REVIEW ARTICLE

PHARMACOKINETIC DRUG-DRUG INTERACTIONS MEDIATED BY ORGANIC CATION TRANSPORTERS: ARE ANTIMALARIAL DRUGS SIGNIFICANTLY AFFECTED?

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Abstract

A clear understanding of all the processes that influence drug disposition is important to enable a prediction of pharmacokinetic drug interactions. Xenobiotics are transported across bio-membranes and the process is mediated by various membrane transporters which include "Organic Cation Transporters" (OCTs). OCTs are specifically involved in the transport of several molecules that have positive charges *in vivo* and these include a wide variety of weakly basic drugs. As several antimalarial drugs are weakly basic and can be cationic in biological fluids, the contribution of OCTs to the drug disposition appears to be underestimated because most studies on the pharmacokinetic drug interaction with antimalarial drugs are focused on the interactions at the sites of drug metabolism. This review provides an update on the significance of OCTs on the pharmacokinetic disposition of antimalarial agents with a view to identifying potentials for drug interactions that could involve concurrently administered drugs which are either inhibitors or substrates of OCTs. A very significant likelihood exists for concurrent use of antimalarial drugs with other medicines because of the occurrence of comorbidities with malaria. There are limited studies on antimalarial pharmacokinetic drug-drug interaction studies in which role of OCTs are investigated. From the literature, and using *in vitro* studies, the following antimalarial drugs, chloroquine, piperaquine, proguanil, and cycloguanil have been reported to be substrates of different OCTs while tafenoquine, pyrimethamine, trimethoprim, quinine, and mefloquine were shown to be inhibitors. Atovaquone and artesunate were shown not to be substrates and did not demonstrate any inhibitory potency. This information provide basis for prediction of any potential interaction between antimalarial drugs and other co-administered medicines which are inhibitors/substrates of the transporter proteins.
Keywords: Antimalarial drugs, drug-drug interactions, organic cation transporters, pharmacokinetics.

INTRODUCTION

The OCTs along with "Organic Anion Transporters" (OATs) belong to the family of membrane transporters which itself is a part of the "Solute Carrier" (SLC) super family which consists of 65 SLC families. The function of the various SLC families is to control the transport of most endogenous compounds and xenobiotics across bio-membranes[1]. OCTs are specifically involved in the transport of several molecules that are positive in charge at the pH of biological fluids, examples of which include the endogenous amines and a variety of weakly basic drugs[2]. These Transporters include OCT3, OCT2, OCT1, OCTN1, OCTN2, Plasma membrane Mono-amine Transporter (PMAT), "Multidrug And Toxin

Extrusion-1" (MATE-1), and "Multidrug And Toxin Extrusion-2-k"(MATE2–K)[2,3]. They all have differences in their organ or tissue localizations. In humans, for example, OCT1 is most abundant on the membrane of intestines and hepatocytes where it is involved in drug uptake, while OCT2 is most abundant on the cell membrane of kidney tubules where it facilitates drug secretion[4]. The other OCTs are distributed in different specific tissues in the body but the MATEs are more found at the hepatocytes and kidney where they mediate the efflux of diverse organic cation substrates[1]. OCT2 operates in concert with MATE in facilitating renal tubular secretion of cationic species, as OCT2 drives cationic uptake into the proximal tubule epithelial cells while MATE mediates efflux into the renal tubules for elimination

into urine. From the tissue localization of these OCTs, it is not surprising that OCT2 and OCT1 play more prominent roles in intestinal drug absorption, as well as hepatic plus renal elimination of several drugs[5].

All the processes that influence disposition of drugs in the body ought to be fully understood as this will enhance the prediction of potential pharmacokinetic drug interactions which have attracted increased attention due to popularity of co-administration of several drugs, especially in the elderly. It is reported that approximately 40% of orally applied drugs are cationic at the pH of body fluids. Since these cationic moieties are hydrophilic, they undergo minor or no passive transfer across biological membranes, necessitating the involvement of OCTs[6]. Indeed, different Drug regulatory Agencies including the "Food and Drug Administration" (FDA) and "European Medicines Agency" (EMA) have recommended preclinical testing of new drug molecules for their inhibition potentials for OCT1, OCT2, MATE1, and MATE2-K[6]. Most studies on the pharmacokinetic drug interactions with antimalarial drugs are focused on interactions at the sites of drug metabolism. As most antimalarial drugs are weakly basic and can be cationic at pH of biological fluids, it is likely that OCTs contribute to disposition of the drugs. The World Malaria Report of 2023 indicates that higher levels of treatment failure have been shown in some studies in the WHO African Region, and these results could be an indication of emergence of resistance to ACT partner drugs[7]. Although several investigators are working on development of new antimalarial medicines, optimization of the therapeutic utility of the existing ones is still an important approach. A full understanding of processes of DDIs involving antimalarials will, undoubtedly, contribute to enhancing the treatment outcomes with these drugs. This review provides an update on the significance of OCTs on the disposition kinetics of antimalarial drugs with a view to identifying potentials for drug interactions that could involve concurrently administered medicines which are either inhibitors or substrates of OCTs.

Relevant keywords were employed to perform a thorough search of selected databases including PubMed, Elsevier, Scopus and Science Direct, to obtain the articles published in the English language that were used for this review.

Drug interactions at OCTs

Drug with drug interactions (DDIs) through drug transporter proteins have been receiving increased attention following several observations that inhibition of these transporters affect drug pharmacokinetics especially drug absorption and elimination[8]. There is a high potential for occurrence of OCT-mediated DDI since OCTs have high affinity to bind to a wide range of drug molecules that have positive charges *in vivo*[9]. These DDIs can result in increased plasma drug levels leading to increase in drug efficacy or toxicity, if renal secretion of the drug occurring at the OCT2 expressed at the tubular cells of the kidney, is inhibited by a concurrently administered drug. On the other hand, the DDI may result in decreased efficacy or therapeutic failure following decreased absorption as a result of inhibition of OCT1 at the enterocytes which mediate intestinal drug absorption of cationic drugs. The relevance of OCT-mediated DDI is re-enforced by the fact that the pharmacokinetics of at least 120 drugs is influenced by the activities of OCTs[9,10]. There are several drugs and compounds demonstrating *in vitro* inhibitory activities on OCTs but translation to clinically significant effects are limited.

Clinically relevant DDIs at OCTs

The cellular uptake of several organic cationic drugs through membranes of hepatocytes and enterocytes is facilitated by OCT1 and this contributes to regulating the gastrointestinal uptake and metabolism of these drugs[11]. When two or more drugs that are substrates of OCT are co-administered, they can compete for binding at the OCT site resulting in inhibition of transport of the drug with lower binding affinity or lower concentration. Also, similar to other transporter proteins, there are several compounds that are non-substrates of OCT but can inhibit substrates of OCT. These inhibitors can undergo competitive or non-competitive inhibition. In general, the molar mass of these inhibitors of OCT are larger than those of the substrates[12]. Although there is abundance of pre-clinical studies supporting a role of OCT in DDI, only a few of these OCT-mediated DDIs have been reported in humans[9]. Also, the clinically relevant effects of individual OCTs on the modulation of the pharmacokinetics of specific drugs have only been elucidated in a few cases. This is attributable to the fact that more than one OCT with different effects are often available at different biological membranes that are involved in the drug uptake or excretion[6]. Thus, the effect of inhibition of an OCT at a location on plasma drug levels can counteract or mask the effect of inhibition of the same OCT at another tissue location. For example, inhibition of OCT1 at intestinal membrane can result in a decrease in drug absorption and subsequent decreased plasma drug levels. On the other hand, if OCT1 is inhibited at the hepatocytes, there would be decreased hepatic uptake (and decreased metabolism) which can cause blood levels of OCT1 substrates to increase. Drug-drug interactions in human subjects involving OCTs have been severally documented with metformin and a few other drugs shown in Table 1[13-25].

It is evident in these studies that inhibition of OCT2 and MATE at the proximal renal tubules results in increase in plasma drug concentrations due to reduction in drug secretion. Hence, OCT2 and MATEs at the kidneys do contribute to DDIs with clinical relevance as they accept several substrates of OCT1[2]. This informs the decision for drug interactions through these transporter proteins to now be recognized in the drug development and approval process[6]. It is pertinent to note that when no inhibitors in clinical use are available for an OCT, additional evidence of involvement of the OCT in drug disposition can be provided by pharmacogenetic studies in carriers of the OCT null alleles[26].

Table 1: Some clinically observed drug-drug interactions resulting from modulation of organic cation transport proteins.

Perpetrator Drug	Victim Drug	Outcome	Reference
Cimetidine	Metformin	Decreased renal secretion and increased plasma concentration of metformin following interaction with cimetidine at OCT2 and MATE in renal tubules.	Tsuda et al.[13]
Pyrimethamine	Metformin	Decreased renal secretion and increased plasma concentration of metformin following interaction with pyrimethamine at OCT2 and MATE1 in renal tubules.	Kusuhara et al.[14]
Vandetanib	Metformin	Co-administration of vandetanib and metformin resulted in decreased renal metformin clearance and C_{max} of metformin in systemic blood was markedly increased due to MATE1 inhibition.	Johansson et al.[15]
Dolutegravir	Metformin	Dolutegravir increased the AUC of metformin by more than 200% by inhibiting OCT2 and MATE1 at renal tubules.	Song et al.[16]
Peficitinib	Metformin	Peficitinib reduced AUC of metformin and this was ascribed to inhibition of OCT1 uptake of metformin.	Shibata et al.[17]
Rifampin	Metformin	Expression of OCT1 in peripheral blood cells is up-regulated by co-administration of rifampin resulting in increased blood concentration of metformin along with enhanced hypoglycemic effect of metformin.	Cho et al.[18]
Tucatinib	Metformin	Co-administration of tucatinib with metformin resulted in significant reduction of the renal metformin clearance attributable to MATE inhibition at the renal tubules.	Topletz-Erickson et al.[19]
Trimethoprim	Lamuvidine	Trimethoprim, when co-administered with Lamuvidine, resulted in significant increase in lamuvidine AUC along with a 35% decrease in the drug renal clearance, due to interactions at OCT2 and MATE1 at the kidney.	Moore et al.[20]
Cimetidine	Ranitidine	Cimetidine produced a marked increase in ranitidine AUC along with reduction in renal clearance of the victim drug through interactions at OCT2 and MATE1 at the kidney.	van Crugten et al.[21]
Cimetidine	Pindolol	Through inhibitory interactions at renal OCT2 and MATE1, cimetidine caused a significant increase in blood levels of pindolol	Somogyi et al.[22]
Cimetidine	Dofetilide	Concurrent administration of Cimetidine inhibited OCT2-mediated tubular secretion of dofetilide resulting in marked increase in dofetilide AUC.	Abe et al.[23]
Trimethoprim	Procainamide	Significant increase in procainamide AUC was observed following trimethoprim concurrent administration and this was attributed to interaction at the OCT2 at the kidney.	Kosoglou et al.[24]
Vandetanib	Cisplatin	The AUC of cisplatin was significantly increased by vandetanib through renal OCT2 inhibition resulting in diminished drug secretion.	Blackhall et al.[25]

For example, individuals carrying OCT1 alleles of reduced function were observed to have higher "area under plasma drug concentration" (AUC) and "maximum plasma drug concentration" (C_{max}) attributed to reduced hepatic clearance of the drug[27].

Pharmacokinetic interactions of antimalarials through Organic Cation Transporters

Concurrent administration of antimalarial drugs with other medicines is very common because of the occurrence of comorbidities with malaria. A number of studies have shown that a significant percentage of patients with malaria had a reported comorbidity[28,29]. In addition, the common environmental and socioeconomic factors in some resource-limited countries promote the coexistence of different infectious and/or noninfectious diseases in the same individual resulting in comorbidity[30,31]. Therefore, there is a high prevalence of concurrent administration of antimalarial drugs with other drugs for treatment of comorbidities, and these can potentially result in significant drug-drug interactions[31]. For example, in a study in our laboratories, plasma quinine concentrations increased 4-fold following concurrent ritonavir administration and this was accompanied by a marked reduction in plasma drug clearance (CL/F) of quinine[32]. There are limited studies on antimalarial pharmacokinetic DDI studies in which role of OCTs are investigated. With availability of copious literature

on compounds and medicines that are OCT substrates or inhibitors[33], it may be possible to predict the possibility of a pharmacokinetic DDI through the OCT pathway. Also, previous DDI studies can be re-evaluated to ascertain the involvement of OCTs in the overall outcome of the interaction. A summary of the antimalarial drugs with reported DDIs mediated through OCTs are presented in Table 2. Also, suggestions are proffered on potential DDIs involving antimalarial drugs reported as substrates of OCTs and other drugs that are potent OCT inhibitors which may likely be co-administered with the antimalarial. A compilation of drugs which are MATE1 inhibitors is available at drug bank[34]. In this list are commonly used drugs such as cimetidine, levofloxacin, and trimethoprim. While a list of drugs which include codeine, cimetidine, desipramine, probenecid, clopidogrel, efavirenze, nevirapine etc, that are inhibitors of OCT1 is also available at drug bank[35] and complied by Zhou et al[9].

4-Aminoquinoline

Amodiaquine: *In vitro* inhibition of OCT2 by amodiaquine demonstrated that the calculated DDI index of the drug is below 0.1, indicating that the occurrence of DDIs with clinical significance is unlikely for amodiaquine through the involvement of OCTs[36].

Table 2: Some observed antimalarial drug-drug interactions and predicted interactions due to inhibition of organic cation transporters.

Perpetrator Drug	Victim Drug	Outcome	Reference
OCT2 inhibitors, *in vitro*	Amodiaquine	Calculated DDI index of amodiaquine was below 0.1, indicating that it is unlikely for DDIs of clinical relevance to occur through OCT1 and OCT2.	Velden *et al.* [36]
OCT inhibitors, *in vitro*	Chloroquine	Chloroquine was shown to be a MATE substrate, hence, can be a competitive inhibitor. This finding suggests that inhibitors of MATE1, if concurrently administered with chloroquine, canalter chloroquine renal secretion.	Muller *et al.* [37]
Quinidine, *in vitro*	Primaquine	Primaquine transport was inhibited by quinidine, an OCT1 inhibitor. Increased uptake of primaquine into hepatocyte may be mediated by OCT1. The clinical implication of inhibition of OCT1 on the efficacy of primaquine is not elucidated.	Louisa *et al.* [38]
Tafenoquine	Metformin	*In vitro* studies have shown that Tafenoquine inhibited metformin transport by OCT2 and MATEs This shows that, following a concurrent administration of OCT2 and MATE substrates with tafenoquine, there is a potential for increased concentrations of these substrates.	FDA [39]
Artemisinin	*In vitro* OCT1 probe substrate	*In vitro*, artemisinin inhibited probe substrate for the OCT1 showing that artemisinin can inhibit OCT1-mediated transport. This may have implications for drugs that are OCT1 substrates.	Hubeny *et al.* [40]
OCT inhibitors	Proguanil and Cycloguanil	Proguanil and cycloguanil, were found to be substrates of OCTs and MATEs. This entails that there is possibility of DDI when drugs that are substrates/inhibitors of OCTs/MATEs are co-administered with proguanil or cycloguanil.	Velden *et al.* [36]
Pyrimethamine	Metformin	The achieved plasma concentrations of pyrimethamine when given at therapeutic doses are sufficient to inhibit MATE-mediated renal drug excretion as evident in a substantial decrease in metformin renal clearance. Metformin, is a MATE substrate.	Kusuhara *et al.* [14] Ito *et al* [41]
Trimethoprim	Metformin	Trimethoprim has been identified to possess an inhibitory potency for MATE1-mediated transport. It was observed that a concentration-related reduction of metformin (MATE1 substrate) transport was produced by trimethoprim.	Muller *et al.* [37]
Quinine	OCT and MATE substrates, *in vitro*	At therapeutic doses, quinine achieves plasma concentrations high enough to inhibit MATEs. Studies have also revealed *in vitro* that quinine is a potent inhibitor of OCT1 and OCT2. This will have implications if quinine is co-administered with substrates of these transporters.	Nies & Schwab [10] Hubeny *et al.* [40]
Mefloquine	*In vitro* Probe Substrates for OCTs	Mefloquine showed *in vitro* inhibition of OCT1 and OCT2. The implication of this finding for mefloquine disposition *in vivo* is not certain.	Hubeny *et al.* [40]
Atovaquone	Substrates of OCTs	An *in vitro* study failed to demonstrate the involvement of OCTs and OATs in atovaquone liver uptake and excretion into bile. Hence, co-administration of atovaquone with OCT substrates is not expected to result in any DDI.	Patel *et al.* [42]
	Sulphadoxine and Dapsone	There is no report in the literature on inhibitory potency of sulfonamides on OCTs neither are they substrates. Thus, DDIs with sulphadoxine or dapsone with OCT substrates or inhibitors are theoretically not expected to occur.	

Chloroquine: In a study to elucidate the renal molecular mechanism of chloroquine tubular secretion, it was demonstrated that OCT2 appears not to be involved in chloroquine transport into the kidney, however, the drug is a MATE substrate. This finding suggests that inhibitors of MATE1 can potentially alter chloroquine elimination at renal pathway, if concurrently administered[37].

8-Aminoquinolines

Primaquine: In an *in vitro* study to verify the involvement of OCT1 in uptake of primaquine into the hepatocytes, it was observed that primaquine transport was inhibited by quinidine, an OCT1 inhibitor. The study concluded that OCT1 effectively transports primaquine and that increased uptake of primaquine into hepatocyte may be mediated by OCT1[38]. The clinical implication of inhibition of OCT1 on the efficacy of primaquine is not clear as the drug is

effective at the hypnozoites phase of *P. vivax* in the liver.

Tafenoquine: Studies have shown that tafenoquine inhibited metformin transport by the OCTs and MATEs[39]. This shows that, following a concurrent administration of OCT2 and MATE substrates with tafenoquine, there is a potential for increased plasma concentrations of these substrates with an attendant increased efficacy or risk of toxicity of the drugs. Therefore, concurrent administration of tafenoquine with OCT2 and MATE substrates should be done with caution.

Artemisinin derivatives

Artemisinin derivatives are not weakly basic compounds and they are not cationic *in vivo*, hence, are not expected to be transported by OCTs or MATE. However, an *in vitro* study that used transporter-overexpressing MDCKII cells and probe substrate for OCT1 showed that artemisinin but not artesunate

inhibited OCT1-mediated transport[40]. Elucidation of the clinical implications of co-administration of artemisinin with OCT1 substrates requires more studies.

Biguanides

Proguanil and its major active metabolite, cycloguanil, have been reported to be substrates of OCTs and MATEs, and these suggest that these setransporters can play significant roles in pharmacokinetics of both drugs[38]. This entails that there is possibility of DDI when OCT substrates are concurrently administered with proguanil or cycloguanil. Thus, for typical substrates of these transporters such as metformin, DDIs may likely occur following simultaneous drug administration.

Diaminopyrimidines

Pyrimethamine: *In vitro* studies have shown Pyrimethamine to be a specific MATE inhibitor[10,41]. The achieved plasma concentrations of the drug when given at therapeutic doses are sufficient to inhibit MATE-mediated renal drug excretion as evident in a marked decrease in metformin (MATE substrate) renal elimination[14]. Thus, DDI between pyrimethamine and metformin results in significantly increased metformin AUC and has been ascribed to MATEs inhibition and not OCT2[14]. It is recommended that pyrimethamine can serve as a probe in inhibition studies of MATE transport proteins[41].

Trimethoprim: Trimethoprim has been identified to possess an inhibitory potency for MATE1-mediated transport, and this was further investigated by using metformin (a model substrate). It was observed that a concentration-related MATE1 inhibitory effect was produced by trimethoprim[37].

Phenanthrene methanol

Phenanthrene methanol antimalarials include halofantrine and lumefantrine. An exhaustive search of the literature did not reveal any study indicating that these drugs are substrates or inhibitors of OCTs or MATE. Until this is verified, DDIs with these drugs mediated through cationic transporters pathway cannot be ascertained.

Quinoline-methanol

Quinine: Studies have demonstrated *in vitro* that quinine is not only a substrate but also an inhibitor of MATEs. At therapeutic doses, quinine achieves plasma concentrations high enough to inhibit MATEs[10]. Further studies have also revealed that quinine is effective as an inhibitor of OCTs[40]. In a pharmacokinetic study that investigated the interaction of quinine with ritonavir, the reported four-fold increase in plasma levels of quinine was attributed to interaction at the level of metabolizing enzyme, CYP3A4[32]. With the increasing knowledge of involvement of OCTs in drug disposition, the remarkable increase in quinine blood concentrations along with modest increase in ritonavir blood levels, may, in part, be as a result of inhibition of MATEs since ritonavir[10] just like quinine, is an inhibitor of MATEs. Elucidation of impact of inhibition of renal secretion of quinine by ritonavir through inhibition of efflux by MATEs, requires further studies.

Mefloquine: The interactions of different antimalarial drugs (artesunate, artemisinin, chloroquine, mefloquine, pyrimethamine, and quinine) with OCTs were evaluated in an *in vitro* study that used MDCKII cells and relevant OCTs probe compounds[40]. The results indicated that all the compounds except artesunate demonstrated OCT1 and OCT2 inhibition. The inhibitory potencies for OCT1 were: quinine> artemisinin>mefloquine>pyrimethamine> chloroquine; while the degrees of inhibition of OCT2 by the antimalarials were: pyrimethamine>quinine> chloroquine>mefloquine[40]. The implication of this finding for mefloquine disposition *in vivo* is not certain.

Quinone

Atovaquone: Atovaquone is known to be predominantly cleared from the body through biliary excretion as the drug concentration in bile is ≥100-fold higher compared to that of the blood, and this is indicative of active biliary excretion. An *in vitro* study failed to demonstrate the involvement of OCTs and OATs in atovaquone liver uptake and excretion into bile[42]. Hence, co-administration of atovaquone with OCT substrates is not expected to result in any DDI.

Sulfonamides/sulfones

Antimalarial Sulfonamides include sulphadoxine and Dapsone. Sulfonamides dissociate in aqueous media into anionic moieties while OCTs substrates are cationic or weakly basic compounds that have positive charges *in vivo*[6]. There is no report in the literature on inhibitory potency of sulfonamides on OCTs. Thus, DDIs with sulphadoxine or dapsone with OCT substrates or inhibitors are theoretically not expected to occur.

CONCLUSIONS

Malaria continues to constitute a source of major concern to health authorities and this merits embarking on more research including pharmacokinetic studies on interactions of antimalarial agents with other drugs that may be co-administered in situations of malaria comorbidity. There is a high prevalence of concurrent administration of antimalarials together with other medicines used for malaria comorbidities. This can potentially result in significant DDIs through drug metabolism and/or transporter proteins. The relevance of OCT-mediated DDI is re-enforced by the fact that there is a high number of drugs demonstrating inhibitory potencies toward OCTs and MATEs. However, translation to clinically significant outcomes has not been very apparent. There are limited studies on antimalarial pharmacokinetic drug-drug interaction studies in which role of OCTs are investigated. From the literature, and using *in vitro* studies, some antimalarial drugs (Chloroquine, Piperaquine, proguanil, and cycloguanil) have been reported to be substrates of different OCTs while Tafenoquine, pyrimethamine, trimethoprim, quinine, and mefloquine were shown to be inhibitors. Atovaquone and artesunate were shown not to be substrates and did not demonstrate any inhibitory potency. This information provide basis for prediction of any potential interaction between antimalarial drugs and other co-administered

medicines which are substrates/inhibitors of OCTs and MATEs. Generally, investigations on drug-drug interactions coupled with studies of impact of pharmacogenetics have demonstrated that OCTs and MATEs contribute to the pharmacokinetics of some drugs, including the antimalarials.

AUTHOR'S CONTRIBUTION

ONYEJI CO: Writing original draft, review, methodology, data curation, literature survey, editing.

DATA AVAILABILITY

Data will be made available on request**.**

CONFLICT OF INTEREST

There is no conflict of interest.

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