ELEVATED ALPHA-1-ACID GLYCOPROTEIN REDUCES THE VOLUME OF DISTRIBUTION AND SYSTEMIC CLEARANCE OF SAQUINAVIR

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ABSTRACT:

The purpose of this study was to characterize the relationship between plasma protein binding and the pharmacokinetic disposition of saquinavir during a normal and elevated alpha-1-acid glycoprotein condition. The extent of plasma binding of [14C]saquinavir to human plasma, human albumin, and human alpha-1-acid glycoprotein was also assessed. Transgenic mice, which overexpress plasma alpha-1-acid glycoprotein, and control mice were given a single intravenous injection of saquinavir (10 mg/kg) and plasma samples were harvested as a function of time. The extent of [14C]saquinavir (0.5–30 μg/ml) plasma protein binding in each group of mice was determined by ultrafiltration. Plasma saquinavir concentrations from in vivo administration were determined by high performance liquid chromatography with tandem mass spectrometry. Saquinavir binding in human plasma and control mouse plasma was similar (approximately 3% unbound). In contrast, the extent of binding was significantly increased in transgenic mice (1.5% unbound). Furthermore, saquinavir was more extensively bound to alpha-1-acid glycoprotein than to albumin (2.1 versus 11.5% unbound). The systemic clearance and volume of distribution of saquinavir were significantly reduced in transgenic mice compared with control mice. The results of this study show that alpha-1-acid glycoprotein is the predominant plasma protein to which saquinavir binds. In addition, elevations in plasma alpha-1-acid glycoprotein considerably alter the pharmacokinetic disposition of saquinavir. This is consistent with the observations that systemic exposure to saquinavir in human immunodeficiency virus patients is greater than that in healthy volunteers and that alpha-1-acid glycoprotein levels increase with the degree of HIV infection.

1 Abbreviations used are: HIV, human immunodeficiency virus, AGP, alpha-1-acid glycoprotein; HPLC, high performance liquid chromatography; ICG, indocyanine green; AUC, area under the saquinavir plasma concentration versus time profile; fu, unbound fraction.

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The variability of pharmacokinetic data for saquinavir is considerable in HIV1-positive patients. Systemic exposure of saquinavir, as measured by the area under the plasma concentration versus time curve (AUC), has been reported to vary by approximately 70% in a group of HIV-1-infected patients (Gieschke et al., 1999; Regazzi et al., 1999). The hard gelatin capsule formulation of saquinavir (Invirase) exhibits low oral bioavailability after a single dose to healthy volunteers (4%) and is estimated to be approximately 10% at steady state in HIV-positive patients (Steimer et al., 1998). A new soft gel formulation of saquinavir (Fortovase) provides a 3-fold increase in the bioavailability of saquinavir compared with the hard gelatin formulation. Several physicochemical and physiological factors reduce the bioavailability, including poor aqueous solubility, metabolism in the gut wall and liver, and the recent finding that saquinavir is a substrate for intestinal P-glycoprotein (Alsenz et al., 1998; Kim et al., 1998; Lee et al., 1998).

It is known that most HIV protease inhibitors bind primarily to alpha-1-acid glycoprotein (AGP) in the plasma (Kageyama et al., 1994). Additionally, plasma AGP concentrations vary considerably (>50%) in normal and diseased patients, including HIV (Kremmer et al., 1988; Øie et al., 1993). This is of particular importance, since plasma AGP levels are highest in the more severe cases of HIV-infected patients as shown by an inverse correlation with CD4 levels (Merry et al., 1996).

Increases in circulating AGP have been reported to alter the pharmacokinetic disposition and pharmacological action of numerous drugs to which it binds. For example, elevated AGP was associated with a higher bioavailability, and lower systemic clearance and volume of distribution of clindamycin in AIDS patients (Gatti et al., 1993). This change in disposition was found to correlate with an increase in plasma binding of clindamycin as a result of an increase in plasma AGP concentration in AIDS patients (Flaherty et al., 1996). In another report, an increase in plasma drug binding in vitro has led to a reduction in the activity of an investigational HIV protease inhibitor (KNI-272) (Kageyama et al., 1994). This reduction in activity was attributable to drug binding to plasma components, including AGP.

These previous in vitro and in vivo observations show the need to...
determine the exclusive influence of elevated plasma AGP on the pharmacokinetic disposition of saquinavir. The information needed in relation to the plasma protein binding of a drug is both quantitative and qualitative. The quantitative information relates to the extent of binding over the therapeutic and toxic plasma concentration range. This will indicate whether saturation of binding is likely and provide a value for the unbound drug concentration that should correlate more closely with the pharmacological activity, particularly if binding is altered by disease. The fraction unbound can also be used in the estimation of pharmacokinetic parameters such as free drug clearance. The qualitative information relates to the protein(s) that is involved in binding.

The aims of this study were to characterize the binding of saquinavir to human plasma, purified human albumin, and AGP. Additionally, the consequences of elevated AGP on the extent of saquinavir plasma protein binding and pharmacokinetic disposition were assessed in a novel strain of transgenic mice.

Materials and Methods

Chemicals and Reagents. Micronized saquinavir and [14C]saquinavir (26.5 Ci/mg) (Wiltshire et al., 1998) were supplied by Roche Discovery, Welwyn, England. Dextrose (5%) injection USP was purchased from VWR Scientific (Suwanee, GA). ScintiVerse II scintillation cocktail, borosilicate scintillation vials, and sterile, 4-ml Vacutainers were purchased from Fisher Scientific (St. Louis, MO). All buffer constituents were purchased from Sigma Chemical Co. Ltd., (London, UK).

[14C]Saquinavir Binding to Human Plasma, Albumin, and AGP. Blood donated by healthy volunteers was collected in heparinized blood tubes at the University of Liverpool, Liverpool, England. Plasma was obtained by centrifugation at 2000g for 15 min. Patient plasma was pooled and used within 2 h. Human albumin fraction V (A1653, 96–99% albumin, remainder mostly globulins) and human AGP (G9885, purity 99%) were obtained from Sigma (Sawanee, GA). ScintiVerse II scintillation cocktail, borosilicate scintillation vials, and sterile, 4-ml Vacutainers were purchased from Fisher Scientific (St. Louis, MO). All buffer constituents were purchased from Sigma Chemical Co. Ltd., (London, UK).

Equilibrium dialysis was used to determine the unbound fraction of [14C]saquinavir in human plasma, albumin, and AGP preparations. Dialysis was performed with a Diannorm apparatus (Diachema AG, Zurich, Switzerland). The cells consisted of 2 Teflon half-cells each with a capacity of 1 ml and separated by a semipermeable cellulose membrane (molecular mass cut-off 12–14,000 Da; Medicell International Ltd.). The membrane was prepared by soaking in three changes of distilled water followed by three changes of buffer, each for at least 10 min. One compartment contained buffer solution and the other a ligand-protein solution supplemented with [14C]saquinavir. The binding of [14C]saquinavir (0.1–30 μg/ml) was studied with plasma and typical physiological concentrations of human albumin (600 μM) and AGP (22 μM). The cells were immersed in a water bath at 37°C and rotated gently for 28 h until equilibrium had been reached (Table 1). Aliquots (200 μl) from each compartment were measured by liquid scintillation counting for 10 min.

Calculations. The unbound fraction was calculated by the method of Giacomini et al. (1984). Equation 1 was used for the plasma and albumin samples. This corrects for any osmotic volume shift that occurred. Equation 2 was used for AGP where there was no volume shift:

\[
\text{fu} = \frac{C^*B}{C^*B + P^*C/P} \quad (1)
\]

where \( \text{fu} \) is fraction unbound; \( P \) is protein concentration in solution before dialysis; \( P^* \) is protein concentration in solution after dialysis; \( C^*B \) is radioactivity in buffer compartment after dialysis; \( C^*P \) is radioactivity in plasma compartment after dialysis; \( C^*B \) is concentration of bound drug had no volume shift occurred, \( C^*B \) is bound (1 + \( \delta \)); and \( \delta \) is fractional increase in the volume of the plasma compartment due to volume shift:

\[
\delta = \frac{P - 1}{P} \quad (3)
\]

Animals. Adult (20–30 g, 2–4-month-old) control and transgenic mice were used in this study. Male and female mice were used in this study randomly. The transgenic line AGP 9.5-5 contained the rat AGP gene along with sufficient cis-acting regulatory information to direct its liver-specific expression (Dewey et al., 1990). Line AGP 9.5-5 was developed by standard transgenic technology involving microinjection of the rat AGP genomic clone into the pronuclei of (C57BL/6 × DBA/2)F1 mouse embryos. The level of AGP expression in this transgenic line (homozygous for the transgene) was 15-fold greater than that of nontransgenic C57BL/6 mice. The transgenic mice used in this study were hybrids of AGP 9.5-5 and C57BL/6, which expressed elevated plasma AGP levels 8.6-fold over normal. The control mice were pure strain C57BL/6 mice. All in vivo experiments adhered to principles of laboratory animal care and were approved by the institutional animal care and use committee. This transgenic mouse model has been used in previous pharmacokinetic assessments of imipramine and fluoxetine (Yoo et al., 1996; Holladay et al., 1998).

Several steps were taken before and during the experiments to minimize the variance between individual mice of each strain. First, the same vendor for C57BL/6 mice was used (Charles River Breeding Laboratories, Wilmington, MA) and mice of similar weight and age were used. In the transgenic strain, mice were obtained by sequential generations of brother-sister mating. Such breeding is common in murine studies and promotes less variance in the physiology in the mice.

[14C]Saquinavir Binding to Transgenic and Control Mouse Plasma. Saquinavir plasma protein binding in mouse plasma was determined by ultrafiltration using the Centrifree micropartition system (Amicon Inc., Beverly, MA). This method was different from that used in the assessment of saquinavir binding to human plasma and protein preparations due to preferences of the individual laboratories. Aliquots of a 10 μg/ml methanolic [14C]saquinavir solution were dried under nitrogen gas and reconstituted with drug-free transgenic or control mouse plasma (500 μl) to obtain saquinavir concentrations of 1, 2, 4, 8, 16, and 32 μg/ml (in triplicate). Plasma samples were incubated at 37°C for 2 h. Immediately before centrifugation, 25 μl of saquinavir-supplemented plasma was harvested to allow the determination of the total drug concentration. Subsequently, each transgenic and control mouse plasma sample was placed in ultrafiltration tubes and centrifuged at 2000g for 30 min. After centrifugation, 25 μl of ultrafiltrate was collected for the determination of the unbound saquinavir concentration. Precentrifugation plasma samples and ultrafiltrate samples (25 μl) were supplemented with 10 ml of ScintiVerse II cocktail and each sample was analyzed by scintillation counting. The fu was determined as the ratio of the measured drug concentration in the ultrafiltrate to the total drug concentration measured before centrifugation. Recovery evaluation was determined as a mass balance ratio between the sum of the amount of saquinavir in the retentate and ultrafiltrates and the amount of saquinavir in plasma before centrifugation. Data are expressed as the mean of triplicate samples.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Percentage of Unbound (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.84 ± 0.38</td>
</tr>
<tr>
<td>5</td>
<td>0.93 ± 0.32</td>
</tr>
<tr>
<td>8</td>
<td>1.30 ± 0.36</td>
</tr>
<tr>
<td>18</td>
<td>2.52 ± 0.66</td>
</tr>
<tr>
<td>24</td>
<td>2.3</td>
</tr>
<tr>
<td>28</td>
<td>2.63 ± 0.83</td>
</tr>
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</table>
In Vivo Saquinavir Administration to Mice. To characterize the pharmacokinetic disposition of saquinavir, transgenic and control mice (n = 3–4 for each strain at each time point) received a single intravenous injection of unlabeled saquinavir (10 mg/kg, 1.33 mg/ml as free base). The total volume of intravenous drug solution injected was 0.0075 ml/kg of body weight. Each mouse was anesthetized by halothane vapor, and whole-blood samples (0.8 ml) were harvested into Vacutainer, heparinized tubes by cardiac puncture (destructive sampling) at 0, 5, 15, and 30 min and 1, 2, 3, 4, 6, and 8 h post dose. Whole-blood samples were subsequently centrifuged at 3000g for 5 min and plasma was stored in disposable borosilicate culture tubes (100 ml) in duplicate at –20°C until high performance liquid chromatography (HPLC) analysis.

Hepatic Blood Flow Determination. The apparent hepatic blood flow in transgenic and control mice was estimated as the clearance of a bolus injection of indocyanine green (ICG) as described by Wynne et al. (1990). Historically, ICG clearance has been used as a reliable measure of the apparent hepatic blood flow, since ICG is exclusively eliminated by the liver. Transgenic and control mice (n = 3 for each strain) were given an intravenous bolus dose (1.0 mg/kg) of ICG, and at 2, 5, 10, 15, 30, and 60 min after ICG administration, each mouse was anesthetized with halothane vapors. Whole-blood samples were collected from anesthetized mice by cardiac puncture and the harvested serum was stored at –20°C until HPLC analysis. The possibility of differential binding of ICG to transgenic and control mouse plasma was investigated using the ultrafiltration procedure described for the determination of saquinavir binding in mouse plasma. Briefly, portions of a methanolic solution of ICG were dried and pooled mouse plasma was added to the residue to yield a concentration of 5 µg/ml (n = 3 samples/strain). Plasma ICG samples were centrifuged at 2000g for 30 min. Hematocrit for transgenic and control mice were determined using a Coulter counter and expressed as percentage values. The hepatic blood flow of each strain of mice was determined by the following formula: ICGBLOOD ICGSERUM × (1 – hematocrit).

Plasma and ultraltrafiltrate ICG quantification was performed by HPLC with ultraviolet detection using a modification of a method described by Hopton et al. (1999). Briefly, the mobile phase of acetonitrile/methanol and 5 mM phosphate buffer (37:3:40) was used to separate ICG and the internal standard, respectively. The range of quantification was 0.5 to 500 µg/ml of plasma. Plasma samples were centrifuged at 2000g for 30 min. Hematocrits for transgenic and control mice were determined using a Coulter counter and expressed as percentage values. The hepatic blood flow of each strain of mice was determined by the following formula: ICGBLOOD ICGSERUM × (1 – hematocrit).

Table 1: Data Analysis

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Plasma Albumin</th>
<th>Plasma Alpha-1-Acid Glycoprotein</th>
</tr>
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<tbody>
<tr>
<td>0.1</td>
<td>2.2 ± 0.5</td>
<td>13.1 ± 1.2</td>
</tr>
<tr>
<td>0.5</td>
<td>2.8 ± 0.6</td>
<td>12.0 ± 2.7</td>
</tr>
<tr>
<td>1</td>
<td>2.7 ± 0.5</td>
<td>12.4 ± 1.2</td>
</tr>
<tr>
<td>5</td>
<td>2.8 ± 0.4</td>
<td>12.3 ± 2.4</td>
</tr>
<tr>
<td>10</td>
<td>3.2 ± 0.8</td>
<td>11.4 ± 3.4</td>
</tr>
<tr>
<td>20</td>
<td>3.1 ± 1.0</td>
<td>9.4 ± 1.5</td>
</tr>
<tr>
<td>30</td>
<td>3.1 ± 0.6</td>
<td>10.2 ± 1.4</td>
</tr>
</tbody>
</table>

Results

Initial studies focused on the time required for saquinavir to reach binding equilibrium in the dialysis experiments with human plasma and albumin. On the basis of these results (Table 1), 28 h was chosen as the optimum equilibration time of saquinavir with human plasma and purified proteins. The extents of 14Csaquinavir binding in the range of 0.1 to 30 µg/ml to human plasma, human albumin, and human AGP are shown in Table 2. The percentage of unbound saquinavir was approximately 3% in human plasma over this concentration range. In addition, binding to human AGP was markedly greater than to human albumin (98 compared with 88%). At the highest concentrations of saquinavir (20 and 30 µg/ml) the binding to AGP decreased from 98.5 to 97%, but such changes did not occur in whole plasma. Volume shifts due to osmosis were seen in the plasma binding studies, smaller volume shifts occurred in the binding studies involving albumin, but no volume shift was observed with AGP. Consistent with the values obtained from human plasma, the extent of in vitro murine plasma saquinavir binding was approximately 97% over the concentration range studied (Table 2). In addition, saquinavir binding was significantly increased in transgenic mouse plasma as opposed to control mouse plasma (i.e., 1.5 versus 3.0% unbound) (Table 2). This increase in binding was consistent with the elevation of plasma AGP in transgenic mice. The mean recovery of 14Csaquinavir from the ultrafiltration devices ranged from 72% for the lowest concentration (1 µg/ml) to 81% for the highest concentration tested (30 µg/ml).

The mean plasma clearance of ICG was significantly reduced in transgenic mice compared with control mice (32.1 versus 46.7 ml/min/kg). The extent of ICG plasma binding in the transgenic (81%) and control (79%) mouse sera was similar. Thus, the hepatic blood flow was significantly reduced in transgenic mice (17.0 ± 0.91 versus 23.4 ± 3.3 ml/min/kg). The mean plasma saquinavir concentration versus time profiles in transgenic and control mice after 10-mg/kg intravenous bolus doses are shown in Fig. 1 and the pharmacokinetic parameters are reported in Table 3. Significantly slower clearance in the transgenic mice caused a doubling in systemic exposure. In addition, as a consequence of increased protein binding, the steady-state volume of distribution was reduced by 87% in transgenic mice and the central compartment volume of distribution in transgenic mice was only 5.2% of the control value (Table 3).

Discussion

Considerable variability in the serum level of AGP exists in the general population. The basal AGP level in persons of the same race,
For transgenic mice, observed values are displayed as black boxes and predicted values as a continuous line. For control mice, observed values are displayed as open circles and predicted values as a dashed line.

**TABLE 3**

Pharmacokinetic parameters of saquinavir in transgenic and control mice (n = 3–4) after a single 10-mg/kg i.v. injection

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Transgenic Mice</th>
<th>Control Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µg · min/ml)</td>
<td>438.1 ± 46.7a</td>
<td>124.4 ± 24.0</td>
</tr>
<tr>
<td>Vₔ (l/kg)</td>
<td>2.6 ± 0.7a</td>
<td>8.2 ± 0.8</td>
</tr>
<tr>
<td>VₐS (l/kg)</td>
<td>0.7 ± 0.1a</td>
<td>4.6 ± 0.5</td>
</tr>
<tr>
<td>T₁/2z (min)</td>
<td>80.0 ± 19.7</td>
<td>71.4 ± 17.9</td>
</tr>
<tr>
<td>fu (%)</td>
<td>1.5 ± 0.4a</td>
<td>3.0 ± 1.4</td>
</tr>
<tr>
<td>CLₐ (mL/min/kg)</td>
<td>22.7 ± 2.4a</td>
<td>80.1 ± 17.8</td>
</tr>
<tr>
<td>CLₐ (l/min/kg)</td>
<td>1.5 ± 0.2a</td>
<td>2.7 ± 0.6</td>
</tr>
</tbody>
</table>

*Mean transgenic mouse value is significantly different from the control mouse value (p < 0.05).

Figure 1. Mean (±S.D.) plasma saquinavir concentration versus time profile in transgenic and control mice after a single intravenous dose of 10 mg/kg (n = 3–4 for each group).

Gender, and age may vary 40% or more (Blain et al., 1985; Kremer et al., 1988; Duchêne et al., 1998). For example, a recent study showed that the mean basal serum AGP concentration in Caucasians was 20% lower than that observed in comparable African-American subjects. In addition, a 45% variance in the level of AGP was found within each group (McCollum et al., 1998). The results of this study show that saquinavir is bound extensively in the plasma (≥95%) and primarily to AGP. Additionally, saquinavir binding to AGP increases in proportion to increases in plasma AGP levels. This is of importance in the treatment of HIV illness due to the fact that serum AGP levels are proportionally elevated as a function of the severity of the disease (Merry et al., 1996) as well as the observations of intersubject variability in AGP levels in AIDS patients (Okie et al., 1993). This variation in basal and elevated serum AGP level has direct and multiple consequences on drug disposition and action that may produce considerable interpatient variability in drug response.

Elevations in serum AGP led to an expected increase in saquinavir plasma binding and a resultant decrease in the volume of distribution. In addition, the clearance of saquinavir in the transgenic mice was significantly reduced. The fundamental mechanisms that define these differences may not be strictly due to alteration of the unbound plasma concentration of saquinavir. Our data suggest that the volume of distribution at steady state of the unbound portion of drug is substantially lower in AGP mice as opposed to control mice. Although our study was not designed to specifically address this issue, this discrepancy in the unbound portion of drug can be explained by the possible existence of more AGP in the microvascular endothelium of AGP mice as opposed to control mice, and thus, a restriction of drug passage into the tissues of control mice. The issue of endothelial AGP overexpression in our transgenic mice will be explored in the future.

The role of AGP in maintaining the microvascular endothelium has been investigated, and this protein appears to be fundamentally important in membrane integrity (Curry et al., 1989; Schnitzer and Pinney 1992; Huxley et al., 1993; Sörensson et al., 1999). Data from several laboratories suggest several distinct, constitutive roles for AGP in the endothelium (Curry et al., 1989; Schnitzer and Pinney 1992; Huxley et al., 1993; Sörensson et al., 1999). The presence of this glycoprotein in endothelium presents numerous questions on its function and importance to drug permeability and ultimately, drug activity. Currently, it is believed that AGP plays a role in increasing the net negative charge in the endothelium (Schnitzer and Pinney, 1992; Huxley et al., 1993; Sörensson et al., 1999). Through this effect, substrate permeability into tissues, including the liver, may be altered as well as the level of charge repulsion or steric hindrance effects.

Further evidence that AGP may influence drug disposition beyond its ability to bind drugs was found in the hepatic blood flow assessment. Since the liver strictly and efficiently clears ICG, the rate-limiting step of its clearance is the delivery to the liver. Our data show a reduction in the apparent hepatic blood flow in transgenic mice that could not be explained by ICG plasma binding differences. This limitation in flow would then reduce the delivery of saquinavir to the liver and thus reduce its clearance.

The saquinavir plasma concentration versus time curves obtained after intravenous dosing into transgenic and control mice was modeled by noncompartmental analysis. Such treatment of the data is appropriate for analyzing population data obtained by destructive sampling. The reduction in the volume of distribution of saquinavir agreed with the increased plasma binding and elevated AGP concentration, and this reduction correlates with the marked increase in the mean initial drug concentration in transgenic mice (74.8 versus 4.8 µg/ml) (Fig. 1). This increase in binding is of particular interest, since plasma AGP concentrations are variable among normal volunteers and HIV-infected patients. It is critical to note that AGP levels increase with the degree of HIV infection as evidenced by proportionally decreasing CD4 cell counts in patients (Merry et al., 1996). This is consistent with the observed higher plasma levels of saquinavir in HIV patients compared with healthy volunteers (Roche Laboratories, 1997). Saquinavir binding to plasma AGP could explain some of the observed variability in saquinavir population pharmacokinetic parameters among HIV-infected patients.

The in vivo protein binding data showed that AGP is the main binding protein involved in the transport of saquinavir through the bloodstream. At high concentrations, saquinavir binding to AGP is partially saturated. This is in agreement with previous studies in which the extent of plasma protein binding of the HIV protease inhibitor A-80987 to AGP was found to be saturable at higher drug concentrations (Billelo et al., 1996). However, albumin can also bind saquinavir and thus, there is little change in the percentage of unbound saquinavir within the therapeutic range. As seen in Table 1, the extent of saquinavir binding to purified albumin is fairly constant; however, binding to AGP decreases as saquinavir concentration increases.
Therefore, the contribution of albumin to saquinavir protein binding may become more important at higher saquinavir plasma concentrations.

Previous studies have shown a proportional decrease in the in vitro efficacy of experimental HIV protease inhibitors (e.g., A80987, A77003, CGP61755) and incremental increases in AGP. However, this reduction in activity apparently reaches the maximum when blood AGP levels reach 2 mg/ml (Billelo et al., 1995, 1996; Lazdins et al., 1997). As seen in the transgenic mouse model, elevations in plasma AGP led to reductions in the volume of distribution as a result of increased plasma saquinavir binding. Despite the higher total saquinavir exposure during an elevated AGP condition, saquinavir efficacy is predicted to be less, primarily due to the increase in plasma binding. Therefore, during elevated AGP conditions, the efficacy of HIV-protease therapy may not directly correlate to total plasma HIV-protease inhibitor exposure.

In summary, the extent of [14C]saquinavir binding to purified human AGP and albumin confirmed that the major drug binding protein of saquinavir is AGP, and this binding displayed a slight trend toward saturation. Nevertheless, [14C]saquinavir did substantially bind to human albumin. Taken together, these results indicate that during elevated AGP conditions, as in patients with low CD4 counts, the extent of saquinavir binding may increase, and thus lead to in a significantly higher systemic exposure and significantly lower systemic clearance and volume of distribution of saquinavir.

References


