The P-Glycoprotein Antagonist PSC 833 Increases the Plasma Concentrations of 6α-Hydroxypaclitaxel, a Major Metabolite of Paclitaxel

Min H. Kang, William D. Figg, Yuichi Ando, Mikhail V. Blagosklonny, David Liewehr, Tito Fojo, and Susan E. Bates

Clinical Sciences, National Cancer Institute, NIH, Bethesda, Maryland 20892

ABSTRACT

Purpose: Overexpression of P-glycoprotein (Pgp) is one mechanism of drug resistance in cancer chemotherapy. A Phase I trial was conducted using PSC 833, a Pgp antagonist, in combination with paclitaxel in patients with refractory cancer. The objective of this study was to assess the effect of PSC 833 on the metabolism of paclitaxel and characterize the differences in 6α-hydroxypaclitaxel pharmacokinetics. In addition, we examined the possibility of enhanced cytotoxicity of paclitaxel by the coexistence of 6α-hydroxypaclitaxel.

Experimental Design: Patients received paclitaxel 35 mg/m²/day by continuous intravenous infusion (CIVI) × 4 days without PSC 833 in cycle 1 and escalating doses of paclitaxel (13.1, 17.5, or 21.3 mg/m²/day CIVI × 4 days) with 5 mg/kg PSC 833 by mouth every 6 h in cycle 2. Plasma samples were analyzed for both paclitaxel and its major metabolite with high-performance liquid chromatography methods. Using human liver microsomes, we studied the effect of PSC 833 on the metabolism of paclitaxel. In addition, the in vitro cytotoxicity of 6α-hydroxypaclitaxel alone and in combination with paclitaxel was evaluated.

Results: Twenty-one of 22 patients had a metabolite peak (6α-hydroxypaclitaxel) observed in the chromatogram of plasma samples from cycle 2 when they received paclitaxel in combination with PSC 833. This metabolite was not detectable in plasma obtained during the first cycle when they received paclitaxel without PSC 833. During cycle 2, the mean concentrations of 6α-hydroxypaclitaxel and paclitaxel were 0.10 ± 0.074 and 0.079 ± 0.041 μg/ml, respectively. A moderate association was observed between total bilirubin and 6α-hydroxypaclitaxel concentrations (P = 0.015, r = 0.52; n = 21). Human liver microsome experiments showed that a PSC 833 concentration as high as 10 μM did not affect the production of 6α-hydroxypaclitaxel. Paclitaxel cytotoxicity in HL60 and K562 human leukemia cells was increased in the presence of noncytotoxic concentrations of 6α-hydroxypaclitaxel.

Conclusions: PSC 833 increases the plasma concentration of 6α-hydroxypaclitaxel during paclitaxel therapy. Inhibition of cytochrome P-450 3A4 by PSC 833 may explain this in part, although other mechanisms cannot be excluded.

INTRODUCTION

Pgp is a multidrug transporter that is expressed in normal tissues, including the apical surface of intestinal epithelia, endometrial glands, the blood-brain barrier, and the proximal tubule of the kidney (1, 2). Although the physiological function of Pgp is not known, it has been suggested that Pgp may play a role in defense against xenobiotics in normal tissues (3). Overexpression of Pgp, which is encoded by the MDR1 gene, confers multidrug resistance in cancer cells (4). In patients, overexpression can correlate with a poor prognosis (5–10). A number of chemotherapeutic agents including the Vinca alkaloids, the anthracyclines, the taxanes, and other natural products have been identified as substrates for Pgp (11). In addition, numerous antagonists have been identified including verapamil, cyclosporine A, quinidine, and several potent second-generation antagonists, currently under clinical investigation. PSC 833, a cyclosporine D analogue, is a nonimmunosuppressive, nonnephrotoxic Pgp antagonist (12). Biotransformation of PSC 833 is CYP3A dependent (13).

Paclitaxel was originally isolated from the bark of the Pacific yew tree and was subsequently identified as an antineoplastic agent (14). Paclitaxel stabilizes microtubules resulting in cell cycle arrest. Clinical trials have documented paclitaxel activity against ovarian, breast, lung, and other types of cancer (15–19). Paclitaxel metabolism has been characterized in several studies with three major metabolites identified: 6α-hydroxypaclitaxel, 3′-p-hydroxypaclitaxel, and 6α,3′-p-dihydroxypaclitaxel. CYP2C8 is responsible for the transformation of paclitaxel to 6α-hydroxypaclitaxel and the formation of 6α,3′-p-dihydroxypaclitaxel from 3′-p-hydroxypaclitaxel (20–23).

The abbreviations used are: Pgp, P-glycoprotein; CIVI, continuous intravenous infusion; CYP, cytochrome P450; HPLC, high-performance liquid chromatography; ANC, absolute neutrophil count; CsA, cyclosporine A; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.
The trial was a Phase I dose escalation study in which both PSC 833 and paclitaxel were escalated. Paclitaxel dose of 13.1 mg/m²/day by CIVI × 4 days in combination with PSC 833 at 5 mg/kg every 6 h was established as the maximum tolerated dose. Then, to support an advance of the paclitaxel dose, filgrastim was added to the regimen. The maximum tolerated dose with the support of filgrastim was determined as 17.5 mg/m²/day by CIVI × 4 days in combination with PSC 833 5 mg/kg every 6 h. For this report, the analysis was confined to patients who received a paclitaxel dose of 35 mg/m²/day CIVI × 4 days without concurrent PSC 833 in cycle 1 and 5 mg/kg PSC 833 every 6 h × 7 days with a paclitaxel dose of either 13.1, 17.5, or 21.3 mg/m²/day CIVI × 4 days in cycle 2. Patients receiving both drugs in cycle 2 started PSC 833 3 days prior to the start of the paclitaxel infusion and received PSC 833 until the end of the paclitaxel infusion, when both drugs were discontinued.

**Sampling Schedule.** Serial blood samples were collected for pharmacokinetic analysis. Blood samples were drawn in heparinized tubes prior to treatment and at 24, 48, 72, and 96 h after the start of the paclitaxel infusion in the first and second cycle. Up to 96 h after infusion, blood samples were drawn from one patient. Samples were centrifuged immediately, and the plasma was collected and stored at −80°C until analysis.

**Analytical Methods.** The concentrations of paclitaxel and 6α-hydroxypaclitaxel in plasma were determined using HPLC with UV detection, as described previously (26). A Hewlett-Packard 1090 Series II liquid chromatograph equipped with a photodiode-array detector was used. Paclitaxel was extracted from 0.6 ml of plasma, with 200 ng/ml harmine added as an internal standard. 0.6 ml of 0.2 M ammonium acetate was added to the plasma, and solid-phase extraction was performed using a C18 elution column (Varian). The columns were equilibrated with 2 ml of methanol, followed by 2 ml of 10 mM ammonium acetate (pH 5.0). The plasma-buffer mixtures were loaded onto the columns, and the columns were washed with 2 ml of 10 mM ammonium acetate, followed by 2 ml of 20% methanol in 10 mM ammonium acetate and 1 ml of n-hexane. The columns were dried and eluted with 2 × 1 ml of 0.1% triethylamine in acetonitrile. The eluents were dried and reconstituted in 200 μl of acetonitrile:methanol:water (4:1:5 v/v/v).

**MATERIALS AND METHODS**

**Clinical Protocol.** Eligible patients were >18 years of age and had a Karnofsky performance status of 70% or better, a life expectancy of >3 months, aspartate aminotransferase and alanine aminotransferase ≤2 × upper limit of normal, creatinine clearance ≥50 ml/min, WBC ≥3,000/mm³, ANC ≥1,000/mm³, and platelet count ≥100,000/mm³. Patients who had received chemotherapy, immunotherapy, or radiation therapy in the 4 weeks before study entry, or had undergone a prior bone marrow transplantation or extensive radiation resulting in compromised bone marrow reserve, were not eligible. Agents proven to interact with CsA or suspected to interact with P-glycoprotein were restricted during the study. The protocol was approved by the Institutional Review Board of the National Cancer Institute, and all patients signed an informed consent document prior to treatment.

A Phase I trial combining oral PSC 833 and infusional paclitaxel in patients with advanced cancer was conducted at the National Cancer Institute (25). The objectives of the study were to determine the maximum tolerated dose of PSC 833 in combination with paclitaxel and to compare the pharmacokinetics of paclitaxel administered alone with the pharmacokinetics of paclitaxel with concomitant administration of PSC 833. Four different dose levels of PSC 833 ranging from 1.25 to 5 mg/kg p.o. every 6 h × 7 days were explored. Fifty patients received paclitaxel and PSC 833 separately in the first cycle and a combination of paclitaxel and PSC 833 in subsequent cycles. The maximum tolerated doses identified were: 5 mg/kg PSC 833 administered every 6 h × 7 days in combination with a paclitaxel dose of either 13.1 mg/m²/day by CIVI × 4 days without filgrastim or 17.5 mg/m²/day CIVI × 4 days with filgrastim. Paclitaxel doses of 13.1 or 17.5 mg/m²/day CIVI × 4 days with PSC 833 resulted in mean plasma concentrations that were equivalent to those achieved with a paclitaxel dose of 35 mg/m²×days CIVI × 4 days without PSC 833. However, considerable interpatient variation was observed in the magnitude of paclitaxel concentration changes with PSC 833.

In the course of analyzing patient plasma samples, we observed, in a majority of patients who received 5 mg/kg PSC 833 administered p.o. every 6 h, unusually high concentrations of a metabolite subsequently identified as 6α-hydroxypaclitaxel. A peak corresponding to 6α-hydroxypaclitaxel was not detected in the first cycle when paclitaxel was administered alone. This study describes the identification of this metabolite as 6α-hydroxypaclitaxel and its quantification. Attempts to understand the mechanisms responsible for the appearance of the metabolite and to find a correlation between the metabolite and the occurrence of toxicities are also discussed.

**FIGURE 1** Chemical structure of paclitaxel and its metabolites (left) and the metabolic pathways for paclitaxel biotransformation (right). Paclitaxel: R₁ = H, R₂ = H; 6α-hydroxypaclitaxel: R₁ = OH, R₂ = H; 3-p-hydroxypaclitaxel: R₁ = H, R₂ = OH; 6α,3-p-dihydroxypaclitaxel: R₁ = OH, R₂ = OH (modified from Ref. 24).
containing 0.01 M ammonium acetate. The reconstituted sample, 170 μl, was injected onto a Waters Nova-Pak C18 (3.9 × 300 mm) column. The mobile phase (25% acetonitrile, 5% methanol, 70% water in 10 mM NH₄Ac) with gradient was used at a flow rate of 1.0 ml/min at room temperature. UV detection was at 230 nm (bandwidth, 10 nm).

Enzymatically produced 6α-hydroxypaclitaxel and 3-p-hydroxypaclitaxel were obtained from Gentest Co. (Woburn, MA). The content of a vial was dissolved in 500 μl of methanol. The final concentration was determined by absorbance at 230 nm using a molar extinction coefficient of 26.2 mM⁻¹. The concentrations used for the standard curve ranged from 20 to 300 ng/ml. The plasma concentrations of 6α-hydroxypaclitaxel were measured using the same analytical method used for paclitaxel. Average retention times were 13.3, 12.6, and 9.7 min for paclitaxel, 6α-hydroxypaclitaxel, and the internal standard, harmine, respectively. The limits of quantification were 25 ng/ml for paclitaxel and 20 ng/ml for 6α-hydroxypaclitaxel. The intraassay and interassay coefficients of variation for paclitaxel were <6.2% between 25 and 100 ng/ml. The intraassay and interassay coefficients of variation for 6α-hydroxypaclitaxel over the entire concentration range were <6.7%, respectively.

Human Liver Microsome Experiment. PSC 833 was kindly provided by Novartis, Inc. (East Hanover, NJ). The purity of PSC 833 was >98%. Ketoconazole, CsA, NADP+, glucose-6-phosphate, and glucose-6-phosphate dehydrogenase were purchased from Sigma Chemical Co. (St. Louis, MO). Pooled human liver microsomes were purchased from Gentest Co. A reaction mixture consisted of: (a) 300 μl of a 2:1 mixture of 0.5 M sodium-potassium phosphate buffer (pH 7.4):0.5 mM EDTA; (b) 100 μl of NADPH-regenerating system (2 mM NADP+, 40 mM MgCl₂, 40 mM glucose 6-phosphate, and 10 units/ml glucose 6-phosphate dehydrogenase); (c) 0.5 mg (25 μl) of human liver microsomes; and (d) distilled water to make a final volume of 1 ml after adding inhibitors and the substrate. CsA, PSC 833, or ketoconazole at the concentrations of 0.1, 0.3, 1, 3 and 10 μM were added to tubes to yield the final vehicle concentration of 0.5%. After a 5-min preincubation with inhibitors at 37°C in a shaking water bath, 10 μl of 1 mM paclitaxel (10 μM in a final concentration) were added and incubated for additional 20 min. The reaction was terminated by adding 5 ml
of cold acetonitrile containing the internal standard. The sample was vortexed and centrifuged. The organic phase was evaporated to dryness, and the residue was reconstituted with 200 μl of the mobile phase. The analysis using HPLC is described in “Analytical Methods.” Calibration curves of 6α-hydroxypaclitaxel and 3β-p-hydroxypaclitaxel were made to measure the absolute concentrations of each metabolite. Control incubations were performed in the absence of the regenerating system or in the absence of microsomal protein. The production of 6α-hydroxypaclitaxel was linear up to a final paclitaxel concentration of 20 μM or 20 min of incubation time.

Cytotoxicity (MTT) Assay. HL60 and K562 human leukemia cell lines were obtained from American Type Culture Collection (Manassas, VA) and cultivated in RPMI 1640 plus 10% FBS. Paclitaxel was a Bristol-Myers product. Cells (15,000) in 100 μl plated in each well of 96-well flat-bottomed plate were exposed to increasing concentrations of paclitaxel, 6α-hydroxypaclitaxel, or both added in 100 μl of the medium. After 3 days, 20 μl of 5 mg/ml MTT solution in PBS were added to each well for 2 h. After removal of the medium, 170 μl of DMSO were added to each well to dissolve the formazan crystals. The absorbance at 540 nm was determined using a Biokinetics plate reader (Bio-Tek Instruments, Inc., Winooki, VT). Triplicate wells were assayed for each condition, and SDs were determined.

Statistical Analyses. A Spearman rank correlation coefficient (r) was used to evaluate the association between the concentrations of total bilirubin and those of maximum concentrations of 6α-hydroxypaclitaxel, a Cochran-Armitage trend test was used. In addition, among patients who did not receive filgrastim during cycle 1 or cycle 2, the difference in percentage of decrease of ANC from baseline (delta) between the two cycles was formed by subtraction (delta = % decrease in cycle 2 − % decrease in cycle 1; n = 10) and tested for equality to zero with the Wilcoxon signed rank test.

RESULTS

Forty-five patients received a paclitaxel dose of 35 mg/m²/day CIVI 3–4 days in cycle 1. Of these, 22 patients completed at least the second cycle in which they received a PSC 833 dose of 5 mg/kg every 6 h × 7 days. These 22 patients included 12 females and 10 males with a median age of 56 years and a range of 35–67. The paclitaxel doses administered concurrently with PSC 833 in the second cycle were 13.1 mg/m²/day CIVI × 4 days in 6 patients, 17.5 mg/m²/day CIVI × 4 days in 14 patients, and 21.3 mg/m²/day CIVI × 4 days in 2 patients.

Pharmacokinetics of 6α-Hydroxypaclitaxel. Examination of the HPLC chromatogram revealed the appearance of a
metabolite peak in the second cycle when paclitaxel was administered with PSC 833. This peak was subsequently identified as 6α-hydroxypaclitaxel by demonstrating the same retention time and UV absorbance wavelength as 6α-hydroxypaclitaxel. The chemical structure of paclitaxel and its metabolites, and the metabolic pathways of paclitaxel biotransformation, are shown in Fig. 1. In the first cycle, when patients received paclitaxel alone, 6α-hydroxypaclitaxel was not detectable. However, a metabolite peak corresponding to 6α-hydroxypaclitaxel appeared in the second cycle when patients received concomitant PSC 833 and paclitaxel. Fig. 2 shows the chromatograms of plasma obtained from a patient during cycles 1 and 2. In cycle 2, paclitaxel and 6α-hydroxypaclitaxel peaks are observed during the paclitaxel infusion and up to 24 h after the discontinuation of the infusion. As seen here, in some patients, the 6α-hydroxypaclitaxel peak was higher than the paclitaxel one. The concentrations of paclitaxel and 6α-hydroxypaclitaxel from the first cycle and second cycles from the same patient are plotted in Fig. 3. Twenty-four h after the initiation of the paclitaxel infusion, 6α-hydroxypaclitaxel was quantifiable. As the infusion continued, the concentration of 6α-hydroxypaclitaxel increased and at 72 h was higher than paclitaxel. The metabolite reached a maximum concentration 2 h after the end of the infusion in this patient. The maximum concentrations of 6α-hydroxypaclitaxel obtained with paclitaxel doses of 13.1, 17.5, and 21.3 mg/m²/day CIVI × 4 days plus 5 mg/kg PSC 833 every 6 h × 7 days are shown in Table 1. The concentrations of 6α-hydroxypaclitaxel increased during the 96-h infusion (Fig. 4). The mean steady-state concentration, $C_{\text{ss max}}$, and clearance of paclitaxel from C1 is reported previously (25).

**Correlation between Toxicity and Metabolites.** Hyperbilirubinemia, which has been observed previously in patients treated with CsA, was observed with PSC 833 but was not considered a dose-limiting toxicity. Fig. 5 presents scatterplots of bilirubin levels and the concentrations of paclitaxel ($C_{\text{pacl}}$, defined as the mean of the drug concentrations at 48, 72, and 96 h) or 6α-hydroxypaclitaxel ($C_{\text{max max}}$, defined as the highest concentration during the infusion, which in all cases was the concentration at the end of infusion). As shown, the level of total bilirubin was not associated with plasma paclitaxel concentrations (Fig. 5A; $P = 0.68$, $r = -0.09$; $n = 22$) but was moderately associated with 6α-hydroxypaclitaxel concentrations (Fig. 5B; $P = 0.015$, $r = 0.52$; $n = 21$). Fig. 6 shows scatterplots of the toxicity grade of neutropenia and thrombocytopenia versus 6α-hydroxypaclitaxel ($C_{\text{max max}}$) concentration. For analysis, the data were divided into two groups based on filgrastim administration ($n = 12$ with filgrastim support; $n = 10$ without filgrastim). In neither group could a significant trend between 6α-hydroxypaclitaxel concentration and neutropenia be demonstrated ($P = 0.12$ with filgrastim; $P = 0.20$ without filgrastim). Similarly, no trend was observed when the concentrations of 6α-hydroxypaclitaxel and toxicity grade of thrombocytopenia were correlated ($P = 0.28$). The percentage of decrease of ANC in cycle 2 was also not significantly different from that in cycle 1 ($P = 0.56$).

**Effects of PSC 833 on the Production of 6α-Hydroxypaclitaxel.** Human liver microsome experiments were performed to evaluate whether the appearance of 6α-hydroxylation in cycle 2 was attributable to alterations in the metabolism of paclitaxel by PSC 833 (Fig. 7). Low concentrations of ketoconazole, the positive control, inhibited the formation of 3′-p-hydroxypaclitaxel (IC$_{50}$ < 1 μM), whereas higher concentrations reduced the production of 6α-hydroxypaclitaxel (53 ± 6.1% of control) as well as 3′-p-hydroxypaclitaxel (complete inhibition), as reported previously (27). In contrast to ketoconazole, PSC 833 and CsA only affected the formation of 3′-p-hydroxypaclitaxel (IC$_{50}$: between 3 and 10 μM and between 1 and 3 μM, respectively) without substantially changing the production of 6α-hydroxypaclitaxel at concentrations ranging from 0.1 to 10 μM. This resulted in an increase in 6α-hydroxypaclitaxel relative to 3′-p-hydroxypaclitaxel.

**Cytotoxicity of Paclitaxel and 6α-Hydroxypaclitaxel.** We evaluated the cytotoxicity of paclitaxel, 6α-hydroxypaclitaxel, and a combination of both in HL60 and K562 cells (Fig. 8). 6α-Hydroxypaclitaxel alone was ~10 times less potent than paclitaxel; 20 nm (23 ng/ml) 6α-hydroxypaclitaxel was not cytotoxic. However, in the presence of 20 nm 6α-hydroxypaclitaxel, the cytotoxicity of paclitaxel was increased, especially at...
low paclitaxel concentrations. In both cell lines the IC$_{50}$ of paclitaxel in the presence of 20 nM 6a-hydroxypaclitaxel was 2–3-fold less than the IC$_{50}$ of paclitaxel alone. These observations suggest that 6a-hydroxypaclitaxel at concentrations that were achieved during cycle 2 can increase the cytotoxicity of paclitaxel in vitro.

**DISCUSSION**

Previous clinical trials have reported the ratio of 6a-hydroxypaclitaxel to paclitaxel in the presence of 20 nM 6a-hydroxypaclitaxel was 2–3-fold less than the IC$_{50}$ of paclitaxel alone. These observations suggest that 6a-hydroxypaclitaxel at concentrations that were achieved during cycle 2 can increase the cytotoxicity of paclitaxel in vitro.

There are several possible explanations for the clinical presence of 6a-hydroxypaclitaxel, none of which are mutually exclusive. The first possibility is that the metabolic pathway via CYP3A4 is competitively inhibited by PSC 833, resulting in a shift from production of 3p-hydroxypaclitaxel to 6a-hydroxypaclitaxel via CYP2C8. This shift could result in increased formation of 6a-hydroxypaclitaxel and inhibition of subsequent 3p-hydroxylation of paclitaxel. This possibility is supported in part by the results with the human liver microsomes experiments demonstrating a concentration-dependent PSC 833 inhibition of 3p-hydroxylation of paclitaxel without a substantial effect on the formation of 6a-hydroxypaclitaxel (converted by CYP2C8), resulting in increased 6a-hydroxypaclitaxel relative to 3p-hydroxylation at concentrations >1 μM PSC 833, which are within the range achieved in the patients in this study. One could argue that 6a-hydroxylation is a major pathway of paclitaxel metabolism, and inhibiting CYP3A4 with...
PSC 833 may not critically affect 6α-hydroxylation. However, further metabolism of 6α-hydroxypaclitaxel by CYP3A4 may have been inhibited by PSC 833, resulting in increased 6α-hydroxypaclitaxel. Therefore, an alteration in the metabolism of paclitaxel may provide an important explanation for the increased 6α-hydroxypaclitaxel concentration in plasma.

A second explanation may be through inhibition of intestinal Pgp. The primary route of elimination of paclitaxel is via hepatic metabolism and biliary excretion (33, 34). Paclitaxel and its metabolites have been found in human bile (21, 24). Furthermore, the bioavailability of oral paclitaxel has been shown to increase up to 8-fold with coadministration of oral CsA, with an increase in the ratio of 6α-hydroxypaclitaxel:paclitaxel, as well as an increase in other metabolites (35–37). p.o. administered PSC 833 could have increased the absorption of excreted paclitaxel and its metabolites, resulting in higher plasma concentrations by enhancing the enterohepatic circulation.

Finally, there is evidence that PSC 833 can affect bile flow rate and biliary excretion in a reversible manner (38). Although the exact mechanism is unclear, we observed a significant correlation (P = 0.015) between total bilirubin concentrations and the concentration of 6α-hydroxypaclitaxel in plasma. It is thus possible that PSC 833 increased the reabsorption of paclitaxel metabolites, including 6α-hydroxypaclitaxel, by promoting cholestasis.

The biological activity of 6α-hydroxypaclitaxel has been investigated previously (31, 39). In MOLT-4 and U-937 leukemia cell lines, they found the IC_{50} of 6α-hydroxypaclitaxel to be 52 and 29 nM, respectively, whereas in human ovarian carcinoma (A2780) and rat colon carcinoma (CC531) cells, 50 nM 6α-hydroxypaclitaxel was inactive (39). As a single compound, 6α-hydroxypaclitaxel was shown to be weakly myelotoxic (39). In the present study, we observed 6α-hydroxypaclitaxel to be less cytotoxic than paclitaxel. This observation is not unexpected because hydroxylation of a cytotoxic drug is usually a detoxification process. Therefore, the clinical significance of an increase in 6α-hydroxypaclitaxel may be negligible when the ratio of 6α-hydroxypaclitaxel to paclitaxel is small, as would be expected with shorter paclitaxel infusions, where paclitaxel concentration in plasma.

In conclusion, we have found that coadministration of PSC 833 with paclitaxel increases the concentrations of both paclitaxel and 6α-hydroxypaclitaxel. Several possible explanations for the increase in 6α-hydroxypaclitaxel concentrations are discussed. The clinical significance of 6α-hydroxypaclitaxel and paclitaxel concentrations may depend on the schedule of administration. The results of this study emphasize once again that the concurrent use of a agent such as PSC 833 can considerably alter the pharmacokinetics and metabolism of chemotherapeutic agents.

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