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The Role of Transporters in the Pharmacokinetics of Antibiotics

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Abstract

Aims: Various transporters including efflux transporters and uptake transporters play an important role in the pharmacokinetics of drugs. At present, interestingly, more and more studies had found that numbers of antibiotics were the substrates of transporters, and these antibiotics were usually combined with other drugs to treat disease more effectively in clinic. Therefore, it is necessary to focus on the role of transporters in pharmacokinetics and drug-drug interactions of antibiotics.

Methods: This review summarized the findings of recent studies as well as information obtained from several databases (update to June 2012): ISI Web of Knowledge SM (ISI WoK), SciFinder (Caplus, Medline, Registry, Casreact, Chrmlist, Chemcasts) and PubMed (indexed for Medline).

Results: The present review will provides useful information for studying the role of transporters in pharmacokinetics and drug-drug interactions of antibiotics, and should be of help to those intending to further research on these topics.

Conclusions: The drug transporter plays a significant role in the pharmacokinetics and drug-drug interactions of antibiotics.

Keywords: Antibiotics; CYP; Drug transporters

Introduction

Various drug transporters, including efflux transporters and uptake transporters, are widely expressed in body and play an important role in the absorption, distribution, excretion and metabolism of drugs [1]. At present, more and more drugs, including antibiotics, have been found as the substrates of transporters. Most of the antibiotics are eliminated by kidney and or biliary excretion, and this process mainly depends on renal or biliary tubular secretion through the function of transporters. Therefore, transporters play an important role in the pharmacokinetics of antibiotics.

Antibiotics are widely applied in infected patients of China and some other drugs may be combined with antibiotics to treat disease more effectively. Because transporters are involved in secretion and reabsorption of antibiotics, we should recognize which antibiotics were the substrate of transporter and considered that drug-drug interaction may be occurred between antibiotics and other drugs by inhibiting or inducing the same drug transporters .This paper makes a review on the roles of drug transporters in the pharmacokinetics of antibiotics.

OATPs/Oatps and antibiotics

OATPs/Oatps are expressed in a wide range of tissues in the body and are responsible for the Na+-independent uptake of large amphipathic organic anions into cells [2]. This suggests that OATPs/Oatps may act as an important role in drugs pharmacokinetic. At present, some antibiotics are found as the substrates or inhibitors of OATPs/Oatps.

Fluoroquinolones and OATPs/Oatps

Fluoroquinolones are antimicrobial drugs that are widely used for the treatment of bacterial and fungal infections. Although has hydrophilic nature, most fluoroquinolones are absorbed efficiently from the small intestine and show relatively high bioavailability [3]. The reasons for this might be explained by an involvement of carrier-mediated transport of fluoroquinolones across intestinal epithelial cells [4]. By using Xenopus oocytes expressing OATP1A2 model, a study found that ciprofloxacin and levofloxacin can be transported by organic anion transporting polypeptide 1A2 (OATP1A2/SLCO1A2) [5]. Therefore, both ciprofloxacin and levofloxacin are the substrates of OATP1A2. In rats, a study furtherly found that Oatp1a5 is involved in the intestinal absorption of ciprooxacin and naringin inhibited the uptake with an IC50 value of 18 uM by Xenopus oocytes expressing Oatp1a5 [6]. However, other investigations have shown that naringin has a significant inhibitory effect not only on Oatps but also P-gp and Bcrp [7,8]. Therefore, Oatp1a5 is involved in the intestinal absorption of ciprofloxacin in rats, but other influx and/or efflux transporters cannot be excluded.

Macrolide antibiotics and OATPs/Oatps

A study showed that when co administered with rifamycin SV, an OATP inhibitor, the exposures of erythromycin and clarithromycin were reduced 65 and 45%, respectively, but rifamycin SV had no affect on the total blood clearance of these macrolides. The study also confirm that rifamycin SV did not cause induction of metabolizing enzymes and/or transporters. Therefore, it suggests that the intestinal Oatps may be involved in the p.o. absorption of erythromycin and clarithromycin in the rat [9]. However, although the inhibition of OATP/Oatp-mediated transport by rifamycin SV is well documented, it is possible that the decreased oral exposure of the macrolides following co administration

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of rifamycin SV is caused by inhibition of other members of the OATP/Oatp family or other non-Oatp uptake transporters involved in the intestinal absorption of the macrolides.

Therefore, further study should be explored to confirm that OATPs /Oatps be involved the transport of macrolide antibiotics. In fact, more studies were proved that macrolide antibiotics act as inhibitor of OATPs/Oatps.

For intance, by using HEK293 cells stably expressing the human uptake transporters OATP1B1 or OATP1B3, the study explored the influence of macrolide antibiotics on the OATP1B1-and OATP1B3-mediated uptake of organic anions and drugs, and demonstrated that the OATP1B1-and OATP1B3-mediated uptake of BSP and pravastatin can be inhibited by increasing concentrations of all macrolides except azithromycin [10]. The results were showed in Tables 1 and 2.

Furthermore, the study found that azithromycin and clarithromycin can inhibite the uptake of taurocholate in rat Oatp1a5-transfected Madin-Darby canine kidney (MDCK) cell [9]. The same result also be found in another study , which showed that azithromycin and clarithromycin were potent inhibitors of rat Oatp1a5-mediated taurocholate uptake with apparent inhibitor constant (Ki) values of 3.3 and 2.4 uM, respectively [11]. However, azithromycin and clarithromycin did not significantly inhibit OATP2B1 mediated uptake of estrone-3-sulfate, a prototypical substrate of OATP. Simultaneously, the study showed that no significant transport of azithromycin or clarithromycin was observed in direct uptake studies using COS cells transfected with OATP1A2 or human/rat OATP2B1/Oatp2b1 [11]. Therefore, macrolide may play different role in different OATPs/Oatps.

The influence of macrolide antibiotics on the pharmacokinetic of substrate of OATPs/Oatps was also found in a study. The study demonstrated that the macrolides clarithromycin and erythromycin significantly increase pravastatin plasma concentrations [12]. Although cytochrome P450 (CYP) 3A is mainly responsible for 3''-hydroxy pravastatin formation, there is no clinically important pharmacokinetic interaction of pravastatin with a number of common CYP3A inhibitors [13]. In fact, pravastatin is little metabolized by cytochrome P450 enzymes. Therefore, macrolides may act as the inhibitor of OATPs/Oatps that acted as main transporters in the hepatic uptake of pravastatin.

Rifampin and OATPs/Oatps

Rifampin, an antibiotic mainly used for the treatment of tuberculosis, is an effective inhibitor of OATP [14]. We previously showed that concomitant dosing of rifamycin SV, a general OATPs/Oatps inhibitor [15], significantly reduced the oral area under the blood-concentration time curve (AUC) for azithromycin and clarithromycin in rats [16]. Simultaneously, rifampin also is a strong inducer of CYP3A4 and MDR1 expression by pregnane X receptor (PXR)-mediated pathways [17].

Macrolide	OATP1B1 (IC50)	OATP1B3(IC50)
Telithromycin	121 ± 19 uM	11 ± 0.3 uM
Clarithromycin	96 ± 5 uM	32 ± 7 uM
Erythromycin	217 ±19 uM	34 ± 14 uM
Roxithromycin	153 ± 4 uM	37 ± 6 uM
Azithromycin	no inhibition	no inhibition

Table 1: The influence of macrolide antibiotics on the OATP1B1- and OATP1B3-mediated uptake of BSP [18].

Macrolide	OATP1B1	Macrolide	OATP1B3
Telithromycin (10 uM)	Moderate inhibition	Telithromycin (100 uM)	19%
Clarithromycin (10 uM)	64%	Clarithromycin (100 uM)	37%
Erythromycin (100 uM)	24%	Erythromycin (100 uM)	36%
Roxithromycin (10 uM)	65%	Roxithromycin (100 uM)	52%
Azithromycin	no inhibition	Azithromycin	no inhibition

Table 2: The influence of macrolide antibiotics on the OATP1B1- and OATP1B3-mediated uptake of pravastatin (the reduction of intracellular accumulation of pravastatin compared with the control experiments) [18].

β-Lactam antibiotics and OATPs/Oatps

Most of the β-lactam antibiotics were taken up by hepatocytes via a common carrier-mediated transport mechanism. For instance, by using cell models of Xenopus laevis oocytes expressing organic anion transporting peptides (Oatp1, 2, and 4) , the study showed that nafcillin was transported by multiple Oatps with Km values of 4120 microM (Oatp1/Oatp1a1), 198 microM (Oatp2/Oatp1a4), and 1570 microM (Oatp4/Oatp1b2), and indicated that Oatp2 is the predominant contributor to the hepatic uptake of nafcillin. This study also found that cefadroxil, cefazolin, cefmetazole, cefoperazone, cefsulodin, and cephalexin, but not cefotaxime or ceftriaxone, were also the substrates of Oatp2 [18]. In another study, by using Xenopus oocytes and cultured cells expressing human OATPs, revealed that OATP1B3 and OATP1B1 transported nafcillin with Km values of 74 microM and 11 mM, respectively, and suggested that OATP1B3 contributes mainly to nafcillin uptake and OATP1B1 contributes moderately [19]. Furthermore, the study also found that all the tested β-lactam antibiotics were transported by OATP1B3, while OATP1B1 transported cefazolin, cefditoren and cefoperazon, but not cefmetazole, cefadroxil or cephalexin.Compared with OATP1B3, OATP1B1showed limited activity for the transport of β-lactam antibiotics. The study showed that the contributions of OATP1B1 and OATP1B3 to the overall uptake of nafcillin in human hepatocytes were determined to 20.5% and 53.3%. The rank orders of affinity (Km) and particularly uptake clearance obtained as V_{max}/km, were similar for OATP1B3 and Oatp1a4, which indicates a functional correlation between human OATP1B3 and rat Oatp1a4 and suggests that Oatp1a4 plays a major role in the hepatic uptake of nafcillin in rats. This result is the same as former [19].

Ciprofloxacin, a drug of fluoroquinolones, was also found may be the substrate of oatp. The study showed that the Oatp1a5-mediated uptake of ciprofloxacin was saturable with a Km value of 140 mM, and naringin inhibited the uptake with an IC50 value of 18 uM by Xenopus oocytes expressing Oatp1a5. Naringin reduced the permeation of ciprofloxacin from the mucosal-to-serosal side, with an IC50 value of 7.5 uM by the Using-type chamber method. The estimated IC50 values were comparable to that of Oatp1a5. These dates suggest that Oatp1a5 is partially responsible for the intestinal absorption of ciprofloxacin [20]. However, recent investigations have shown that naringin has a significant inhibitory effect not only on Oatp1a5 but also P-gp and Bcrp. The present study demonstrates that Oatp1a5 is involved in the intestinal absorption of ciprofloxacin in rats, although other influx and/or efflux transporters cannot be excluded [21].

BCRP/Bcrp and antibiotics

Breast cancer resistance protein (BCRP/ABCG2), one important member of the ABC family of transporters, is apically expressed and mediates the active and outward transport of a range of anticancer drugs, dietary compounds, food carcinogens, and antibiotics. BCRP/Bcrp is found not only in tumor cells but also in a variety of normal tissues such as intestine, liver, brain, and mammary gland. Several *in vivo* and *in vitro* studies indicated that BCRP/Bcrp mediates the excretion of antibiotics.

BCRP/Bcrp and fluoroquinolone antibiotics

A study has demonstrated that ciprofloxacin is likely to be a substrate for BCRP in human intestinal cells (Caco-2), as indicated by sensitivity to Ko143 (BCRP inhibitor) inhibition. It is possible that BCRP is the predominant transporter responsible for ciprofloxacin secretion in both rat and human intestine [22]. But, other transport pathway cannot be excluded. Furthermore, by using the polarized canine kidney cell line MDCK-II and its subclones transduced with murine Bcrp1 and human BCRP cDNAs to test the possible role of murine Bcrp1 and human BCRP in the in vitro transport of ciprofloxacin, ofloxacin, and norfloxacin, the results showed that ciprofloxacin, ofloxacin, and norfloxacin were efficiently transported by murine Bcrp1 and moderately transported by human BCRP in the cell lines used [23]. Furthermore, this study also found that Bcrp1 play an important role in rat. The plasma concentration of ciprofloxacin was more than 2-fold increased in Bcrp1_/_ compared with wild-type mice (1.77 ± 0.73 versus 0.85 ± 0.39 ug/ml, $p<0.01$) 15 min after oral administration. At the same time, to test whether Bcrp1 plays a role in the secretion of fluoroquinolones into milk, ciprofloxacin (10 mg/kg) was administered i.v. to lactating Bcrp1_/_ and wild-type females, and 10 min after administration, milk and blood were collected. The result showed that the concentration of ciprofloxacin was 2-fold lower in the milk of Bcrp1_/_ mice (2.19 ± 0.13 vs. 4.44 ± 0.84 ug/ml, $p<0.01$). Ciprofloxacin appears to be actively transported into the milk of mice by Bcrp1 [23].

Plasma and bile concentrations of fluoroquinolones were determined in wild-type and Bcrp (_/_) mice after i.v. bolus injection. The cumulative biliary excretion of fluoroquinolones was significantly reduced in Bcrp (_/_) mice, resulting in a reduction of the biliary excretion clearances to 86, 50, 40, and 16 of the control values, for ciprofloxacin, grepafloxacin, ofloxacin, and ulifloxacin, respectively [24]. This study also showed that, in Madin-Darby canine kidney II cells expressing human BCRP or mouse Bcrp, the basal-to-apical transport of grepafloxacin and ulifloxacin was greater than that of the mock control, which was inhibited by a BCRP inhibitor(Ko143) [24]. Therefore, BCRP/Bcrp play a significant role in the biliary excretion of fluoroquinolones.

β-lactam antibiotics and BCRP/Bcrp

By using membrane vesicles of Sf9 cells transfected with Bcrp, an uptake study revealed that the uptake of cefoperazone, cefbuperazone, cefpiramide, cefotetan, ceftriaxone, cefotiam, cefamandole, and cefazolin by rBcrp-expressing vesicles was significantly higher than that by control vesicles, which suggests that all these compounds all are substrates of rBcrp. Whether the same result has in hBCRP is not explored in this study. Simultaneously, it is not exclude that other transporters are involved the efflux transporting of these β-lactam antibiotics [25].

Other transporters (P-gp and MRP) and antibiotics

ATP dependent efflux transporter P-glycoprotein (P-gp, MDR1) and multidrug resistance associated protein (MRP) also play an important role in the pharmacokinetics of antibiotics.

Fluoroquinolone and P-gp and MRP

MDCKII-MDR1 was employed as an in vitro model to evaluate the effects of antiretrovirals, azole antifungals, macrolide, and fluroquinolone antibiotics on efflux transporters. These in vitro studies indicate that grepafloxacin, levofloxacin, and sparfloxacin are potent inhibitors of P-gp-mediated efflux of 14C erythromycin and (3) H cyclosporine [26].

Gatifloxacin (2.5 mM) also raised the uptake of [14C] erythromycin by 1.6-fold and 1.7-fold in MDCKII-MDR1 cells and MDCK-MRP2 cells, respectively, suggests that this fluoroquinolone is a potent inhibitor of P-gp and MRP2 [27].

A studies also demonstrated that gemifloxacin is effluxed by both P-gp and MRP2. This compound inhibited both P-gp and MRP2 mediated efflux of [14C] erythromycin in a dose dependent manner with IC50 values of 123 ± 2 μM and 16 ± 2 μM, respectively [28]. The P-gp inhibitors PSC833 and GF120918 and the MRP-inhibitor MK571 partially decreased the secretion of Danofloxacin-Mesylate (DM) and increased its absorption rate in Caco-2 cells .Therefore, DM is a substrate for the efflux transporters P-gp and MRP29 [29].

Macrolide Antibiotics and P-gp and MRP

Azithromycin is a substrate for P-gp, the product of the ABCB1 (ATP-binding cassette B1) gene [30] A number of Single Nucleotide Polymorphisms (SNPs) have been identified in ABCB1 gene between individuals and ethnic groups [31]. Three of the most frequently occurring SNPs within ABCB1 include C1236T in exon 12, G2677T/A in exon 21 and C3435T in exon 26 [32]. Azithromycin pharmacokinetics may be influenced by particular polymorphisms of the ABCB1 gene. Cmax was significantly lower among individuals with 2677TT/3435TT genotype (468.0 ± 173.4 ng • h/ml) than those with 2677GG/3435CC (911.2 ± 396.4 ng • h/ml, $p=0.013$). However, the t_{max} value was higher among subjects with 2677TT/3435TT (2.0 ± 0.5 h) than those with 2677GT/3435CT (1.6 ± 0.3 h) or 2677GG/3435CC (1.4 ± 0.4 h) genotypes ($p=0.068$ and $p=0.026$, respectively). Furthermore, the $AUC_{0\text{-}24}$ tended to be higher among subjects with 2677GG/3435CC than those with 2677GT/3435CT or 2677TT/3435TT genotypes (5000.2 ± 1610.0 vs. 4558.0 ± 805.0 vs. 4131.0 ± 995.1 ng/ml) [33]. Therefore, polymorphisms of the ABCB1 gene have significantly effect on the pharmacokinetics of azithromycin.

Bidirectional transport studies were conducted using our Caco-2 subclone with high P-gp expression (CLEFF9).Clarithromycin and roxithromycin are likely to exhibit drug interactions with digoxin via inhibition of efflux mechanisms, but azithromycin appears to have little influence on P-gp–mediated digoxin absorption or excretion and would be the safest macrolide to use concurrently with oral digoxin. As well, the study found that erythromycin had no effect on the transport of digoxin [34].

Mrp2 acted as a major canalicular transport protein responsible for spiramycin biliary excretion Mrp2-knockout mice was also confirmed. The study found that approximately 8-fold decrease in the recovery of spiramycin in the bile of Mrp2-knockout mice [35].

β-Lactam antibiotics and MRP

A study found that the uptake of cephalosporins by rMrp2- and hMRP2-expressing vesicles was also examined, and uptake of cefoperazone, cefbuperazone, cefpiramide, and ceftriaxone was significantly higher than that in control vesicles. Uptake of cefotetane and cefotiam was also significantly higher in hMRP2-expressing vesicles than that in control vesicles. This means that β-lactam antibiotics were the substrates of Mrp and MRP. Because most β-Lactam antibiotics are mainly excreted by kidney, therefore, MRP may act as one of efflux transporter in kidney tubules membranes. Simultaneously, possible involvement of other transporters on kidney tubules membranes,

such as P-glycoprotein and/or bile salt export pump, should also be considered for the kidney excretion of all the cephalosporins [36].

Conclusion

In clinic, patients are usually treated by multiple drugs. Therefore, it is necessary to pay close attention to drug-drug interactions when these drugs are combined to treat the diseases. At present, more and more antibiotics agents are found as the substrates of transporters. There may be potential drug-drug interactions based on transporters binding site competition. Therefore, further study should be explored when these antibiotic agents are combined with other drugs to treat diseases.

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