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Effect of various cytochrome P450 3A and P-glycoprotein modulators on the biliary clearance of bromosulphaphthalein in male wistar rats

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The main aim of this study was to investigate the effect of various selective cytochrome P4503A (CYP3A) and/or P-glycoprotein (P-gp) modulators on biliary clearance of bromosulphaphthalein (BSP) in male albino wistar rats. Male albino wistar rats were divided into different groups, treated with CYP3A and P-gp modulators and BSP was administered intravenously (bolus or infusion) to each treated group. BSP in serum and bile samples was analyzed using spectrophotometric analysis at 580 nm. There was a statistically significant ($p < 0.05$) increase in serum BSP levels with CYP3A and P-gp substrates and/or inhibitors, cyclosporine-A, nitrendipine,quinidine, indinavir, daxorubicin, etoposide and erythromycin by 27%, 35%, 32%, 12%, 5%, 22%, and 106%, respectively. There was a slight increase (4%, $p > 0.05$) observed in serum BSP levels in the presence of ketoconazole, whereas CYP3A and P-gp inducers, rifampicin and sodium butyrate significantly ($p < 0,05$) decreased the serum BSP levels by 30% and 14% respectively, when compared to control group after 62 min of BSP i.v. bolus administration. In BSP infusion studies, Cyclosporine A, nitrendipine, quinidine, indinavir, ketoconazole, doxorubicin, etoposide, and erythromycin significantly decreased the bile BSP levels by 23%, 22%, 17%, 59%, 3%, 15%, 10%, 29%, respectively. Upon 60 min of BSP infusion, rifampicin and sodium butyrate significantly ($p < 0.05$) increased bile BSP levels by 33% and 25%, respectively. Finally, we observed that the P-gp and CYP3A inducers significantly decreased the total serum BSP levels and increased the total biliary levels of BSP, this could be by inducing P-gp in biliary canalicular membrane in male wistar rats. P-gp and CYP3A inhibitors and substrates significantly increased the total serum BSP levels and reduced the biliary excretion of BSP by inhibiting P-gp in biliary pathway. There was no significant difference observed between inhibitors and substrates of P-gp on BSP disposition. We suggest that the biliary transport of BSP could be useful as a simple and economical *in vivo* screening model for identifying P-gp and CYP3A substrates and/or inhibitors and/or inducers in wistar rats.

1. Introduction

The main purpose of this study was to investigate the influence of various selective CYP3A and/or P-gp modulators on biliary clearance of bromosulphaphthalein (BSP) in male albino wistar rats. Important reason for selecting BSP, an anionic dye in our investigation was ist almost exclusive ($\sim 98\%$) excretion through bile canaliculi of the liver and the evidence of influence of P-glycoprotein (P-gp) on the biliary pathway in eliminating xenobiotics.

The functional role of P-gp on the bile canalicular membrane was originally demonstrated by studying the transport of daunomycin into rat canalicular membrane vesicles in the presence of other P-gp substrates, vincristine, adriamycin, verapamil and quinidine (Kamimoto et al. 1989). It had been reported that the inhibitory effect of PSC 833, an analog of immunosupressant, on the biliary clearance of colchicine and doxorubicine in rats (Kusuhara et al. 1998). These *in vivo* and *in vitro* studies suggested the strong influence of P-gp on the canalicular membrane, acting as a drug efflux pump to extrude xenobiotics into bile. There are several reports proving that the substrates of CYP3A overlap with the substrate or inhibitor of P-gp (Wacher et al. 1995). Recently, the emphasis shifted towards CYP3A and/or P-gp modulators due to their role in oral bioavailability enhancement and in reversing multi-drug-resistance in cancer cells. Most of the life saving drugs like immunosupressants (cyclosporine, tacrolimus etc.,), HIV-protease inhibitors (indinavir, saquinavir etc.,) are substrates of CYP3A and P-gp (Benet and Cummins 2001).

Similarly, multi-drug resistance in tumor cells can be minimized by co-administering these P-gp modulators with anticancer compounds (Dalmark et al. 1991; Rodenburg et al. 1991; Verweij et al. 1991). All these factors may lead to improved efficiency, decreased dose related toxicities and considerably reduced therapy costs. Hence, several *in vitro* and *in vivo* screening models were devel-

oped to identify P-gp and CYP3A substrates and/or inhibitors. One of the prominent models determines the transport of rhodamine-123, a fluorescent dye, and a P-gp substrate, in rat intestinal everted sacs, Caco-2 cell lines etc., (Yumoto et al. 1999).

With this theoretical background, we investigated the influence of various CYP3A and P-gp modulators on the biliary clearance of BSP in rats. Almost 98% of BSP is excreted through the bile, which is also catalyzed its conjugation with glutathione (Priestly and Plaa 1970). So far, no systematic study has been conducted to see the effect of various CYP3A and P-gp substrates and/or inhibitors on the biliary disposition of BSP. We studied the influence of some selected CYP3A and P-gp substrates, inducers and inhibitors on the biliary clearance of BSP in male wistar rats. We used, i). CYP3A and P-gp inducers (rifampicin and sodium butyrate) (Chin et al. 1990; Mickley et al. 1989; Schuetz et al. 1996), ii). CYP3A and P-gp inhibitors (quinidine, erythromycin and ketoconazole) (Wu et al. 1995) iii). CYP3A and P-gp substrates (doxorubicin and etoposide) (Wacher et al. 1995; Zhang and Benet 2001) and iv). CYP3A and P-gp substrates and inhibitors (cyclosporine A, indinavir and nitrendipine) (Hochman et al. 2001; Wacher et al. 1995; Wu et al. 1995; Zhang and Benet 2001).

2. Investigations and results

Cumulative mean ± s.d (n = 6) serum concentration (μg/ml) patterns of intravenous bolus BSP and mean cumulative ± s.d (n = 6) serum concentrations (μg/ml) in male wistar rats were shown in Table 1.

After 32 min of i.v. bolus administration of BSP, P-gp inducers rifampicin and sodium butyrate reduced the serum BSP levels from 270.8 ± 56.8 μg/ml to 75.7 ± 5.8 ($p < 0.05$) and 87.0 ± 37.3 μg/ml ($p < 0.05$), respectively. Similary, cyclosporine A, nitrendipine, quinidine, indinavir, ketoconazole, etopside and erythromycin increased the serum BSP levels from 270.8 ± 56.8 μg/ml to 275.8 ± 12.5 ($p > 0.05$), 553 ± 21.7 ($p < 0.05$), 405.6 ± 65 ($p < 0.05$), 320.8 ± 41.3 ($p < 0.05$), 337 ± 16.1 ($p < 0.05$), 443.1 ± 37.5 ($p < 0.05$), 664.1 ± 96 μg/ml ($p < 0.05$), respectively.

A slight increase was observed treating with cyclosporine A, and a decrease was observed in serum BSP levels with doxorubicin (from 270.8 ± 56.8 to 259.8 ± 25.3 μg/ml). However, both were not statistically significant ($p > 0.05$) at the dose levels tested. There was a statistically significant increase in serum levels of BSP observed with the CYP3A and P-gp inhibitors/substrates, whereas a statistically significant decrease in serum BSP levels was observed with P-gp inducers, rifampicin and sodium butyrate. Cyclosporine A, nitrendipine, quinidine, indinavir, ketoconazole, etoposide and erythromycin significantly ($p < 0.05$) increased mean serum BSP levels by 2%, 104%, 50%, 18%, 24%, 60%, 145%, respectively, when compared with control. Rifampicin and sodium butyrate significantly ($p < 0.05$) decreased the serum BSP levels by 72% and 68%, respectively.

A similar trend was observed with the serum BSP levels after 64 min of i.v. bolus administration, there was a statistically significant ($p < 0.05$) increase with cyclosporine by 27%, 35%, 32%, 12%, 5%, 22%, and 106%, respectively. There was a slight increase (4%, $p > 0.05$) in serum BSP levels in the presence of ketoconazole, whereas rifampicin and sodium butyrate significantly ($p < 0.05$) decreased the serum BSP levels by 30% and 14%, respectively, when compared to the control group after 62 min of BSP i.v. bolus administration.

Cumulative mean ± s.d (n = 6) biliary concentrations (μg/ml) of intravenous infusion of BSP and cumulative mean ± s.d concentrations (μg/ml) of bile BSP levels in male wistar rats are shown in Table 2. In intravenous infusion studies, cylcosporine A, nitrendipine, quinidine, indinavir, ketoconazole, doxorubicin, etoposide and erythromycin decreased the bile BSP levels from 1492 ± 41.15 μg/ml to 1136.5 ± 107.17 μg/ml, 1159.17 ± 57.47, 1249.3 ± 96.15, 810.5 ± 13.34, 1429 ± 32, 1205.17 ± 89.88, 1325.3 ± 96.76, and 1076.3 ± 13.13 μg/ml, respectively after 30 min of BSP infusion. Rifampicin and sodium butyrate increased the bile BSP levels to 2002.5 ± 78.66 and 2004.5 ± 11.29, respectively. All these observations were statistically significant at $p < 0.05$. A statistically significant ($p < 0.05$) decrease was observed with the pretreatment of cyclosporin A, nitrendipine, quinidine, indinavir, ketoconazole, doxorubicin, etoposide, and erythromycin by 24%, 22%, 16%, 46%, 4%, 19%, 11%, 28%, respectively after 30 min of BSP infusion. Rifampicin and sodium butyrate decreased the bile BSP levels by 34% ($p < 0.05$). A similar pattern was observed after 60 min of BSP infusion, cyclosporine A, nitrendipine, quinidine, in-

Table 1: Mean ± s.d (n = 6) serum bromosuphaphthalein concentrations (μg/ml) after 60 mg/kg of intravenous bolus administration in the presence of various CYP3A and P-gp modulators in male albino wistar rats

Group	After 32 min of BSP administration (% increase/ decrease (−))	After 64 min of BSP administration (% increase/ decrease (−))
Control	270.8 ± 56.8	4226.8 ± 266
Cyclosporin A	275.8 ± 12.5 (2)	5373.3 ± 141.2 (27)*
Nitrendipine	553 ± 21.7 (104)*	5719.7 ± 177.7 (35)*
Quinidine	405.6 ± 65 (50)*	5577.2 ± 350.1 (32)*
Indinavir	320.8 ± 41.3 (18)*	4735.7 ± 276 (12)*
Ketoconazole	337 ± 16.1 (24)*	4377.2 ± 178.6 (4)
Doxorubicin	259.8 ± 25.3 (−4)	4436.7 ± 126.8 (5)*
Etoposide	433.1 ± 37.5 (60)*	5165.2 ± 154.7 (22)*
Erythromycin	664.1 ± 96 (145)*	8717.5 ± 723 (106)*
Rifampicin	75.7 ± 5.8 (−72)*	2948.7 ± 107.5 (−30)*
Sodium butyrate	87 ± 37.3 (−68)*	3641.8 ± 441.3 (−14)*

'*' indicates statistically significance, one way ANOVA ($p < 0.05$)

Table 2: Mean ± s.d (n = 6) bromosulphaphthalein concentrations (μg/ml) after 2.5 mg/kg of intravenous infusion in the presence of various CYP3A and P-gp modulators in male albino wistar rats

Group	After 30 min of BSP administration (% increase/ decrease (−))	After 60 min of BSP administration (% increase/ decrease (−))
Control	1492 ± 41.15	7711.8 ± 273.3
Cyclosporin A	1136.5 ± 107.17 (−24)	5957.2 ± 463.2 (−23)*
Nitrendipine	1159.17 ± 57.47 (−22)*	6007.7 ± 253.4 (−23)*
Quinidine	1249.3 ± 96.25 (−16)*	6405.5 ± 330.5 (−17)*
Indinavir	810.5 ± 13.74 (−46)*	3149.5 ± 43.9 (−59)*
Ketoconazole	1429 ± 32 (−4)*	7517.5 ± 160 (−3)
Doxorubicin	1205.17 ± 89.88 (−19)	6535.7 ± 344 (−15)*
Etoposide	1325.3 ± 96.76 (−11)*	6975.5 ± 382.2 (−10)*
Erythromycin	1076.3 ± 13.13 (−28)*	5496.2 ± 73.3 (−29)*
Rifampicin	2002.5 ± 78.66 (34)*	10263 ± 159.9 (33)*
Sodium butyrate	2004.5 ± 11.29 (−34)*	9618.7 ± 107.9 (25)*

'*' indicates statistically significance, one way ANOVA ($p < 0.05$)

dinavir, ketoconazole, doxorubicin, etoposide, and erythromycin significantly ($p < 0.05$) decreased the bile BSP levels by 23%, 22%, 17%, 59%, 3%, 15%, 10%, 29%, respectively, whereas rifampicin and sodium butyrate significantly ($p < 0.05$) increased the biliary BSP levels by 33% and 25%, respectively.

3. Discussion

Earlier studies reported that the biliary clearance of BSP may be influenced by P-gp in biliary canaliculi (Kamimoto et al. 1989; Kusuhara et al. 1998). Based on these reports, we systematically investigated the role of various known CYP3A and P-gp modulators on the biliary elimination of BSP in male wistar rats. The role of P-gp in elimination of xenobiotics through biliary canaliculi was established to some extent. In our study, P-gp and CYP3A inducers, rifampicin and sodium butyrate significantly decreased the serum BSP levels by enhancing biliary elimination of BSP through induction of P-gp in biliary canaliculi. P-gp and CYP3A inhibitors and/or substrates increased the serum BSP levels by inhibiting the P-gp at biliary canaliculi. In an i.v. infusion study, BSP was estimated in bile in induced/inhibitory conditions of P-gp using CYP3A and P-gp modulators. Rifampicin and sodium butyrate increased the BSP levels in bile by inducing P-gp in biliary canaliculi, whereas the P-gp substrates and/or inhibitors, cyclosporine A, nitrendipine, quinidine, indinavir, ketoconazole, and erythromycin etc. decreased the biliary transport of BSP by reducing the BSP levels in bile by inhibiting P-gp. However, no clear difference among P-gp substrates and inhibitors in terms of BSP disposition in male wistar rats was observed. There may be some differences in the biliary clearance of total BSP and its glucuronide conjugation. In our investigation, the influence of these known P-gp and CYP3A modulators on the disposition of total BSP was studied but not the glucuronide and other conjugates of BSP. We expected a significant difference in the biliary metabolism of BSP in biliary canaliculi in the presence of these CYP3A inhibitors, substrates and inducers. Our study was also been supported by several reports where colchicine (canalicular multi specific organic anion transporter) treatment significantly inhibited the biliary excretion of indocyanine green, dinitrophenyl glutathione and pravastatin, and had no effect on biliary excretion of BSP and dibromosulfophtalein. Phenothiazine (P-gp inducer) treatment did not effect biliary excretion of indocynanin green and pravastatin, but it increased biliary BSP glutathione excretion. Phenothiazine treatment also led to a 6.5-fold increase in the expression of P-gp on the biliary canalicular membrane leading to a 60% increase in the cumulative amount of vincristine (P-pg substrate) excreted into bile up to 15 min after administration (Takikawa et al. 1998; Watanabe et al. 1995).

Unfortunately, it was difficult to quantitatively evaluate the role of P-gp on the bile canalicular membrane, in terms of the biliary clearance of P-gp substrates, since there were no reports in which the time profiles for both the plasma concentrations and amount excreted into the bile were simultaneously determined (Schinkel et al. 1997; van Asperen et al. 1996). A number of compounds, including verapamil and cyclosporine A, were found to inhibit the P-gp function in *in vitro* experiments with cultured tumor cells. PSC833, a compound with no immunosuppressive action, was synthesized as a cyclosporin A analogue. PSC833 is one of the most potent agents as far as MDR reversal was concerned, and therefore, was introduced into clinical trials (Kusuhara et al. 1998; Raderer and Scheithauer 1993). Although many studies were performed to examine the effect of MDR modulators on the plasma and/or tissue concentrations of antitumor drugs, there is only a limited number of reports describing quantitatively changes in the biliary clearance and/or tissue-to-plasma concentration ratio. Speeg and Madonado reported the inhibitory effect of PSC833 on the biliary clearance of colchicine and doxorubicin in rats (Kusuhara et al. 1998). Wacher et al. reported that the substrates of P4503A overlap with the substrate or inhibitor of P-gp (Wacher et al. 1995). Previously, Schuetz et al. 1996 reported that rifampicin treatment increased the mRNA of P4503A in LS180 and its derived cell line LS180/AD50 which acquired the resistance to adriamycin by the over expression of P-gp in a concentration dependent manner (Kusuhara et al. 1998). Some researchers (Sato et al. 1999) studied the biliary excretion of erythromycin in rats. They found that the infusion of BSP and taurocholate significantly decreased the biliary excretory pathway for organic cations, and reported that there was an additional pathway for transporting organic cations apart from P-pg in biliary canaliculi. Ben-Zvi and Hurwitz (1986) studied the effect of morphine and clonidine on BSP disposition in mice and found that these agents elevated BSP levels in plasma and liver.

In our study, we observed that the P-gp and CYP3A inducers significantly decreased the total serum BSP levels and increased the total biliary levels of BSP by inducing P-gp in the biliary canalicular membrane of male wistar rats, whereas P-gp and CYP3A inhibitors and substrates significantly increased the total serum BSP levels and reduced the biliary excretion of BSP by inhibiting P-gp in the biliary pathway. No significant difference was observed between inhibitors and substrates of P-gp regarding BSP disposition.

We suggest that the biliary transport of BSP could be useful as a simple and economical *in vivo* screening model for identifying P-gp and CYP3A substrates and/or inhibitors and/or inducers in wistar rats.

4. Experimental

4.1. Materials

Bromosulphaphthalein (BSP) and sodium butyrate were purchased from Himedia India Ltd, Mumbai, India and E. Merck, India, Ltd., respectively. NaOH (AR grade) and HCl (ER grade) were obtained from S.D. Fine chemicals Ltd., Mumbai, India, and Qualigens Chemicals, Mumbai, India. Cyclosporine A, nitrendipine, quinidine, indinavir, ketoconazole, erythromycin, and rifampicin were obtained as gift samples from Panacea biotech Ltd, India, US Vitamins Ltd, India, Franco-Indian Pvt Ltd, India, Aurobindo Pharma Ltd, India, Torrent Pharma Ltd, Ahmedabad, India, Sun Pharma, Baroda, India, Lupin Laboratories, Pune, India, respectively. Doxorubicin and etoposide were obtained as gift samples from Biological. E Ltd Hyderabad, India.

4.2. Animals

Male Albino wistar rats weighing 250–300 g were purchased from the National Institute of Nutrition (NIN), Hyderabad, India, and acclimatized to laboratory conditions for one week prior to experiments. Each group of rats was housed in a cage and maintained at about 25 °C and 60% relative humidity with a 12 h light/dark cycle. Rats were fed with controlled diet and distilled water ad libitum. All the experiments were conducted after taking approval from institutional animal ethical committee of University College of Pharmaceutical Sciences, Kakatiya University. Rats were randomly divided into groups, each group consisting of 6 rats.

4.3. Methods

All the animals were grouped and treated with the following regimens.

i. Rifampicin, 50 mg/kg/ip, dispersed in 0.25% (w/v) sodium salt of carboxy methyl cellulose (NaCMC), once daily for 7 days.

ii. Sodium butyrate, 0.5 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC, once daily for 7 days.

iii. Ketoconazole, 50 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
iv. Quinidine, 40 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
v. Erythromycin, 50 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
vi. Nitrendipine, 50 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
vii. Etoposide, 50 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
viii. Doxorubicin, 36 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
ix. Cyclosporin, 100 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
x. Indinavir, 50 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
xi. Control, 10 mg/kg/ip, dispersed in 0.25% (w/v) NaCMC.
One hour after the administration of above mentioned drugs, 60 mg/kg (bolus) or 2.5 mg/min/kg (infusion) of BSP was administered intravenously to each group.

4.3.1. Bolus study

Rats were administered with 60 mg/kg of BSP in distilled water intravenously as bolus through their vein. Aliquots of 0.2 ml blood samples were collected via orbital plexus at 2, 4, 8, 16, 32 and 64 min after BSP administration and BSP was analyzed in serum samples. Temperature was maintained at 37 °C with a heat lamp to prevent hypothermic alterations in biliary excretion (Priestly and Plaa 1970).

4.3.2. Infusion study

Rats were infused through jugular vein cannualation with 2.5 mg/min/kg BSP for a period of 1 h using an infusion pump (Ambala, Inco, India) with a flow rate of 1 ml/h. Bile duct was cannulated with polyethylene tubing. Bile was collected at 10, 20, 30, 40, 50, and 60 min after begining of infusion. Total BSP was estimated in the bile samples.

4.3.3. Analysis

BSP in serum and bile samples was analyzed using spectrophotometric analysis (Elico SL 159, Hyd, India). The difference in absorbance at 580 nm in acid and alkaline solution was a measure the concentration of BSP which is purple in alkaline solution and colorless in acid (Priestly and Plaa 1970).

4.3.4. Statistical analysis

One way ANOVA at $p < 0.05$ was used for statistical analysis of the obtained data.

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