorubicin[f] flecainide[f] rivaroxaban[d]	(55, 56, 58, 60–62)
amlodipine	non to good	NA	NA	*C_{ss}: No change*	simvastatin[g]	(65, 66, 68)
digoxin	good	-	Yes	-	quinidine[h]	(61, 69, 70, 72, 73, 78)
diltiazem	weak	36 μM	NA	*AUC*: increases 34%[c] C_{max}: increases 31%[c]	quinidine[h]	(61, 64, 82).
dronedarone	non	NA	NA	*AUC*: increases 150% CL_R: decreases 60%		(59)
flecainide	good	NA	NA	C_{avg}: increased ~20%		(57, 84)
mibefradil	non	7.5 μM	NA	*AUC*: increases 31% C_{max}: increases 41%	atorvastatin[g]	(61, 87)
nicardipine	non	<1 μM	NA	*AUC:* increases 6% C_{max}: increases 6%		(61, 64)
nifedipine	non	<1 μM	NA	*AUC:* increases 21%[c] C_{max}: increases 5%[c]		(61, 64)
ouabain	X	No	Yes	NA		(71, 78, 80, 81)
phenytoin	non to good	NA	NA	*AUC*: decreases 23% *CL*: increases 27% CL_R: no change V_D: no change	paclitaxel[i]	(90, 91, 93, 96)
quinidine	good	21 μM	Yes	*AUC:* increases 121%[c] *CL:* decreases 56% CL_R: decreases 51% C_{max}: increases 75% *F:* increases 16% $t_{1/2}$: decreases 47% V_D: decreases 38%	edoxaban[d] fentanyl[j] flecainide[f] methadone[j]	(57, 61, 70, 72, 98–102)

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Drug	Sub.[a]	Inh.[b]	Ind.	Digoxin PK	Other	References
verapamil	non to good	1–200 μM	NA	*AUC*: increases 51% *CL*: decreases 34% CL_H: decreases 62% CL_R: decreases 21% C_{max}: increases 44% $t_{1/2}$: increases 31% V_D: decreases 23%	colchicine[k] dabigatran[d] prazosin[l] quinidine[h] vinblastine[k]	(61, 64, 75, 86, 106, 112–114)

[a]Classification of a drug as a non-substrate (non), weak substrate (weak), good substrate (good) or non-ligand (X) to Pgp. A non-substrate had an efflux ratio = 1, a weak substrate had an efflux ratio >1 and <2, a good substrate had an efflux ratio >2 and a non-ligand was neither a substrate or inhibitor for Pgp.

[b]*In vitro* inhibition concentration range of Pgp-mediated digoxin transport by the drug.

[c]Average pharmacokinetic values.

Abbreviations:-, not applicable; *AUC*, area under the curve; C_{avg}, average drug plasma concentration; C_{SS}, steady-state drug plasma concentration; CL, total clearance CL_H, extrarenal clearance; CL_R, renal clearance; C_{max}, peak drug plasma concentration; DEA, monodesethyl-amiodarone; Ind., inducer; Inh., inhibitor; NA, not available; Sub., Substrate; $t_{1/2}$, terminal elimination half time; V_D, apparent volume of distribution.

[d]The more severe ADRs were myopathy (115),

[e]digitalis-associated toxicities (116),

[f]cardiotoxicity (117, 118),

[g]bleeding and thrombosis(119),

[h]thrombocytopenia (120),

[i]cardiac arrest (121),

[j]respiratory depression (122, 123),

[k]neutropenia (124, 125) and

[l]orthostatic hypotension (126)[l].

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