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SHORT COMMUNICATION

Pazopanib interacts with irinotecan by inhibiting UGT1A1-mediated glucuronidation, but not OATP1B1-mediated hepatic uptake, of an active metabolite SN-38

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Abstract

Purpose Pazopanib is an orally active, multi-targeted tyrosine kinase inhibitor. A previous phase I study demonstrated that coadministration of pazopanib with irinotecan increases the area under the plasma concentration–time curve (AUC) for SN-38, an active metabolite of irinotecan. To clarify the possible mechanism underlying that drug–drug interaction, we investigated the potential for pazopanib to inhibit UDP-glucuronosyltransferase (UGT)1A1 and organic anion-transporting polypeptide (OATP)1B1, which are involved in detoxification and hepatic uptake of SN-38, respectively.

Methods Human liver microsomes (HLMs) and recombinant human UGT1A1, and HEK293 cells stably transfected with OATP1B1 were used to evaluate the inhibitory effects of pazopanib against glucuronidation, and hepatic uptake of SN-38, respectively. Kinetic analysis was performed to estimate inhibition constants, which were corrected for non-specific binding to enzyme sources ($K_{i,u}$ values).

Results Concentration-dependent inhibition of SN-38 glucuronidation was observed in the HLMs and recombinant human UGT1A1 experiments: Pazopanib noncompetitively inhibited SN-38 glucuronidation by HLMs ($K_{i,u} = 1.6 \pm 0.05$ μM) and recombinant human UGT1A1 ($K_{i,u} = 0.69 \pm 0.02$ μM). Pazopanib-induced increases in SN-38 AUC estimated using $K_{i,u}$ values were comparable to those observed in patients of the phase I study who received both irinotecan and pazopanib. Such results suggest that the drug–drug interaction is at least partially mediated by inhibition of UGT1A1. In contrast, pazopanib did not inhibit OATP1B1-mediated SN-38 uptake at concentrations up to 60 μM.

Conclusions Results showed that pazopanib inhibits UGT1A1-mediated SN-38 glucuronidation, but not OATP1B1-mediated SN-38 uptake.

Keywords Pazopanib · UGT1A1 · SN-38 · Pharmacokinetics · Drug–drug interaction

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Introduction

Pazopanib, an orally active, second-generation tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma and soft tissue sarcoma [1], targets multiple proteins, including vascular endothelial growth factor receptors and platelet-derived growth factor receptors. A variety of combination therapies that pair pazopanib with cytotoxic anticancer or molecular-targeted drugs have been evaluated for efficacy and toxicity against various solid tumors [2–5]. In such pharmacotherapies, additive and/or synergic pharmacological activities are generally desired. However, unexpected pharmacokinetic drug–drug interactions sometimes occur. Elucidation of the mechanism of such interactions can facilitate the development of drugs that lack undesirable interactions, as well as aid in the appropriate use of therapeutic drugs in clinical practice.

A previous phase I open-label study examined the pharmacokinetics of pazopanib in combination with irinotecan hydrochloride in patients with relapsed or refractory metastatic colorectal cancer [3]. The study revealed that coadministration of 400 and 800 mg pazopanib with 120 mg/m^2 irinotecan hydrochloride increases the area under the plasma concentration–time curve (AUC) for SN-38 (an active metabolite of irinotecan produced by carboxylesterase) [6] by approximately 40 and 90%, respectively. Although that suggests a pharmacokinetic drug–drug interaction, the detailed mechanism remains unclear. To understand the mechanism, factors associated with SN-38 pharmacokinetics must be considered. SN-38 is reportedly detoxified by the hepatic drug-metabolizing enzyme UDP-glucuronosyltransferase (UGT)1A1 to inactive SN-38 glucuronide [6]. Organic anion-transporting polypeptide (OATP)1B1, expressed in the sinusoidal membrane of hepatocytes, is responsible for the uptake of SN-38 into hepatocytes [7]. UGT1A1 is also involved in endogenous bilirubin metabolism. Administration of pazopanib results in elevation of plasma bilirubin concentration, which could be attributable to inhibition of UGT1A1 [8]. Furthermore, pazopanib inhibits hepatic uptake transporter OATP1B1, but not OATP1B3 [9]. Coadministration of pazopanib with docetaxel reportedly increases the AUC of docetaxel by possibly inhibiting OATP1B1 and/or CYP3A, which are responsible for the uptake and metabolism of docetaxel, respectively [10]. The above lines of evidence suggest that pazopanib inhibits UGT1A1-mediated metabolism and/or OATP1B1-mediated hepatic uptake of SN-38.

In this study, we investigated pazopanib inhibition of UGT1A1-mediated SN-38 glucuronidation using human liver microsomes (HLMs) and recombinant human UGT1A1, and OATP1B1-mediated SN-38 uptake.

Materials and methods

Chemicals

SN-38 was obtained from Toronto Research Chemicals (Toronto, Canada) and Tokyo Chemical Industry (Tokyo, Japan) for experiments on UGT1A1-mediated SN-38 glucuronidation and OATP1B1-mediated SN-38 transport, respectively. Pazopanib was purchased from Phoenix pharmaceuticals (Burlingame, CA, USA) and SYNkinase Pty Ltd. (San Diego, CA, USA) for inhibition of UGT1A1-mediated SN-38 glucuronidation and OATP1B1-mediated SN-38 transport, respectively. SN-38 glucuronide was acquired from Toronto Research Chemicals. Camptothecin was obtained from FUJIFILM Wako Pure Chemical Corporation (Tokyo, Japan). UGT reaction mix solution A [25 mM UDP-glucuronic acid (UDPGA) cofactor in water] and UGT reaction mix solution B [5X-UGT buffer containing 250 mM Tris–HCl (pH 7.5), 40 mM $MgCl_2$, and 0.125 mg/mL alamethicin in water] were acquired from BD Biosciences (Woburn, MA, USA). All other chemicals and reagents were of analytical grade and obtained from commercial sources.

HLMs and recombinant human UGT1A1

Pooled HLMs were obtained from Human and Animal Bridging Research Organization (Tokyo, Japan), a nonprofit organization. The pooled HLMs (microsomal protein content: 20 mg/mL) were derived from ten donors (80% Caucasian and 20% Hispanic; eight men and two women) with a median age of 55 years (range 16–80). Recombinant human UGT1A1 Supersomes expressed in baculovirus-infected insect cells (microsomal protein content: 5.0 mg/mL) were purchased from BD Biosciences (Woburn, MA, USA).

SN-38 glucuronidation inhibition assay

Effect of pazopanib on SN-38 glucuronidation by HLMs and recombinant human UGT1A1 was assessed per the methods by Fujita et al. [11], with minor modifications. A typical incubation mixture consisted of 1X-UGT reaction mix solution B [50 mM Tris–HCl (pH 7.5), 8 mM $MgCl_2$, and 25 µg/mL alamethicin], and 0.5 mg/mL HLMs or 0.2 mg/mL recombinant human UGT1A1 Supersomes in a final volume of 0.2 mL. After preincubation of the mixture with SN-38 (1.25–20 µM), and either pazopanib (0.1–25 µM) or solvent alone at 37 °C for 5 min, UGT reaction mix solution A (2 mM UDPGA) was added to initiate the enzyme reaction. Pazopanib and SN-38 were dissolved in dimethyl sulfoxide (DMSO). The final concentration of the solvent in the reaction mixture was 2.6% (v/v). The reaction was

terminated by a twofold volume of acidified acetonitrile including camptothecin as an internal standard, and then subjected to reverse-phase high-performance liquid chromatography (HPLC). Incubation periods were 5 min for HLMs and 30 min for recombinant UGT1A1. Each assay was performed three times in duplicate. SN-38 and SN-38 glucuronide were analyzed by HPLC according to the methods by Fujita et al. [7, 11], with modifications. We utilized Shimadzu Prominence UFLC™ system (Shimadzu, Kyoto, Japan) consisted of CBM-20A communication bus module, LC-20AD pump, SIL-20A automated sample injector, and L-7480 fluorescence detector (Hitachi, Tokyo, Japan) equipped with a Capcell Pak C18 MGIII (4.6 × 250 mm, 5 µm; Shiseido, Tokyo, Japan). Data were processed with LC solution software (Shimadzu, Kyoto, Japan). Linear ranges of 1–2000 nM and 6.25–500 nM, and detection limit of 1 and 3 nM, were established for SN-38 and SN-38 glucuronide, respectively.

Estimation of kinetic parameters

HLMs and recombinant human UGT1A1 were used to estimate K_m and V_{max} values of SN-38 glucuronidation and the inhibition constant (K_i value) of pazopanib against UGT1A1-catalyzed SN-38 glucuronidation. SN-38 concentrations ranged from 1.25 to 20 µM in the absence or presence of pazopanib (0.1–25 µM). The maximum plasma concentrations of SN-38 and pazopanib in clinical practice are approximately 0.1 and 150 µM, respectively.

The Michaelis–Menten equation was fitted to data points to estimate K_m and V_{max} values via nonlinear least-squares regression analysis, which was performed using GraphPad Prism version 7 software (GraphPad Software, La Jolla, CA, USA). The K_i values were also estimated by nonlinear regression analysis with GraphPad Prism version 7 software by fitting all the data points obtained from substrate concentrations ranging from 1.25 to 20 µM and inhibitor concentrations from 0 to 25 µM to the Michaelis–Menten equations that assumed competitive, noncompetitive, or mixed inhibition [11]. The type of inhibition was determined from enzyme inhibition models fitted to the data. Goodness of fit was estimated from F statistics, R^2 values, parameter standard error estimates, and 95% confidence intervals. Kinetic parameters (K_m, V_{max}, and K_i values) were reported as the means ± standard error. Because pazopanib reportedly bind non-specifically to HLMs [12, 13], K_i values were multiplied to the unbound fraction of pazopanib to obtain corrected value ($K_{i,u}$). Per Miners et al. [13], the unbound fraction of pazopanib in 0.5 mg/mL HLMs is 0.5. Assuming that the unbound fraction of pazopanib is the same in Supersomes as it is in HLMs, we calculated that the unbound fraction of pazopanib in 0.2 mg/mL of Supersomes was 0.77.

Equilibrium dialysis was used to evaluate non-specific binding of SN-38 to HLMs according to the method by Fujita et al. [14] with modifications. Briefly, phosphate buffered serine (150 µL) and an equal volume of that containing 0.5 mg/mL HLMs and 1 µM SN-38 were added to the dialysate and sample sides of a 96-well equilibrium apparatus (HTD 96b; HTDialysis, Gales Ferry, CT, USA), respectively. After incubation at 37 °C for 24 h, dialysate and HLM samples were collected and subjected to HPLC analysis as describe above.

Estimation of inhibition potential of pazopanib against UGT1A1 in humans

Potential inhibition of UGT1A1 by pazopanib in vivo in humans was evaluated by comparing K_i values obtained from the present study with the estimated average unbound concentration of pazopanib in circulating plasma ($f_u \cdot [I]_{av}$, where f_u is the unbound fraction in plasma and $[I]_{av}$ is the average total plasma concentration) in cancer patients receiving both irinotecan hydrochloride and pazopanib. $[I]_{av}$ was calculated using the following equation:

$$[I]_{av} = D/\tau/(\mathrm{CL/F}), \quad (1)$$

where D, τ, and CL/F are dose, dosing interval, and oral clearance, respectively. According to previously reported data on the recovery of a 450-mg dose of irinotecan administered to a cancer patient with an external biliary drain, the UGT1A1-mediated detoxification and biliary excretion rates of SN-38 were 7.6% and 1.4%, respectively [15]. Therefore, the calculated fraction of SN-38 metabolized via glucuronidation (f_m) is 0.84. The ratio of AUC for UGT1A1 substrates in the presence of pazopanib ($AUC_{+pazopanib}$) to that in its absence ($AUC_{control}$) was estimated using the $K_{i,u}$ values from in the present study as follows [16]:

$$AUC_{+pazopanib}/AUC_{control} = 1/\left[f_m/(1 + f_u[I]_{av}/K_{i,u}) + (1 - f_m)\right]. \quad (2)$$

Transport studies in HEK293 cells stably transfected with OATP1B1

HEK293 cells stably expressing OATP1B1 (HEK293/OATP1B1) were previously established [7] and utilized for the SN-38 uptake experiment, which was performed as previously described [7], with minor modifications. Briefly, cells were seeded at 1×10^5 cells/plate for each reaction and harvested at 48 h later. Cell suspensions were prewarmed at 37 °C for 5 min. Then, transport buffer containing SN-38 (0.03 µM) with or without

pazopanib were added to initiate the transport reaction. This SN-38 concentration was set to be much lower than the K_m value (4.97 μM) for its OATP1B1-mediated transport [7]. Both compounds was initially dissolved in DMSO to give a final concentration of 1% (v/v). Forty minutes after the start of incubation, the mixture was diluted six times with ice-cold transport buffer and centrifuged at 180*g* for 1 min at 4 °C, after which the supernatant was removed. The cells were further washed twice with ice-cold buffer, and then disrupted in distilled water with a sonicator. The concentrations of SN-38 in the medium and cell lysates were measured by a modified reverse-phase HPLC method as previously described [7, 11], with modifications. A 40-μL of disrupted cells or medium was mixed with 60 μL of a mixture of methanol and 10% perchloric acid (50:50, v/v) and 10 μL of camptothecin (internal standard) dissolved in the same mixture. The mixture was centrifuged twice at 21,500*g* for 10 min, and the supernatant was injected into an HPLC system (Shimadzu LC-10Avp series; Shimadzu, Kyoto, Japan), equipped with a TSK-gel ODS-120T analytical column (4.6 × 250 mm, 4 μm; TOSOH, Tokyo, Japan). Rifampicin was used as a positive control for the inhibition of OATP1B1-mediated SN-38 uptake. Uptake was normalized by both the cellular protein content which was determined according to the method of Bradford using a protein assay kit (Bio-Rad Laboratories, Hercules, CA, USA) with bovine serum albumin as the standard, and the SN-38 concentration in the medium, yielding the intracellular distribution volume (μL/mg protein).

Results

Inhibition of UGT1A1 by pazopanib

Figure 1a shows SN-38 glucuronidation versus substrate concentration plots obtained from pooled HLMs in the presence or absence of pazopanib. The calculated values for K_m and V_{max} were 1.3 ± 0.07 μM and 17 ± 0.2 pmol/min/mg protein, respectively. The unbound fraction of SN-38 in the incubation mixture containing 0.5 mg/mL HLMs was 0.44 ± 0.003. Based on that fraction, the calculated unbound base K_m was 0.57 μM. Nonlinear regression analysis indicated noncompetitive inhibition ($R^2 = 0.97$, estimated K_i value of 3.2 ± 0.1 μM). The calculated $K_{i,u}$ value was 1.6 ± 0.05 μM. When recombinant human UGT1A1 was used to analyze the inhibition kinetics of pazopanib against SN-38 glucuronidation (Fig. 1c), the calculated K_m and V_{max} values were 2.0 ± 0.07 μM and 82 ± 0.9 pmol/min/mg protein, respectively. The calculated unbound fraction of SN-38 in 0.2 mg/mL Supersomes was 0.67, assuming that the unbound fraction of pazopanib was the same in Supersomes as in HLMs. The calculated K_m value, corrected for the unbound fraction, was 1.34 μM. Nonlinear regression analysis revealed noncompetitive inhibition ($R^2 = 0.99$; Fig. 1c). The estimated K_i and $K_{i,u}$ values were 0.89 ± 0.03 μM, and 0.69 ± 0.02 μM, respectively.

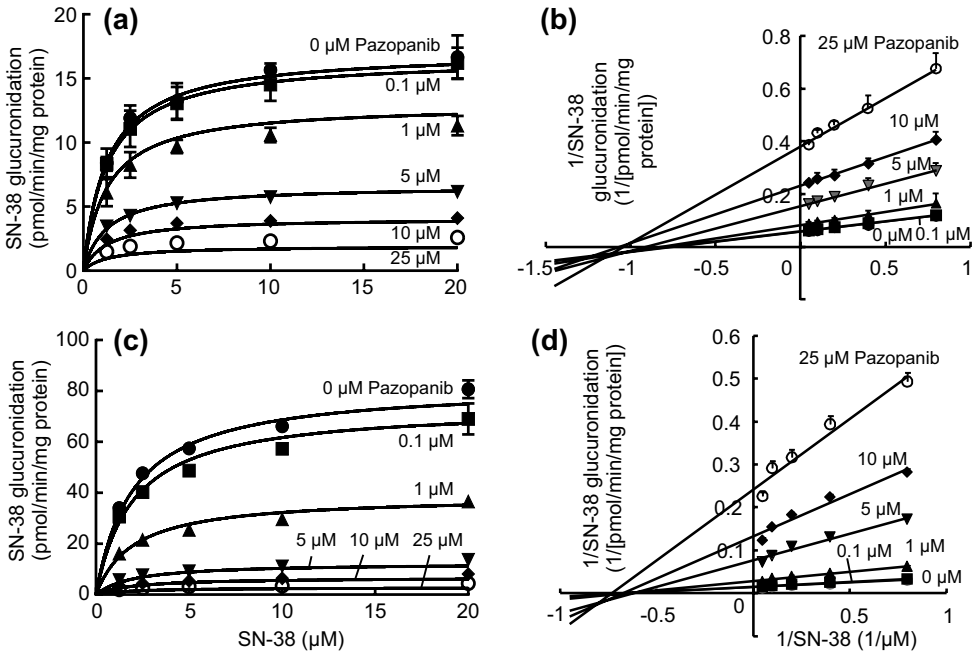

Fig. 1 Inhibition kinetics of pazopanib against SN-38 glucuronidation by HLMs and recombinant human UGT1A1. Plots **a, c** illustrate substrate concentration vs. velocity of glucuronidation by HLMs and recombinant human UGT1A1, respectively. **b, d** depict Lineweaver–Burk plots from the HLM and recombinant human UGT1A1 experiments, respectively. Each point represents the mean of three independent experiments with standard deviation

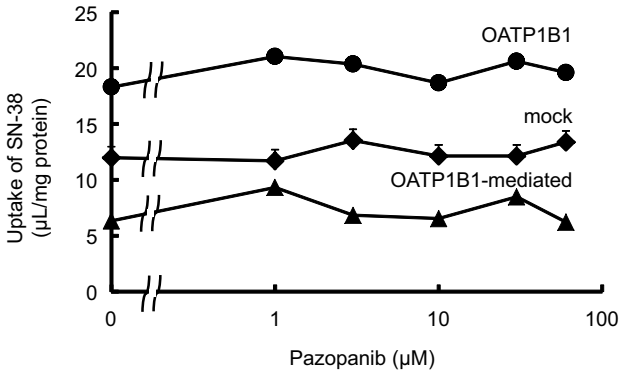

Fig. 2 Human OATP1B1-mediated uptake of SN-38. Uptake of SN-38 (0.03 μM) in HEK293/mock cells (filled diamond) was subtracted from uptake in HEK293/OATP1B1 cells (filled circle) to calculate OATP1B1-mediated uptake (filled triangle). A 36% reduction in the uptake of SN-38 (0.03 μM) in HEK293/OATP1B1 cells was observed by the addition of the representative OATP1B1 inhibitor rifampicin (30 μM). Each point represents the mean ± standard error of the mean ($n = 3$–6). Error bars that are smaller than the symbols are not visible

Minimal effect of pazopanib on OATP1B1-mediated uptake of SN-38

We analyzed the effect of pazopanib on OATP1B1-mediated uptake of SN-38 because OATP1B1 is predominantly responsible for hepatic uptake of SN-38 [7]. Figure 2 shows that OATP1B1-mediated uptake of SN-38 was minimally reduced in the presence of 1–60 μM pazopanib. In contrast, addition of the representative OATP1B1 inhibitor rifampicin (30 μM) resulted in a 36% reduction in SN-38 uptake.

Potential for pazopanib-induced UGT1A1-mediated drug–drug interaction

To examine whether pazopanib-mediated inhibition of UGT1A1-catalyzed SN-38 metabolism can explain the rise in SN-38 AUC in cancer patients who received both irinotecan and pazopanib, inhibition potential of pazopanib for UGT1A1 in vivo in humans was estimated using the $K_{i,u}$ values obtained in the present study and clinically relevant unbound concentration of pazopanib ($f_u \cdot [I]_{av}$) using Eqs. (1) and (2). We used values for f_u, D, τ, and CL/F from previous studies: 0.01 (< 0.01), 800 mg (1.828 mmol), 24 h, and 0.6 L/h, respectively [17–19]. Using the above information in Eq. (1), the estimated $f_u \cdot [I]_{av}$ value for pazopanib was 1.27 μM. This, along with $K_{i,u}$ values obtained from HLM and recombinant human UGT1A1 assays, was entered into Eq. (2). Results showed that compared to that of control, pazopanib increased SN-38 AUC in HLMs and recombinant human UGT1A1 Supersomes by a factor of 1.6 and 2.2, respectively. Those results were comparable to the ~ 90% increase in SN-38 AUC that is clinically observed in patients taking 800 mg pazopanib once daily [3].

Discussion

Pazopanib is known to clinically induce hyperbilirubinemia by inhibiting UGT1A1-mediated glucuronidation of bilirubin [8]. Support for this lies in *UGT1A1*28* genotypes, which are associated with pazopanib-induced elevation of plasma bilirubin levels such that elevation is highest in those with *UGT1A1*28/*28*, followed by those with **1/*28* and **1/*1* [8]. That *UGT1A1*28* is associated with reduced ability to metabolize bilirubin helps confirm the belief that inhibition of UGT1A1-mediated bilirubin conjugation by pazopanib can cause hyperbilirubinemia.

The in vitro half-maximal inhibitory concentration (IC_{50}) value of pazopanib for UGT1A1-mediated bilirubin glucuronidation is reportedly 3.7 μM [13]; the estimated $K_{i,u}$ value of pazopanib for the inhibition of SN-38 glucuronidation from HLM assays was 1.6 μM. Thus, our in vitro inhibition study demonstrated that pazopanib inhibits UGT1A1-catalyzed glucuronidation of SN-38. Taking into consideration our in vitro results and previous reports, we believe that the AUC of SN-38 is higher in cancer patients treated with concomitant irinotecan hydrochloride/pazopanib therapy than in those treated with irinotecan hydrochloride alone [3] because pazopanib inhibits UGT1A1-mediated SN-38 glucuronidation. The estimated increase in SN-38 AUC associated with coadministration of pazopanib (calculated based on Eq. 2) supports this hypothesis. However, the conclusions of this study vary depending on whether the in vitro–in vivo extrapolation is based on $K_{i,u}$ obtained from HLMs (minor interaction predicted) or recombinant UGT1A1 (significant interaction predicted).

Although Xu et al. [8] reported that pazopanib inhibits OATP1B1-mediated uptake of estradiol 17β-D-glucuronide into Chinese hamster ovary cells in a concentration-dependent manner (IC_{50} of 0.79 μM). Pazopanib did not inhibit OATP1B1-dependent SN-38 uptake in our study, even at concentrations as high as 60 μM (Fig. 2). Such opposing results suggest that pazopanib-induced inhibition of OATP1B1-mediated uptake is substrate-dependent.

In conclusion, our in vitro inhibition study revealed that pazopanib inhibits UGT1A1-mediated glucuronidation, but not OATP1B1-mediated transport, of SN-38. Thus, inhibition of UGT1A1 might be clinically relevant, at least partially explaining the interaction between pazopanib and irinotecan in cancer patients.

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Compliance with ethical standards

Conflict of interest We have no conflict of interest to declare.

Ethical standards No human and/or animal studies were performed in this study.

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