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Transport of organic cationic drugs: Effect of ion-pair formation with bile salts on the biliary excretion and pharmacokinetics

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ABSTRACT

More than 40% of clinically used drugs are organic cations (OCs), which are positively charged at a physiologic pH, and recent reports have established that these drugs are substrates of membrane transporters. The transport of OCs via membrane transporters may play important roles in gastrointestinal absorption, distribution to target sites, and biliary and/or renal elimination of various OC drugs. Almost 40 years ago, a molecular weight (Mw) threshold of 200 was reported to exist in rats for monoquaternary ammonium (mono QA) compounds to be substantially (e.g., >10% of iv dose) excreted to bile. It is well known that some OCs interact with appropriate endogenous organic anions in the body (e.g., bile salts) to form lipophilic ion-pair complexes. The ion-pair formation may influence the affinity or binding of OCs to membrane transporters that are relevant to biliary excretion. In that sense, the association of the ion-pair formation with the existence of the Mw threshold appears to be worthy of examination. It assumes the ion-pair formation of high Mw mono QA compounds (i.e., >200) in the presence of bile salts in the liver, followed by accelerated transport of the ion-pair complexes via relevant bile canalicular transporter(s). In this article, therefore, the transport of OC drugs will be reviewed with a special focus on the ion-pair formation hypothesis. Such information will deepen the understanding of the pharmacokinetics of OC drugs as well as the physiological roles of endogenous bile salts in the detoxification or phase II metabolism of high Mw QA drugs.

Contents

Abbreviations: APC, apparent partition coefficient; BCRP, breast cancer resistance protein; CH, cholate; cLPM, canalicular liver plasma membrane; DC, deoxycholate; GC, glycocholate; GDC, glycodeoxycholate; HNAP, hydroxy-2-naphthoic acid; Mw, molecular weight; MATE, multidrug and toxin extrusion antiporter; MPP^+, 1-methyl-4-phenylpyridinium; MRP, multidrug resistance associated protein; OA, organic anion; OC, organic cation; OCT, organic cation transporter; PAMPA, parallel artificial membrane permeability assay; P-gp, P-glycoprotein; QA, quaternary ammonium; TAA, tetraalkyl ammoniums; TC, taurocholate; TCDC, taurochenodeoxycholate; TDC, taurodeoxycholate; TBA, tetrabutyl ammonium; TBuMA, tributyl methyl ammonium; TEA, tetraethylammonium; TEMA, triethyl methyl ammonium; TPC, true partition coefficient; TPeA, tetrapentyl ammonium; TPrA, tetrapropyl ammonium.

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1. Introduction

More than 40% of clinically used drugs are organic cationic (OC) molecules (Neuhoff et al., 2003). The group of OC compounds is composed of a wide variety of drugs and endogenous compounds containing one or more tertiary/quaternary amines or other positively charged groups. They are mainly charged at physiological pH or can be protonated depending on their pKa values (Zhang et al., 1998; Kim & Shim, 2006). These drugs constitute a broad structural spectrum: endogenous amines (e.g. thiamine, choline, N-methylnicotineamide, acetylcholine, monoamine neurotransmitters, and some steroid hormones), clinically relevant drugs (including antihistaminergic drugs, anticholinergic drugs, anticancer drugs, antiviral drugs, biguanide antidiabetics, and beta-blockers), as well as the model compounds including tetraakylammoniums (TEA), decynium 22, and the neurotoxin 1-methyl-4-phenylpyridinium (MPP^+) (Kang et al., 2007; Lee et al., 2009) (Table 1).

Many papers have dealt with the disposition of OCs (Meijer et al., 1997; Kim & Shim, 2006; Koepsell et al., 2007). However, it is worthy of notice that certain OC drugs, such as quaternary ammonium (QA) drugs, demonstrate unique pharmacokinetics in the body. For example, distinct molecular weight (Mw) thresholds of 200 ± 50 Da and 500–600 Da have been reported to exist for substantial biliary excretion (e.g., >10% of iv dose) of mono- and di-QA compounds, respectively, in rats (Hughes et al., 1973a, 1973b). Almost 40 years have passed since the researchers reported the Mw thresholds, but no explanations, except an ion-pair hypothesis by Shim's group (Song et al., 2001, 2003, 2010), have been made thus far to elucidate the underlying mechanism(s). The ion-pair hypothesis assumes that only high Mw QAs that form lipophilic ion-pair complexes in the liver with hepatic bile salts can be substantially excreted in the bile.

As a matter of course, metabolism and biliary and/or urinary excretion represent the detoxification processes that protect the human body from xenobiotics and their toxic metabolites (Leslie et al., 2005). Hepatic detoxification is generally initiated by the uptake of xenobiotics into liver hepatocytes (phase 0 uptake), followed by oxidation related to cytochrome P450 (CYP) (phase I metabolism) and subsequent conjugation such as glucuronidation, sulfation, and glutathione conjugation (phase II metabolism), and ends with excretion of xenobiotics and/or their metabolites to the bile (phase III excretion). Recently, it has been shown that transporters in the sinusoidal and canalicular membranes play crucial roles in the hepatic uptake (phase 0 uptake) and biliary excretion (phase III excretion), respectively, of xenobiotics. Organic cation transporters (OCTs), organic anion transporters (OATs), organic anion transporting polypeptide 1B1 (OATP1B1), and Na^+/taurocholate cotransporting polypeptide (NTCP) in the sinusoidal membrane represent phase 0 transporters that are involved in the hepatic uptake of OCs and organic anions (OAs). Phase III transporters include P-glycoprotein (P-gp), multidrug resistance associated protein 1/2 (MRP1/2), and breast cancer resistance protein (BCRP) in the canalicular membrane that are responsible for biliary excretion of OCs and OAs. Therefore, the phase II conjugation can be regarded as a reaction to give xenobiotics a greater affinity to phase III transporters (Ishikawa & Ali-Osman, 1993; Minamino et al., 1999; Dietrich et al., 2003; Nakata et al., 2006). There is considerable overlapping of substrate specificity among these transporters (Gottesman et al., 2002). For example, certain hydrophobic anticancer drugs (e.g., doxorubicin, daunorubicin, etoposide, nilotinib, imatinib, and mitoxantrone) are substrates for P-gp, MRP1, and BCRP. Some positively charged OCs (e.g., dipyridamole and cimetidine) are excreted via BCRP. Conjugated metabolites of OCs (e.g., glucuronide-, glutathione- and sulfate-conjugates of OCs) are substrates for MRPs and/or BCRP (Dietrich et al., 2003; Staud et al., 2006; Giacomini et al., 2010; Ni et al., 2010).

According to the above-mentioned ion-pair hypothesis, the ion-pair complexes of OCs with bile salts generally demonstrate greater lipophilicity and affinity to P-gp, compared to the OCs themselves, thereby accelerating the excretion of OCs to the bile via the transporters (Song et al., 2001, 2003, 2010). If true, the ion-pair formation can be regarded as a novel phase II metabolism for certain OC drugs like the well-known phase II metabolism (i.e., conjugation) of various xenobiotics.

In this review, therefore, we will examine the transport of OC drugs, particularly in association with the Mw-dependent biliary excretion of QA compounds. Other aspects of OC transport, including intestinal absorption, renal excretion and skin absorption, will also be briefly reviewed.

2. Physicochemical properties of organic cations in relation to their pharmacokinetics

Many studies have been conducted to obtain insight into the relationship between pharmacokinetic properties and physicochemical properties of OCs (Neef & Meijer, 1984; Neef et al., 1984). The n-octanol/aqueous partition coefficient of OCs has been frequently utilized as an index to correlate the lipophilicity of compounds with biological parameters such as protein binding (Wierda et al., 1993). Appropriate lipophilicity seemed necessary for OC molecules to demonstrate efficient absorption and elimination characteristics, because the relative affinity of OC drugs towards membranes and integrated membrane proteins is likely to be influenced by the lipophilicity. Meijer et al. reported a sigmoidal relationship between the lipophilicity (logP −1–4) and hepatic clearance and intestinal absorption for 14 monovalent OCs (Meijer et al., 1997). Interestingly, their observation was in line with the Mw threshold in the hepatobiliary excretion of QA compounds (Hughes et al., 1973a, 1973b). This type of a

Table 1
Categories of organic cations.

Categories	Compounds
Endogenous amines	Thiamine, guanidine, choline, carnitine, N-methylnicotineamide, acetylcholine, dopamine, epinephrine, histamine, prostaglandin E2, progesterone, testosterone
H1/H2 receptor antagonist	Diphenhydramine, pyrilamine, cimetidine, ranitidine, famotidine
Ion channel blockers	Verapamil, pholedrine, procainamide, disopyramide, quinidine, citalopram
Receptor antagonists	Atropine, mepiphenidol, isopropamide, propantheline, transtheline, bretylium, phenoxybenzamine, tacrine, neostigmine
Beta blockers	Acebutolol, alprenolol, atenolol, bisoprolol, bupranolol, carvediol, ceriprolol, metoprolol, nadolol, pindolol, oxoprenolol, propranolol, sotalol, talinolol, timolol
Anticancer drugs	Cisplatin, doxorubicin, daunorubidin, mitoxantrone, vinblastine, homisium
Antiviral (HIV)	Acyclovir, indinavir, ritonavir
Antidiabetes	Metformin, buformin, phenformin
Antiemetics	Emetine, granisetron, ondansetron, tropisetron, troposium
Muscle relaxants	Vecuronium, pancuronium, rocuronium
Model OCs	1-Methyl-4-phenylpyridinium (MPP^+), Decynium 22, Disprocynium 24
Mono QAs	Tetramethylammonium (TMA), tetraethylammonium (TEA), tetrapropylammonium (TPrA), tributylmethylammonium (TBuMA), tetrabutylammonium (TBA), tetrapentylammonium (TPeA), azido-procainamide, N-methylpyridinium, trimethyl phenyl ammonium, diethylmethylphenyl ammonium, dibezyldimethylammonium
Di QAs	Diquat, paraquat, morfamquat, decamethonium, dimethyltubocurarine