Characterization of P-Glycoprotein Transport and Inhibition in Vivo

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ABSTRACT

The P-glycoprotein is an energy-dependent efflux pump capable of decreasing the intracellular concentration of a broad range of chemotherapy agents. [99mTc]Sestamibi, a P-glycoprotein transport substrate, is a sensitive probe of P-glycoprotein function both in vitro and in vivo. A human tumor model in nude mice was evaluated to determine whether [99mTc]Sestamibi could detect in vivo differences in P-glycoprotein expression and P-glycoprotein modulation by the reversal agent SDZ PSC 833. Differential [99mTc]Sestamibi accumulation based upon P-glycoprotein expression was demonstrated in xenografts in vivo. Dose-dependent inhibition of P-glycoprotein function was achieved with SDZ PSC 833. Administration of the reversal agent increased [99mTc]Sestamibi accumulation in the xenografts expressing P-glycoprotein. These observations show that [99mTc]Sestamibi as capable of detecting the modulation of P-glycoprotein in a solid tumor model by the reversal agent SDZ PSC 833.

INTRODUCTION

The P-glycoprotein is an energy-dependent efflux pump capable of decreasing the intracellular concentration of a broad range of cytotoxic compounds (1–5), including many of the most effective chemotherapeutic agents presently used clinically, including the anthracyclines, Vinca alkaloids, actinomycin D, and paclitaxel. This molecule is a member of a large superfamily of transport proteins, termed ABC transporters or traffic ATPases, that are responsible for the translocation of nutrients, peptides, organic ions, and toxins across a variety of cellular membranes (6, 7). Characterization of P-glycoprotein levels in human tumor samples has indicated that high levels of expression may be associated with a poor clinical outcome in acute myelogenous and lymphoblastic leukemia, pediatric sarcoma and neuroblastoma, osteosarcoma, and breast cancer (8).

P-Glycoprotein-mediated multidrug resistance has emerged as one of the most attractive targets for improving cancer chemotherapy. A large number of pharmacological agents that inhibit P-glycoprotein function have been identified (8, 9). These compounds inhibit P-glycoprotein-mediated efflux, resulting in increased intracellular accumulation of cytotoxic agents. Reversal agents that inhibit P-glycoprotein transport at submicromolar concentrations with tolerable mitochondrial membrane potentials, final overall accumulation is inversely proportional to the level of P-glycoprotein expression. As with other P-glycoprotein transport substrates, [99mTc]Sestamibi efflux is energy dependent, and its accumulation is enhanced by traditional reversal agents. This transition metal complex is capable of inhibiting photoaffinity labeling of P-glycoprotein. Multidrug-resistant cell lines survive in higher concentrations of this compound than do sensitive cell lines. [99mTc]Sestamibi has been used to demonstrate high capacity P-glycoprotein transport and efflux against a concentration gradient that cannot be saturated at concentrations up to 10 mM of the complex. Initial tumor imaging studies in mice have also indicated that the accumulation of the complex is a function of P-glycoprotein levels. Tumors that express lower levels of P-glycoprotein accumulate higher levels of [99mTc]Sestamibi (10). An increasing number of tumor types has been imaged in humans with this technetium-labeled compound (13–19).

We assessed whether [99mTc]Sestamibi could detect in vivo differences in P-glycoprotein expression and modulation by a reversal agent. The MDA 435 breast carcinoma tumor cell line and two paclitaxel-resistant derivatives were characterized as xenografts in nude mice. The reversal agent SDZ PSC 833, a nonimmunosuppressive analogue of cyclosporin A, was chosen to evaluate modulation of P-glycoprotein transport activity. We were able to demonstrate differential [99mTc]Sestamibi accumulation in xenografts in vivo based upon P-glycoprotein expression and the SDZ PSC 833 dose-dependent inhibition of [99mTc]Sestamibi transport.

MATERIALS AND METHODS

Preparation of Cells and Radioactive Probes. The parental MDA 435 human breast carcinoma cell line was grown at 37°C in 5% CO2 in a humidified incubator in Eagle MEM (Sigma Chemical Co.) supplemented with 10% heat-inactivated FCS (Sigma), 0.1 mM nonessential amino acids, 10 mM HEPES (pH 7.4), 100 units/ml penicillin, 100 mg/ml streptomycin, 2 mM l-glutamine, and 1 mM sodium pyruvate. Two multidrug-resistant derivatives, the MDA/T0.1 and MDA/T0.3 cell lines, were originally selected to and maintained in 0.1 mM and 0.3 mM paclitaxel, respectively (20). [99mTc]Sestamibi was prepared from a Cardiolite kit (DuPont Merck Pharmaceuticals) by adding 99mTcO4− (1 ml, 740-1110 MBq) obtained from a commercial 99 Mo/99mTc generator and heating the mixture at 100°C for 10 min. The preparation was purified to remove excess free ligand with a Sep-Pak cartridge as described previously (21). Radiochemical purity of the complex was assessed by radiometric detection of reverse-phase high-performance liquid chromatography separations. The high-performance liquid chromatography system consisted of a Brownlee SPHERI-5 RP-8 5-mm column as the stationary phase and a methanol/0.05 mM ammonium sulfate linear gradient (0/100 to 5/95 in 5 min) as the mobile phase. [201Tl]Thallous chloride was obtained from the Mallinckrodt Medical Company.

In Vivo Accumulation of Radioisotopes. The accumulation of [99mTc]Sestamibi and [201Tl]thallous chloride was determined in the cell lines in vitro. Cells were harvested with 0.05% trypsin-0.53 mM EDTA (Life Technologies, Inc.) and washed with ice-cold medium. After incubating for 2 h in ice-cold medium, they were washed once in unsupplemented medium to remove the serum and resuspended at a concentration of 107 cells/ml for uptake studies. Analyses were done in both MEM and RPMI 1640 with identical results. Cell suspensions and [99mTc]Sestamibi and [201Tl]thallous chloride solutions were warmed for 10 min at 37°C prior to use. Cell viability, determined during all experiments by trypan blue dye exclusion, was always greater than 90%.
RESULTS

Characterization of a Breast Carcinoma Tumor Model. Paclitaxel-resistant derivatives of the MDA 435 breast carcinoma cell line were initially derived by stepwise selection in paclitaxel to 0.1 and 0.3 mM (20). The MDA/T0.1 cell line is approximately 200-fold resistant to paclitaxel, and the MDA/T0.3 derivative is approximately 300-fold resistant in vitro, compared with the parent cell line. These cell lines display cross resistance to paclitaxel, vinblastine, and doxorubicin and express increasing levels of P-glycoprotein consistent with their multidrug-resistant phenotype. Neither the parental cell line nor the drug-resistant derivatives express the multidrug resistance-associated protein (24).

The MDA 435 tumor cell line and the resistant derivatives can be grown as xenografts in nude mice. The paclitaxel-resistant derivatives display resistance to paclitaxel, vinblastine, and doxorubicin in vivo (Fig. 1). Although the MDA/T0.3 xenografts survive higher concentrations of cytotoxic agents compared with the MDA/T0.1 xenografts, it is difficult to ascribe specific resistance values. Consistent with the expression of multidrug resistance in vivo, the paclitaxel-resistant xenografts maintain P-glycoprotein expression (data not shown).

\[ ^{99m}Tc \] Sestamibi Accumulation in Vivo. \[ ^{99m}Tc \] Sestamibi accumulation was characterized in the MDA breast carcinoma cell line and its paclitaxel-resistant derivatives. Uptake reached a plateau by 2 min for the resistant derivatives and by 30 min for the MDA 435 parental cell line and remained at maximum values for at least 180 min (Fig. 2). By 30 min, the MDA 435 parental cell line accumulated 9.4% of the total \[ ^{99m}Tc \] Sestamibi activity. The MDA/T0.1 derivative accumulated 3.4% and the MDA/T0.3 derivative 1.0%, approximately one-third and one-tenth as much as the parental cells, respectively (Fig. 2).

Inhibition of P-glycoprotein function was characterized in the breast carcinoma cell lines with several known reversal agents (Fig. 3). Verapamil, cyclosporin A, and SDZ PSC 833 had little effect on the accumulation of \[ ^{99m}Tc \] Sestamibi in the MDA 435 cell line. The MDA/T0.1 derivative uptake of \[ ^{99m}Tc \] Sestamibi was comparable to the parental cell line in the presence of 50 mM verapamil, whereas the MDA/T0.3 derivative required 100 mM verapamil to achieve maximal accumulation. A similar trend was observed with both cyclosporin A and SDZ PSC 833. Higher concentrations were needed for maximal \[ ^{99m}Tc \] Sestamibi uptake in the more highly resistant MDA/T0.3 cell line than in the MDA/T0.1 derivative. The former required 3 mM cyclosporin A and 1 mM SDZ PSC 833 and the latter 2 mM cyclosporin A and 0.75 mM SDZ PSC 833.

\[ ^{201}Tl \] Thallous chloride uptake was 6–7% in all three cell lines, and the reversal agents did not affect its accumulation in either the parental or multidrug-resistant derivatives (data not shown).

\[ ^{99m}Tc \] Sestamibi Accumulation in Vivo. The breast carcinoma tumor cell lines were grown as xenografts in nude mice and characterized for \[ ^{99m}Tc \] Sestamibi accumulation. The MDA 435 parental cell line accumulated the highest percentage of the ID of \[ ^{99m}Tc \] Sestamibi per gram of tissue and had the highest ratio of \[ ^{99m}Tc \] Sestamibi:\[ ^{201}Tl \] thallous chloride for the MDA/T0.1 cell line in the presence of 50 mM verapamil, whereas the MDA/T0.3 derivative required 100 mM verapamil to achieve maximal accumulation. A similar trend was observed with both cyclosporin A and SDZ PSC 833. Higher concentrations were needed for maximal \[ ^{99m}Tc \] Sestamibi uptake in the more highly resistant MDA/T0.3 cell line than in the MDA/T0.1 derivative. The former required 3 mM cyclosporin A and 1 mM SDZ PSC 833 and the latter 2 mM cyclosporin A and 0.75 mM SDZ PSC 833.

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Table 1 and Fig. 4). The 50 mg/kg dose of SDZ PSC 833, thus, revealed a significant difference ($P = 0.007$) between the xenografts of the two resistant derivatives, which could not be detected with $[^{99m}Tc]$Sestamibi alone. The MDA/T0.1 xenografts took up more than 90% of the %ID found in control xenografts, whereas the MDA/T0.3 xenografts accumulated only 50%. Similar differences were observed with the $[^{99m}Tc]$Sestamibi:$[^{201}Tl]$thallous chloride ratio.

However, administration of 100 mg/kg of SDZ PSC 833 resulted in $[^{99m}Tc]$Sestamibi accumulation in the MDA/T0.3 xenografts that did not differ significantly from the parental xenografts, suggesting that the higher dosage was required to completely inhibit P-glycoprotein transport in the MDA/T0.3 xenografts. SDZ PSC 833 given at 50 or 100 mg/kg did not significantly affect the accumulation of $[^{201}Tl]$thallous chloride in either the sensitive or resistant xenografts (data not shown). Similarly, the administration of SDZ PSC 833 did not significantly affect the percentage of the injected $[^{99m}Tc]$Sestamibi dose accumulated per gram of tissue or the $[^{99m}Tc]$Sestamibi:$[^{201}Tl]$thallous chloride ratio in the parental, drug-sensitive xenografts (Table 1 and Fig. 4).

Tissue Distribution of $[^{99m}Tc]$Sestamibi. Treatment of nude mice with 50 or 100 mg/kg of SDZ PSC 833 produced large increases in $[^{99m}Tc]$Sestamibi accumulation in the lungs and spleen 15 min after administration of the radiotracer (Table 1). Modest increases were noted in the brain, blood, muscle, and kidney. The heart and liver did not show any changes in $[^{99m}Tc]$Sestamibi distribution at this time point.

The biodistribution of two different doses of $[^{99m}Tc]$Sestamibi was calculated in nude mouse tissues and xenografts to determine whether differences in serum concentration affect the relative accumulation of the probe. The %ID of $[^{99m}Tc]$Sestamibi per gram of tissue and the $[^{99m}Tc]$Sestamibi:$[^{201}Tl]$thallous chloride ratio in the resistant and sensitive xenografts and tissues were similar with administration of either 10 or 60 mCi of $[^{99m}Tc]$Sestamibi with 6-fold more radioactivity in the tissues and organs of mice injected with the latter (data not shown).

Bioassay of SDZ PSC 833 Serum Levels. The serum concentration of SDZ PSC 833 was determined in an in vitro bioassay using serum obtained from mice 2 h after administration of 100 mg/kg i.p. The effects of this serum on $[^{99m}Tc]$Sestamibi uptake in the MDA/
Table 1  Biodistribution of $^{99m}$TcSestamibi and $^{201}$TlThallous chloride in xenografts and mouse tissue

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SDZ PSC 833$^b$ 50 mg/kg</th>
<th>SDZ PSC 833$^c$ 100 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{99m}$TcSestamibi</td>
<td>$^{201}$TlThallous chloride</td>
<td>$^{201}$TlThallous chloride</td>
</tr>
<tr>
<td>MDA 435</td>
<td>0.80 ± 0.21</td>
<td>0.37</td>
<td>0.96 ± 0.29</td>
</tr>
<tr>
<td>MDA/T0.1$^d$</td>
<td>0.37 ± 0.09</td>
<td>0.15</td>
<td>1.04 ± 0.27</td>
</tr>
<tr>
<td>MDA 435</td>
<td>0.75 ± 0.16</td>
<td>0.35</td>
<td>0.96 ± 0.22</td>
</tr>
<tr>
<td>MDA/T0.3$^e$</td>
<td>0.30 ± 0.07</td>
<td>0.12</td>
<td>0.55 ± 0.07</td>
</tr>
<tr>
<td>Blood$^f$</td>
<td>0.31 ± 0.03</td>
<td>0.63</td>
<td>0.36 ± 0.05</td>
</tr>
<tr>
<td>Heart</td>
<td>7.97 ± 0.92</td>
<td>0.48</td>
<td>10.1 ± 1.54</td>
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<td>Liver</td>
<td>10.2 ± 2.14</td>
<td>3.43</td>
<td>11.1 ± 1.02</td>
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<td>Brain</td>
<td>0.09 ± 0.02</td>
<td>0.41</td>
<td>0.13 ± 0.01</td>
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<tr>
<td>Lung</td>
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<td>0.21</td>
<td>3.18 ± 0.57</td>
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<td>Spleen</td>
<td>1.30 ± 0.37</td>
<td>0.31</td>
<td>2.90 ± 0.28</td>
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<tr>
<td>Kidney</td>
<td>25.2 ± 4.81</td>
<td>0.71</td>
<td>30.5 ± 4.92</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.55 ± 0.28</td>
<td>0.32</td>
<td>2.03 ± 0.34</td>
</tr>
</tbody>
</table>

$^a$ Mean %ID/g ± SD and $^{99m}$TcSestamibi/$^{201}$TlThallous chloride ratios ($^{99m}$Tc/$^{201}$Tl) 15 min after injection of radio-pharmaceuticals delivered 2 h after i.p. administration of SDZ PSC 833.

$^b$ Two experiments (n = 5, each experimental group) for MDA/T0.1 xenografts and 1 experiment for MDA/T0.3 xenografts receiving 50 mg/kg SDZ PSC 833.

$^c$ Two experiments (n = 5, each experimental group) for MDA/T0.1 and MDA/T0.3 xenografts receiving 100 mg/kg SDZ PSC 833.

$^d$ Mouse model containing MDA 435 xenograft on left thigh and drug-resistant xenograft on right thigh.

$^e$ Tissue distribution data derived from all experiments.

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T0.3 cell line were compared directly to those obtained with known concentrations of SDZ PSC 833 diluted in normal mouse serum (Fig. 5). Control serum did not increase the accumulation of $^{99m}$TcSestamibi in the MDA 435 control cell line. Decreasing dilutions of serum containing SDZ PSC 833 increased $^{99m}$TcSestamibi accumulation in the MDA/T0.3 cell line in a dose-dependent fashion. Comparison with known concentrations of SDZ PSC 833 diluted in control serum indicated that the serum concentration was approximately 1 mM (Fig. 5).

DISCUSSION

The observations in this study extend the use of $^{99m}$TcSestamibi in the characterization of P-glycoprotein-mediated transport. In addition, pharmacological inhibition of P-glycoprotein function has been demonstrated in a drug-resistant, solid-tumor model. The reversal agent SDZ PSC 833 increases accumulation of $^{99m}$TcSestamibi specifically in tumors expressing P-glycoprotein.

A breast cancer tumor model with a parental sensitive tumor and a multidrug-resistant derivative tumor grown on opposite flanks of the nude mouse was used. The baseline accumulation of $^{99m}$TcSestamibi was less in the resistant tumors, which express the human MDR1 P-glycoprotein, than in the parental sensitive tumor. Administration of SDZ PSC 833 2 h prior to injection of $^{99m}$TcSestamibi increased accumulation of the radiophore in the resistant xenografts to the same levels found in the sensitive tumors. The modulation of P-glycoprotein function was dependent on both the dose of the reversal agent and the level of P-glycoprotein expression in the tumor. Both MDA/T0.1 and MDA/T0.3 xenografts accumulated increasing amounts of $^{99m}$TcSestamibi with increasing doses of SDZ PSC 833. The amount of SDZ PSC 833 required to achieve concentrations of $^{99m}$TcSestamibi in the MDA/T0.3 xenografts equivalent to those in the MDA 435 xenografts was greater than that required for the MDA/T0.1 xenografts. This was similarly demonstrated in vitro with the same multidrug-resistant, breast carcinoma cell lines used as xenografts. Greater amounts of verapamil, cyclosporin A, and quinidine had been shown previously to be necessary to attain maximal accumulation of...
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Fig. 4. Accumulation of $^{99m}$TcSestamibi in vivo. Ratio of accumulation of $^{99m}$TcSestamibi to $^{201}$Tlthallous chloride in MDA 435, MDA/T0.1, and MDA/T0.3 xenografts with or without prior administration of SDZ PSC 833. Accumulation was determined 15 min after simultaneous injection of radiopharmaceuticals. SDZ PSC 833 was administered i.p. 2 h prior to radiopharmaceuticals. Bars, SD.

$[^{99m}Tc]$Sestamibi in multidrug-resistant cell lines expressing higher levels of P-glycoprotein (10, 11). Whether this need for higher levels of reversal agents is due to the level of P-glycoprotein expression as opposed to differences in P-glycoprotein functional activity or the differential interaction of substrates with the P-glycoprotein is not known.

This model has been designed to have both sensitive and resistant tumors on the same mouse, thus eliminating the potential confounding issue of a pharmacokinetic interaction between the reversal agent and delivery of $[^{99m}Tc]$Sestamibi to the tumors. In both preclinical (25-29) and clinical trials (30) with certain reversal agents, the area under the curve for a variety of P-glycoprotein substrates is increased. This has made it difficult to determine whether increased efficacy of chemotherapeutic regimens is due to a molecular interaction between the reversal agent and the P-glycoprotein, enhancing cellular accumulation of the cytotoxic compounds, or simply due to increased delivery of the chemotherapeutic agent. The same concentration of $[^{99m}Tc]$Sestamibi was delivered to both the sensitive and resistant tumors in this model because both were grown in the same mouse on opposite flanks. In addition, accumulation of $[^{99m}Tc]$Sestamibi was normalized for delivery using $^{201}$Tlthallous chloride as a measure of tissue perfusion. Finally, different serum concentrations of $[^{99m}Tc]$Sestamibi did not affect the relative biodistribution of the radioprobe.

The accumulation of $[^{99m}Tc]$Sestamibi in the MDA/T0.1 and MDA/T0.3 xenografts indicated that different levels of P-glycoprotein functional activity can be characterized in vivo. Both resistant xenografts accumulated 35-50% less $[^{99m}Tc]$Sestamibi than the parental xenograft. There is a trend, although without statistical significance, that the MDA/T0.3 xenografts accumulated less $[^{99m}Tc]$Sestamibi than the MDA/T0.1 xenografts. However, with administration of 50 mg/kg SDZ PSC 833, the amount of $[^{99m}Tc]$Sestamibi accumulating in the MDA/T0.1 xenografts increased to the same concentration as

![Graph showing accumulation of $[^{99m}Tc]$Sestamibi in MDA 435 sensitive, MDA/T0.1 resistant, and MDA/T0.3 resistant xenografts with different concentrations of SDZ PSC 833.](image)

![Graph showing bioassay for serum concentration of SDZ PSC 833.](image)
the parental MDA 435 xenographs, whereas the MDA/T0.3 xenographs took up only a modest amount more than the baseline value. The MDA/T0.3 xenographs required 100 mg/kg of SDZ PSC 833 for complete reversal of P-glycoprotein function. These observations highlight the lack of information for determining the best method to characterize P-glycoprotein function with $^{99m}$TcSestamibi. The sensitivity and specificity remain to be completely defined. Total accumulation, the rate of efflux, and modulation of accumulation in response to a P-glycoprotein reversal agent have each been proposed to characterize P-glycoprotein transport activity with $^{99m}$TcSestamibi (11, 31, 32). Further studies are required to determine the optimal methodology.

SDZ PSC 833 has emerged as one of the most potent modulators of P-glycoprotein functional activity (30). It is a derivative of cyclosporin D, which was initially identified as a nonimmunosuppressive analogue of cyclosporin A. SDZ PSC 833 appears to be approximately 5-10-fold more potent than cyclosporin A (33). Previous analysis indicated that SDZ PSC 833 binds to P-glycoprotein and inhibits photoaffinity labeling of P-glycoprotein similar to other reversal agents (20). However, multidrug-resistant and parental sensitive cell lines incubated with $^{[14C]}$SDZ PSC 833 displayed similar efflux patterns, suggesting that SDZ PSC 833, in contrast to some other reversal agents, may not be transported out of the cell by P-glycoprotein. This is consistent with the continued inhibition of rhodamine-123 efflux from multidrug-resistant cell lines for over 2 h after the removal of SDZ PSC 833 from the incubation medium. Independent analyses have similarly suggested that P-glycoprotein substrates that are poorly transported may represent the best inhibitors of P-glycoprotein functional activity (11, 34). The observations presented here indicate the ability of SDZ PSC 833 to inhibit P-glycoprotein transport activity in a solid tumor model at clinically achievable serum concentrations. Although these experiments were not intended to be an efficacy study, preliminary results using oral administration of SDZ PSC 833 demonstrated increased efficacy in the treatment of human multidrug-resistant tumor xenographs in nude mice with antitumor agents.

Biodistribution studies of $^{99m}$TcSestamibi in normal tissues after the administration of SDZ PSC 833 demonstrated that the largest increases in accumulation occurred in the lung and spleen. There were modest increases in the brain, blood, kidney, and muscle, but no changes in the heart and liver. These observations contrast with the increased accumulation of P-glycoprotein substrate substrates observed in mice lacking mdr1a (35–38). Several possibilities many account for these differences. Most notably, $^{99m}$TcSestamibi biodistribution was performed 15 min after administration of the probe. The observations in the mice lacking mdr1a, showing very high levels of substrate accumulation in the brain and high levels in the muscle, heart, kidney, liver, lung, spleen, and blood, were performed 4–24 h after administration. The difference in the time of analysis could be critical because of potential differences in the pharmacokinetics and biodistribution of the substrates. In addition, the higher levels of nonspecific binding found with most P-glycoprotein substrates compared with that of $^{99m}$TcSestamibi would be expected to augment accumulation over time. Indeed, increasing amounts of several substrates have been demonstrated in the tissues between 4 and 24 h after administration. A pharmacokinetic analysis of vinblastine in mice lacking mdr1a indicated that prolongation of the terminal phase of vinblastine clearance was responsible for the increased accumulation in the tissues (37). There did not appear to be differences in the serum with control mice for the first 4 h, and the largest differences were noted at 24 h after administration of the substrate. In addition, it is possible that there is differential tissue inhibition of P-glycoprotein function by SDZ PSC 833 due to differences in P-glycoprotein expression or tissue perfusion. Preliminary observations indicate that SDZ PSC 833 administration does result in increased accumulation of $^{99m}$TcSestamibi in the liver and kidney 1 h after the administration of the radiophore (data not shown), consistent with a recent case report in a human (38). These differences highlight the difficulty in comparing the pharmacokinetics of different substrates.

The observations in this study demonstrate that it is possible to inhibit P-glycoprotein function in solid tumors. Increased accumulation of $^{99m}$TcSestamibi in tumors expressing high levels of P-glycoprotein indicates that agents such as SDZ PSC 833 can selectively increase the intracellular concentration of chemotherapeutic agents transported by P-glycoprotein. These results suggest that if P-glycoprotein-mediated drug transport is a limiting factor of successful cancer chemotherapy, improvement in therapeutic outcomes is feasible. The current clinical trials with inhibitors of P-glycoprotein function will hopefully provide the definitive answer.

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REFERENCES


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