INTERACTION OF RITONAVIR ON TISSUE DISTRIBUTION OF A [14C]-VALINAMIDE, A POTENT HUMAN IMMUNODEFICIENCY VIRUS-1 PROTEASE INHIBITOR, IN RATS USING QUANTITATIVE WHOLE-BODY AUTORADIOGRAPHY

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ABSTRACT:

Multidrug and/or multitarget, highly active antiretroviral therapy of HIV-1, to overcome progression to acquired immunodeficiency syndrome, is still a method of choice for viral suppression. There is also currently an inclusion of pharmacoenhancers in such treatments, in particular the use of RTV. RTV has been previously demonstrated to boost and maintain exposure levels for various HIV protease inhibitors, such as indinavir, amprenavir, saquinavir, lopinavir, and nalfanavir in the clinic, and maintain exposure levels for various HIV protease inhibitors, such as indinavir, amprenavir, saquinavir, lopinavir, and nalfanavir in the clinic, mainly because of inhibition of the metabolizing enzyme CYP3A4 and the transporter Pgp (Casada et al., 2000; Moyle and Back, 2001). Apart from measuring the systemic exposure to various drugs, it is imperative to determine drug distribution into various organs in which the virus can find a sanctuary (e.g., brain and testes) and escape the onslaught of drugs, allowing the virus to replicate, causing CNS damage and viral mutations. The conventional method for such measurement has been excising each organ separately, homogenizing it, followed by oxidizing and liquid scintillation counting of the trapped radioactivity. Currently, quantitative whole-body autoradiography (QWBA) has provided the means for quantitating radioactivity in whole-body sections of animals, which can determine distribution of radioactivity in many more tissue and fluid compartments (Shigematsu et al., 1995, 1999; Zane et al., 1997; Potchoiba et al., 1998). With the continued improvement and standardization of the process, QWBA is rapidly becoming the method of choice for the study of tissue distribution of radiolabeled compounds in animals. The technique has been shown to yield results similar to those obtained by excision of tissue followed by combustion and liquid scintillation counting (Chay and Pohland, 1994). The technique, apart from its major use for human dosimetry estimations (Duin et al., 1994), has also been used for studies like placental transfer (Chay and Herman, 1998), brain penetration (Polli et al., 1999), and in general, assessing accumulation of drug-related materials in organs for toxicological evaluations. DPC is a potent and selective inhibitor of HIV-1 (Kc, 0.012 nM; IC90, 4 nM), and also of various mutant strains (IC90 of ≥20 nM for various triple to quintuple mutant variants) (Kaltenbach et al., 2001). In the present studies, QWBA was used to determine the effect of RTV on the disposition of DPC in rats. Possible mechanisms for increases in exposure to [14C]DPC in rats and extrapolation of these results to humans are also discussed.

Materials and Methods

DPC (Scheme 1), [14C]DPC, GF120918 were prepared at Bristol-Myers Squibb Company (Wilmington, DE). RTV was obtained from Moravek Biochemicals (Brea, CA). All the other chemicals were of analytical or HPLC grade.
Parameters were calculated using the WATSON program (WATSON version 5.4 of DPC and the internal standard were 6.6 and 7.6 min, respectively. Retention times that was run over 10 min at a flow rate of 0.7 ml/min. Reagents Transwell polycarbonate membranes (0.4-μm pore size) at a density of 10^4 cells/cm^2. The Transwell (Corning) inserts were placed in 12-well plates containing MEM containing 10% fetal bovine serum (Hyclone Laboratories, Logan, UT), 1% nonessential amino acids, 100 U/ml penicillin, and 100 μg/ml streptomycin (Invitrogen). The cell culture media in the basolateral compartment. The culture medium in the transwell was replaced every other day for 21 days before the cells were used for the transport studies.

**Rat Pharmacokinetics.** DPC was dissolved in a vehicle of 0.1% methanesulfonic acid and 1% Tween 80 at a concentration of 5 mg/ml. RTV was formulated at a concentration of 1 mg/ml in a vehicle of 5% aqueous methylcellulose. The dosing formulations of either DPC or RTV were prepared and stored refrigerated on the day before dosing.

Eight, male, Sprague-Dawley rats (ca. 250 g), which were obtained with surgically implanted jugular vein cannuli from Charles River Laboratories Inc. (Wilmington, MA) were acclimated for 5 days prior to administration of test compound. One group of 4 rats was pretreated with oral doses of RTV (10 mg/kg) at approximately 2 and 2 h prior to dosing with a single oral dose of DPC (20 mg/kg). Another group of four rats received only a single oral dose of DPC (20 mg/kg). Following administration of the test material, each animal in both groups was placed into an individual cage and blood samples (ca. 0.5 ml) were collected from each rat, via jugular vein, at 5, 15, and 30 min and at 1, 2, 3, 4, 6, 8, 10 and 24 h postdose. Whole blood from donor rats was infused into each study rat to maintain blood volume lost due to sample collection. The plasma was separated by centrifugation and was stored frozen until analysis. The animals were sacrificed by CO2 asphyxiation after the last blood collection at 24 h postdose.

**Plasma Sample Assay.** Plasma samples were pooled from each rat in each group at each time point to create one sample per time point per group. The plasma concentrations were determined using a standard assay method, in the concentration range of 50 to 10,000 nM, using a structural analog as an internal standard. A 200 μl of aliquot of pooled plasma samples was extracted with 5 ml of methyl r-butyrl ether, after the addition of 2 mM ammonium acetate solution, followed by the addition of 0.2 ml of dilute sulfuric acid (pH~1) to the organic layer. HPLC-fluorescence (excitation 254 nm; emission 377 nm) was performed using a MetaChem Basic C18 HPLC column (3 × 150 mm; ANSYS, Lake Forest, CA) at 30°C and an acetonitrile/water mobile phase that was run over 10 min at a flow rate of 0.7 ml/min. Retention times of DPC and the internal standard were 6.5 and 7.6 min, respectively.

**Pharmacokinetic Analysis.** The noncompartmental pharmacokinetic parameters were calculated using the WATSON program (WATSON version 5.4 v2, 1998; Pharmaceutical Software Systems, Inc. Wayne, PA).

**Substrate Selectivity to P450 Isoforms.** DPC (2 μM) was incubated individually with microsomes prepared from baculovirus-infected insect cells transfected with cDNAs encoding CYP1A1, CYP1A2, CYP3A4, CYP2B6, CYP2C9, CYP2C19, or CYP2D6. Each incubation contained 100 pmols of the individual P450 isozyme, potassium phosphate buffer (0.05 M or 0.1 M, pH 7.4) or 0.05 M Tris buffer (pH 7.4), 2 mM NADPH, and 3 mM magnesium chloride, at 37°C. Aliquots were taken at 0 and 30 min, deproteinized with acetonitrile, and analyzed by a specific liquid chromatography/tandem mass spectrometry method.

**Drug Tissue Distribution by QWBA.** Study design. Specific activity of the final dosing formulation of [14C]DPC was 14.12 μCi/mg in a vehicle of 0.1% methanesulfonic acid and 1% Tween 80 at a concentration of 1.667 mg/ml. RTV was formulated at a concentration of 2 mg/ml in a vehicle of 0.5% aqueous methylcellulose.

[14C]DPC (17 mg/kg) was administered to male Sprague-Dawley rats (n = 1/time point) via oral gavage either alone or approximately 2 h after the last of two oral doses of RTV (10 mg/kg oral gavage, ca. 12 h b.i.d.). Rats were individually housed with free access to water and were fasted overnight before dosing and during the in-life phase of the study. Rats dosed with [14C]DPC alone were euthanized 1 and 8 h postdose and rats given RTV and [14C]DPC were euthanized 1 and 7 h postdose. All rats were processed for whole-body autoradiography, and tissue concentrations of [14C]DPC were quantified using phosphor image analysis as described below.

**QWBA method.** Rats were prepared for QWBA as described by Ullberg (1977). Briefly, one rat each was euthanized by CO2 inhalation at the appropriate time after dosing, and each rat carcass was immediately frozen by immersion in a hexane/dry ice bath (~70°C) for approximately 10 min. Carcasses were drained, blotted dry, and placed on dry ice for at least 2 h to complete the freezing process. Each carcass was removed from the dry ice and placed into appropriately labeled bags with an identification card and stored at approximately ~−20°C until embedding. Frozen rat carcasses were individually embedded along with section thickness quality control standards (14C-spiked rat blood) in carboxymethylcellulose (Chay and Pohland, 1994) (frozen at −70°C). Appropriate sections (~30-μ thick) were collected on adhesive tape (Scotch Brand 810; 3M, St. Paul, MN) using a Leica CM3600 Cryomicrotome (Leica Microsystems, Deerfield, IL) with temperature at approximately ~−20°C. Sections were collected at eight levels of interest in the sagittal plane, and all major tissues, organs, and fluids were included in these levels. Sections were lyophilized, mounted on a black cardboard support along with 14C-autoradiographic calibration standards (Code RPA 511; Amersham Biosciences UK, Ltd., Little Chalfont, Buckinghamshire, UK), wrapped with Mylar film and exposed to phosphor imaging plates (IPs) (BASIII; Fuji Photo Film Co., Ltd., Tokyo, Japan) for 4 days. Exposed IPs were scanned into the WBA imaging system via a FLA 3000 Biodiagnostic Analyzer (Fuji Biomedical Products; Fujifilm Photo Film Co., Ltd.) and digital images of the radioactivity in each section were obtained using M5+ MCID software (Imaging Research Inc., St. Catharine’s, ON). Tissue concentrations were interpolated from each standard curve as nanocuries per gram and converted to μg-equivalents of DPC/g of tissue, and then to μg, assuming 1 g of tissue weight was equivalent to 1 ml, and based on molecular weight of DPC. The concentrations of radioactivity in the calibration standards ranged from 0 to approximately 9400 nCi/g tissue and the r^2 values obtained for the calibration curves used ranged from 0.9994 to 0.9999, which demonstrated the linearity of IPs. Tissue concentrations were obtained from tissues and fluids that could be visually identified on the autoradiograph. The limit of quantitation was determined as the mean background radioactivity concentration value for background plus three times the standard deviation (mean of 10 measurements/IP using sampling tools provided by the image analysis software, in which small tool area = 1 × 1 mm; large sampling tool area = 5 × 5 mm). This was determined for small and large sampling tool areas on each IP (n = 7) used for study. Small tissues included the pituitary gland, adrenal gland, thyroid gland, skin, and bone marrow, and remaining tissues were considered as large tissues. Images were printed in pseudocolor using the image analysis software and viewed using imaging tools provided by the image analysis software, in which small tool area = 1 × 1 mm; large sampling tool area = 5 × 5 mm). This was determined for small and large sampling tool areas on each IP (n = 7) used for study. Small tissues included the pituitary gland, adrenal gland, thyroid gland, skin, and bone marrow, and remaining tissues were considered as large tissues. Images were printed in pseudocolor using the image analysis software.

**QWBA Imaging.** Cell culture. Caco-2 cells were obtained from American Type Culture Collection (Manassas, VA). Cell stocks were maintained in T-75 cm^2 flasks (Corning, Acton, MA) at 37°C in a humidified atmosphere of 5% CO2 and 95% air. The culture consisted of a high glucose (4.5 g/liter) Dulbecco’s modified Eagle’s medium (Invitrogen, Carlsbad, CA) containing 10% fetal bovine serum (HyClone Laboratories, Logan, UT), 1% nonessential amino acids, 100 U/ml penicillin, and 100 μg/ml streptomycin (Invitrogen). The cell media were replaced every other day. Monolayers were subcultured using 0.05% trypsin-0.02% EDTA when they reached 75 to 85% confluency at a split ratio of approximately 1:5.

Single-cell suspensions of Caco-2 cells were plated onto the 12-mm diameter Transwell polycarbonate membranes (0.4-μm pore size) at a density of 6 × 10^5 cells/cm^2. The Transwell (Corning) inserts were placed in 12-well culture plates with 0.5 ml of media in the apical compartment and 1.5 ml of media in the basolateral compartment. The media at both compartments were replaced every other day for 21 days before the cells were used for the transport studies.

**Transport Studies.** Prior to the transport experiments, the integrity of Caco-2 cell monolayers was assessed by determining transepithelial electrical resistances using an Evon Epithelial Voltohmeter (World Precision Instruments, New Haven, CT). The transepithelial electrical resistances values were in the range of 400 to 800 ohms · cm^2. The culture medium in the transwell was aspirated and the wells washed twice with the transport buffer (Hank’s Balance salt solution containing 25 mM glucose and 10 mM HEPES, pH 7.4). The 1.5 ml of transport buffer containing [14C]DPC (23.43 mCi/mmol) was added to...
The determination of the parent compound concentration. Pooled plasmas from four rats at each time point were analyzed for the /H9262 GF120918, a Pgp inhibitor (Evers et al., 2000) at 2 groups, at 1 and 7 h postdose are shown in Fig. 2. At 1 h postdose, there was higher amount of radioactivity (regions in red in Fig. 2) in parts of the body (regions in yellow, green, and blue—decreasing amounts in that order). In RTV-pretreated rats (Fig. 2, b and c), there was a differential distribution of radioactivity in the brain, with CSF (ventricles) showing greater radioactivity than CNS. The 1 h time postdose and 9-fold at 7 h postdose in most tissue. Notably, there was a differential distribution of radioactivity in the brain, with CSF (ventricles) showing greater radioactivity than CNS. The 1 h time difference in measurement between the with and without RTV sections would not alter the overall conclusion that RTV pretreatment increased the radioactivity concentration in tissues. In RTV coadministration, the concentrations of DPC showed a plateau from 1 to 8 h postdose and 9-fold at 7 h postdose in most tissue. Notably, there was a differential distribution of radioactivity in the brain, with CSF (ventricles) showing greater radioactivity than CNS. The 1 h time difference in measurement between the with and without RTV sections would not alter the overall conclusions.

**DPC as a Pgp Substrate.** The DPC appearing in the apical side of the Caco-2 monolayer in the absence of the Pgp inhibitor GF120981 represents the sum of passive diffusion and active transport mediated by Pgp, whereas in the presence of GF120981 this represents only the diffusion since GF120981 at 2 μM completely abolishes Pgp-mediated transport. The difference provided the net of DPC transported by Pgp. The K_m and V_max of DPC transported by Pgp were estimated to be 2.0 ± 0.5 pmol/min, respectively. These results indicated that DPC has high affinity for Pgp. However, the active transport was readily saturated at 10 μM.

**Inhibition of Transport by RTV.** The permeation of DPC from basolateral to apical side in the presence of GF120981 reflects passive diffusion. The permeation of DPC in the presence of 0 (control), 5, 10, 25, and 50 μM of RTV, after subtraction of passive diffusion, reflects net active transport mediated by Pgp. Inhibition of Pgp-mediated transport of DPC by RTV was estimated as difference between total transport in the control group and the transport in the presence of RTV. RTV at concentrations of 5 μM or higher significantly reduced the Pgp-mediated transport of DPC. At RTV concentrations above 10 μM, there was no further inhibition.

The respective C_max and AUC(0–8 h) of DPC in rats following a single oral dose at 20 mg/kg were 11.8 μM and 39.7 μM/h, and following coadministration with RTV were 19.0 μM and 99.4 μM/h. Upon coadministration, the concentrations of DPC showed a plateau from 1 to 4 h, a result not uncommon upon coadministration of drugs with P450 inhibitors.

**Substrate Selectivity to P450s.** DPC was metabolized by rCYP3A4 by 70% and rCYP2D6 by 40% under the conditions used. There was no significant metabolism by other isozymes.

**Results**

**Rat Pharmacokinetics.** The DPC plasma concentration-time plots for rats with and without pretreatment of RTV are shown in Fig. 1. The respective C_max and AUC(0–8 h) of DPC in rats following a single oral dose at 20 mg/kg were 11.8 μM and 39.7 μM/h, and following coadministration with RTV were 19.0 μM and 99.4 μM/h. Upon coadministration, the concentrations of DPC showed a plateau from 1 to 4 h, a result not uncommon upon coadministration of drugs with P450 inhibitors.

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**QWBA.** The concentrations of [14C]D PC in various tissues at 1 and 7 or 8 h postdose in rats with and without pretreatment of RTV, as determined by QWBA, are listed in Table 1. Representative images of whole-body sections from rats from the two dose groups, at 1 h postdose, there was higher amount of radioactivity (regions in red in Fig. 2) in the upper part of the gastrointestinal tract, and lower amounts in other parts of the body (regions in yellow, green, and blue—decreasing amounts in that order). In RTV-pretreated rats (Fig. 2, b and c), there were higher levels of radioactivity than in the controls at 1 h (panel a) and at 8 h postdose (data not shown), in most of the tissues identified. Figure 3 is an expanded image of the head to depict distribution of radioactivity in the CSF and CNS areas. Notably, the ventricles containing CSF were darker, hence more radioactivity, than the brain with RTV (Fig. 3, plot a) than without RTV pretreatment (Fig. 3, plot b). Generally, RTV coadministration with [14C]DPC increased the levels of DPC-derived radioactivity on average of 4-fold at 1 h postdose and 9-fold at 7 h postdose in most tissue. Notably, there was a differential distribution of radioactivity in the brain, with CSF (ventricles) showing greater radioactivity than CNS. The duration of the differences in the measurements between the with and without RTV sections would not alter the overall conclusion that RTV pretreatment increased the radioactivity concentration in tissues.
RTV has been successfully used as a pharmacoenhancer, especially for different HIV protease inhibitors to boost their systemic exposure levels (Moyle and Back, 2001) in test species or patients. For HIV-1 inhibitors to be successful for viral suppression in patients, it is also important to assure that the drug penetrates the blood-brain barrier, as the CNS acts as a sanctuary for the virus. In the current study, QWBA was used to assess the drug-drug interaction with RTV in the tissue distribution of [14C]DPC in rats.

Initial pharmacokinetic studies showed that upon pretreatment of rats with RTV, the AUC\textsubscript{0–10h} of DPC showed 2.5-fold enhancement. RTV is known to cause such effects by potent inhibition of the metabolizing isozyme CYP3A (Kempf et al., 1997; Merry et al., 1997; Koudriakova et al., 1998) and the transporter Pgp (Alsenz et al., 1998). DPC is indeed metabolized prominently by CYP3A4, like most other HIV protease inhibitors, and is also shown to be a good substrate for Pgp, as discussed below. QWBA studies after a single oral dose of [14C]DPC showed that the radioactivity was distributed widely in tissues at 1 h postdose. By 8 h postdose, the radioactivity in most of the tissues dropped significantly. Brain contained extremely low levels of radioactivity (detectable but below the quantitation limit) whereas CSF (in ventricles), lymph nodes, and testes showed low but quantifiable levels of radioactivity. Notably, there was a differential distribution of radioactivity in CNS versus CSF. This is an important finding as previously the general notion has been that CSF concentrations can be used as a surrogate for CNS penetration (Yazdanian, 1999). This differential distribution became more pronounced in animals pretreated with RTV, when the CNS and CSF concentrations

**Discussion**

RTV has been successfully used as a pharmacoenhancer, especially for different HIV protease inhibitors to boost their systemic exposure levels (Moyle and Back, 2001) in test species or patients. For HIV-1 inhibitors to be successful for viral suppression in patients, it is also important to assure that the drug penetrates the blood-brain barrier, as the CNS acts as a sanctuary for the virus. In the current study, QWBA was used to assess the drug-drug interaction with RTV in the tissue distribution of [14C]DPC in rats.

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**Fig. 2.** Representative whole-body autoradiograph of male rats dosed with [14C]DPC, with and without pretreatment of RTV.

The concentration gradient, represented by color, increased from blue to green to yellow to red.
increased approximately 4-fold (Table 1; Fig. 3). Thus, the CSF data alone should be interpreted with caution unless validated using a technique such as QWBA. Other tissues, including testes, also showed a general increase in radioactivity after RTV pretreatment, by ~4-fold at 1 h postdose and 9-fold at 7 h postdose. Similar increases have been reported for other HIV protease inhibitors (Choo et al., 2000; Evers et al., 2000). Although the total radioactivity represents DPC and its metabolites, it is expected to be largely due to unchanged DPC in the presence of the CYP3A inhibitor RTV. In rats, the effect of Pgp on brain penetration of DPC is expected to be minimal, based on RTV concentrations after an oral dose of RTV at 10 mg/kg are estimated to be low at ~1 μM in the plasma (Denissen et al., 1997), and in Caco-2 cells only at higher RTV concentrations of 10 μM, a significant interaction was noted, as shown below. This was also consistent with no change in the tissue (e.g., brain and testes) to blood ratio of radioactivity between the two treatment groups.

Based on the above data from the rat studies, it became desirable to project if such effects could occur in humans. In vitro human studies of DPC have shown that DPC was metabolized prominently by CYP3A4. RTV, being a potent inhibitor of CYP3A4, would inhibit the metabolism of DPC. DPC has also been demonstrated to be a good substrate of Pgp, with $K_m$ of 4 μM, using the Caco-2 cell model. Its transport by Pgp is readily saturated at 10 μM. Since the local concentration of DPC in the small intestine of humans could be much higher than 10 μM (following a 600 mg dose), the effect of Pgp on the absorption of DPC would be expected to be minimal, as majority of the dose would be absorbed not by the active process, and coadministration of other Pgp substrates or inhibitors should have minimal effect on the absorption. On the other hand, because the concentration of DPC in the human plasma (~4 μM, unpublished data) is not high enough to saturate the Pgp, other Pgp substrates or potent inhibitors technically may affect the distribution of DPC into certain tissues, such as brain and testes, the organs where the virus can find a sanctuary.

RTV at 5 μM or higher concentration significantly inhibited the Pgp mediated transport of DPC in the Caco-2 cell model. At concentrations greater than 10 μM, no further inhibition was observed. However, RTV did not inhibit the Pgp-mediated transport of DPC completely at RTV concentration as high as 50 μM. This may be due to either RTV solubility issue or the possibility that Pgp has at least two substrate binding sites (Shapiro and Ling, 1997; Shapiro et al., 1999; Martin et al., 2000), and RTV and DPC do not exactly bind to the same site, although they may still share a certain binding site. However, RTV has been used previously in similar experiments up to 50 μM without any solubility issue (Huisman et al., 2001). Plasma $C_{max}$ of RTV in humans is 20 μM following a 600-mg dose (Denissen et al., 1997). The intestinal concentrations of RTV as well as of DPC are expected to be much greater than 10 μM. Considering saturable Pgp-mediated transport at 10 μM, these results suggest that in humans the effect of RTV on absorption of DPC from the small intestine via Pgp inhibition may be limited. Nevertheless, it may affect the distribution of DPC in tissues expressing Pgp (e.g., brain and testes) since

![Fig. 3. Magnified autoradiograph of head of the rat following an oral dose of [14C]DPC with (a) and without (b) pretreatment of RTV.](image)

The darker regions represent greater radioactivity. Thus, CSF contains more radioactivity than CNS.
RTV concentrations reach 20 μM in human plasma after a single oral dose of RTV at 600 mg. In summary, in rats the inhibition of CYP3A is proposed to play a key role in increasing the tissue concentration of radioactivity, whereas in humans inhibition of both CYP3A and Pgp by RTV is projected to play major role.

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