Comparative Preclinical and Clinical Pharmacokinetics of a Cremophor-Free, Nanoparticle Albumin-Bound Paclitaxel (ABI-007) and Paclitaxel Formulated in Cremophor (Taxol)

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Abstract

Purpose: To compare the preclinical and clinical pharmacokinetic properties of paclitaxel formulated as a Cremophor-free, albumin-bound nanoparticle (ABI-007) and formulated in Cremophor-ethanol (Taxol).

Experimental Design: ABI-007 and Taxol were given i.v. to Harlan Sprague-Dawley male rats to determine pharmacokinetic and drug disposition. Paclitaxel pharmacokinetic properties also were assessed in 27 patients with advanced solid tumors who were randomly assigned to treatment with ABI-007 (260 mg/m^2, 30 minutes; n = 14) or Taxol (175 mg/m^2, 3 hours; n = 13), with cycles repeated every 3 weeks.

Results: The volume of distribution at steady state and clearance for paclitaxel formulated as Cremophor-free nanoparticle ABI-007 were significantly greater than those for paclitaxel formulated with Cremophor (Taxol) in rats. Fecal excretion was the main elimination pathway with both formulations. Consistent with the preclinical data, paclitaxel clearance and volume of distribution were significantly higher for ABI-007 than for Taxol in humans [21.13 versus 14.76 L/h/m^2 (P = 0.048) and 663.8 versus 433.4 L/m^2 (P = 0.040), respectively].

Conclusions: Paclitaxel formulated as ABI-007 differs from paclitaxel formulated as Taxol, with a higher plasma clearance and a larger volume of distribution. This finding is consistent with the absence of paclitaxel-sequestering Cremophor micelles after administration of ABI-007. This unique property of ABI-007 could be important for its therapeutic effectiveness.

Paclitaxel, a naturally occurring hydrophobic diterpenoid product extracted from the bark of the western yew (*Taxus brevifolia*; ref. 1), exerts its anticancer effects by promotion of tubulin polymerization, stabilization of microtubules, blockade of cells at the G_2-M interface, and induction of apoptosis (2, 3). Paclitaxel is used as standard therapy for ovarian, breast, and non–small cell lung cancer and has recognized antitumor activity in several other malignancies (4).

Currently, paclitaxel is marketed commercially in a formulation that contains a solvent system of Cremophor and dehydrated ethanol USP (Taxol, Bristol-Myers Squibb Co., Princeton, NJ; ref. 4). However, the amount of Cremophor in paclitaxel per administration is relatively high and has been associated with serious toxicities, including severe, sometimes fatal, hypersensitivity reactions (5–8). Consequently, patients who receive Taxol must be premedicated with steroids and antihistamines to reduce the risk of such reactions, and special non–di(2-ethylhexyl) phthalate tubing and in-line filters are required for i.v. administration (4). Therefore, the toxicologic and pharmacologic behavior of Cremophor in the context of chemotherapeutic treatment with paclitaxel is important.

ABI-007 (Abraxane, American BioScience, Inc., Santa Monica, CA), a Cremophor-free, albumin-bound, nanoparticle paclitaxel (mean diameter, ~130 nm), was developed to retain the therapeutic benefits of paclitaxel but eliminate the toxicities associated with Cremophor in the Taxol formulation and its generic equivalents. The maximum tolerated dose of ABI-007 was ~70% to 80% higher than that reported for Taxol for both an every-3-weeks regimen (300 versus 175 mg/m^2) and a weekly regimen (150 versus 80 mg/m^2; refs. 9–11).

In a phase III study comparing ABI-007 (260 mg/m^2) and Taxol (175 mg/m^2, every 3 weeks) in 454 patients with metastatic breast cancer (12), response rates were significantly higher for ABI-007 than for Taxol. The overall tolerability of the two regimens was similar, with 98% of the planned dose being given for each drug. Despite the increased dose of paclitaxel on

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the ABI-007 arm, the incidence of grade 4 neutropenia was significantly lower with ABI-007 than with Taxol (9% versus 22%; $P = 0.001$). Consistent with the higher dose of paclitaxel, peripheral neuropathy was higher on the ABI-007 arm. We speculated that the differences in tolerability and efficacy between the two paclitaxel formulations are the result of altered pharmacokinetic characteristics of ABI-007 compared with those of Taxol. The objective of the current study was to evaluate the comparative preclinical and clinical pharmacokinetic properties of the two paclitaxel formulations at the doses and schedules used in the phase III trial.

Materials and Methods

Preclinical studies

Radiolabeled paclitaxel. [^{3}H]Paclitaxel of >99% purity was obtained from Moravek Biochemicals (Brea, CA). The majority of the tritium is in the *m* and *p* positions of the aromatic rings, with minor amounts in the 10, 3′, and 2 positions of the taxane ring system. To prepare [^{3}H]ABI-007, [^{3}H]paclitaxel was diluted isotopically with unlabeled paclitaxel (98.5% purity; Samyang Genex, Seoul, South Korea) by dissolving both in ~3 mL ethanol to a final specific activity of 25 μCi/mg paclitaxel. Diluted [^{3}H]paclitaxel was incorporated into a nanoparticle formulation via a proprietary process and lyophilized to a dry powder. The radiochemical purity of the final product was determined by extracting a 10 mg aliquot from two separate vials of [^{3}H]ABI-007 powder with acetonitrile/0.9% NaCl (2:1) and analyzing the extract by high-performance liquid chromatography (HPLC); the purity of the extract was found to be 100%. The [^{3}H]ABI-007 powder was stored frozen at −70°C until used. Nonradioactive ABI-007 was prepared similarly without radioactive paclitaxel.

Taxol injection concentrate (Mead Johnson, Evansville, IN), containing paclitaxel at 6 mg/mL in a mixture of Cremophor and ethanol USP, was purchased from a local pharmacy and stored at 4°C. To prepare [^{3}H]Taxol, Taxol was added to [^{3}H]paclitaxel to a specific activity of 25 μCi/mg paclitaxel.

Animals. The preclinical study was done under contract at Biological Test Center (Irvine, CA). Sprague-Dawley rats (Harlan Sprague-Dawley, San Diego, CA), 7 to 8 weeks old, were housed at 72°F to 73°F and 36% to 38% relative humidity, with 12-hour light and dark cycles. On arrival, the animals were transferred to a quarantine room, where they were ear-tagged and maintained in individual hanging, stainless-steel cages for ≥7 days and examined for general health. The animals received Teklad certified LM-485 mouse/rat diet (Harlan Teklad, Madison, WI) and local tap water. Food was provided *ad libitum* throughout the quarantine and study periods, except for 16 to 22 hours before dosing until 4 hours after dosing. Water was provided *ad libitum*, except for the first 4 hours after dosing. All animals were reexamined before dosing to ensure normal health and then assigned to treatment groups using a weight-stratified randomization procedure.

Animal treatment. The [^{3}H]ABI-007 and [^{3}H]Taxol dosing solutions were prepared by placing a weighed amount of [^{3}H]ABI-007 powder or measured volume of Taxol injection concentrate and [^{3}H]paclitaxel solution in ethanol into a glass scintillation vial, respectively. Normal saline for injection was added to each vial to achieve a final dosing volume of 10 mL/kg. To quantitate the radioactivity in the dosing preparations, three 100 μL aliquots of each solution were diluted and analyzed for radioactivity by liquid scintillation counting (LSC). [^{3}H]ABI-007 and [^{3}H]Taxol were given into the jugular vein of halothane-anesthetized rats using a 27-gauge needle. Five groups of 10 animals each received ABI-007 at 5, 9, 26, 117, and 148 mg/kg paclitaxel. Two groups of 10 animals each received Taxol at 5 and 10 mg/kg. Higher doses were not possible for Taxol due to acute toxicity.

Blood sample collection. Blood samples were collected from the tail vein of each rat at the following times: 2, 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours after dosing at each of the following levels: 5, 9, 26, 117, and 148 mg/kg. Blood samples were combusted, and radioactivity was determined as described below. Blood paclitaxel concentration was calculated based on the specific activity of the test articles and the disintegrations of the blood per minute (dpm). Alternatively, individual blood samples at each collection time were pooled in red-capped Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) containing 100 μL heparin solution (50 units/mL). A 100 μL aliquot of each pooled blood sample was directly transferred to combustion cones and combusted in a Model OX300 Harvey sample oxidizer (RJ Harvey Instrument Corp., Hillsdale, NJ). The remaining volume of blood was extracted twice with acetonitrile. A portion of the extract was analyzed for paclitaxel and its metabolites; duplicate aliquots (50 or 100 μL) of the acetonitrile extract were weighed directly into scintillation vials, and the amount of radioactivity was determined by LSC.

Tissue distribution analysis. Tissue distribution analysis was done in two separate experiments: one terminated 1 day after drug administration and the other terminated after 5 days. After the terminal blood collections, rats were anesthetized with an i.m. injection of ~1 mL/kg ketamine/xylaxine mixture (7:1; v/v), and the thorax was opened to expose the heart. At least 5 mL blood were collected into a heparinized Vacutainer tube via cardiac puncture. Duplicate 100 μL aliquots of blood were transferred directly to combustion cones, and the remaining blood was centrifuged to separate cells from plasma. Samples were frozen at −20°C until radioassayed.

The following tissues were harvested: gastrointestinal tract, gastrointestinal tract contents, bone, brain, testes, seminal vesicles, prostate, heart, kidneys, liver, lungs, muscle, spleen, pancreas, and residual carcass. Additional tissues collected for the 5-day experiment included uterus, ovaries, aorta, muscle, and fat. Each tissue was individually weighed and frozen at −20°C until analysis.

Large tissues and organs were homogenized in ~5 volumes of distilled water, and duplicate aliquots representing ~100 mg tissue were transferred directly into combustion cones. Carcasses were frozen in liquid nitrogen and pulverized in a blender (Waring Corp., Winsted, CT), and a 5 g homogenous aliquot was treated as described for other large tissues. For small tissues (bone, seminal vesicles, prostate, spleen, aorta, and ovaries), duplicate samples were weighed directly into combustion cones. For blood, duplicate 100 μL samples were transferred into combustion cones. The samples were combusted in a sample oxidizer, and the amount of radioactivity was determined by LSC.

Excreta analysis. Excreta samples were processed for total radioactivity. For urine samples, duplicate 100 μL aliquots were transferred to liquid scintillation vials and 10 mL Insta-Gel were added before radioactive analysis by LSC. Fecal samples were homogenized in 5 volumes of distilled water, and duplicate aliquots corresponding to ~100 mg feces were combusted and radioassayed by LSC. The remaining samples were stored frozen at −15°C.

Sample combustion. Sample combustion was done using a sample oxidizer. Tritiated water liberated from combustion samples was trapped in Monophase S (Packard Instrument Co., Meriden, CT), which was contained in liquid scintillation vials. The combustion efficiency was checked daily before the combustion of samples; ^{3}H recovery was always 95% to 105%.

Liquid scintillation counting. Total radioactivity measurements were done using a Beckman LS6500 liquid scintillation spectrometer (Beckman Instruments, Fullerton, CA). Counting time was for a maximum of 10 minutes or to a statistical accuracy of ±2%, whichever occurred first. The spectrometer was programmed to subtract background values and to convert counts per minute to dpm automatically.

High-performance liquid chromatography analysis for [^{3}H]paclitaxel. The acetonitrile extracts of whole blood were concentrated under nitrogen gas as needed and analyzed by HPLC to separate and quantitate [^{3}H]paclitaxel and its metabolites. HPLC for paclitaxel was done using a Waters RCM, 8 mm × 10 cm C_{18} Nova-Pak HR cartridge

(Waters Associates, Milford, MA). Gradient elution was done at a flow rate of 1 mL/min as follows: 0 to 5 minutes with acetonitrile/water (1:9, v/v) and then 5 to 45 minutes with acetonitrile/water (9:1, v/v). The column effluent was analyzed by a Beckman 171 radioisotope detector with a liquid cell using Beckman Ready Flow III at a rate of 2 mL/min. Peak integration was done using Beckman Chromatographic Software (version 2.3).

Pharmacokinetic analysis. Noncompartmental analysis was done using WinNonlin Software version 4.1 (Pharsight Corp., Cary, NC). Pharmacokinetic variables of interest included area under the concentration-time curve from time 0 to ∞ (AUC_∞), peak concentration (C_{max}), total body clearance (CL), half-life of the terminal phase ($t_{1/2}$), time to peak concentration (T_{max}), volume of distribution (V_z), and percentage of AUC_∞ extrapolated after the last quantified concentration ($AUC_{\infty\%extrap}$). A linear-up/log-down method of estimation was used for the calculation of AUC_∞. $AUC_{\infty\%extrap}$ was estimated as the last quantifiable concentration (C_{last}) divided by λ_z, and AUC from time 0 to C_{last} (AUC_{last}) was added to $AUC_{\infty\%extrap}$ to estimate AUC_∞. CL was calculated as dose divided by AUC_∞ and adjusted for body surface area (BSA). V_z was calculated as CL divided by λ_z and adjusted for BSA; $t_{1/2}$ was calculated as *In2* divided by λ_z.

Statistical evaluation. Paclitaxel tissue concentration was expressed as μg paclitaxel/g tissue (i.e., [net dpm/g treated sample] / [specific activity of [^{3}H]paclitaxel (dpm/μg)]). Paclitaxel in tissue was expressed as percent of the given dose (i.e., [(radioactivity in sample) / (total radioactivity given)] × 100). Paclitaxel blood concentration was expressed as μg paclitaxel/mL blood (i.e., [net dpm/mL treated sample] / [specific activity of [^{3}H]paclitaxel (dpm/μg)]).

Patients and methods

Eligibility and on-study evaluation. Eligible patients included those with a diagnosis of recurrent or metastatic advanced solid tumor (proven cytologically or histologically) who had failed standard therapy. Male and nonpregnant, nonlactating female patients ages ≥18 years were eligible for participation in the study. Patients had to have an expected survival of >8 weeks and baseline hematology and blood chemistry values within normal limits. Patients were excluded from participation if they had brain metastases, a history of allergy or hypersensitivity to the study drugs or their excipients, Eastern Cooperative Oncology Group Zubrod performance status of >1, serious concurrent illness, preexisting peripheral neuropathy of grade ≥1, or AIDS or if they were taking protease inhibitors or any other cancer medication. Patients were also excluded if they had received taxane chemotherapy within the previous 6 months, anthracycline therapy within the previous 3 weeks, or any other investigational drug within the previous 4 weeks. Appropriate washouts were required for patients taking anticancer medication or protease inhibitors.

Study design. This randomized, open-label study was conducted at seven sites in Russia. The study was conducted in accordance with Good Clinical Practice, Guidelines of the International Conference on Harmonisation, and the World Medical Association Declaration of Helsinki. The protocol and other related materials were approved by appropriate institutional review boards. Written informed consent was obtained from all patients before study enrollment. Patients with advanced solid tumors who were not considered curable with standard therapies were randomly assigned to treatment (1:1) in blocks of 4 (14 to ABI-007 and 13 to Taxol).

Treatment. ABI-007 was supplied by American Bioscience. The prescribed dose of ABI-007 was prepared in 100 to 150 mL of 0.9% saline. The drug was administered i.v. as a 30-minute infusion, without in-line filtration and without premedication, at a dose of 260 mg/m^2. One cycle of therapy consisted of a single dose of ABI-007 in a 21-day period. Patients continued treatment at 3-week intervals until either progressive disease or unacceptable toxicity occurred. Paclitaxel formulated in Cremophor-ethanol (Taxol) was diluted in 0.9% NaCl injection USP, 5% dextrose injection USP, 5% dextrose and 0.9% NaCl injection USP, or 5% dextrose in Ringer's injection to a final concentration of 0.3 to 1.2 mg/mL before administration as a continuous 3-hour i.v. infusion at a dose of 175 mg/m^2.

Pharmacokinetic studies. Pharmacokinetic studies were done in 27 patients, and evaluable data were available for 26 patients. Whole-blood samples (5-7 mL each) were taken at serial time points to determine paclitaxel pharmacokinetic properties during the first cycle only: For ABI-007 administration, samples were obtained immediately before the start of infusion, 15 minutes after start of infusion, immediately before the end of infusion (~30 minutes after start), and 15 and 30 minutes and 1, 1.5, 3.5, 9.5, 23.5, 47.5, and 71.5 hours after the end of infusion. For Taxol administration, samples were obtained immediately before the start of infusion, 1 and 2 hours after start of infusion, immediately before the end of infusion (~3 hours after start), and 15 and 30 minutes and 1, 1.5, 3.5, 7, 21, 45, and 69 hours after the end of infusion.

Blood samples were frozen and shipped to Alta Analytical Laboratory (El Dorado Hills, CA) for paclitaxel quantitation using a validated HPLC with tandem mass spectrometric detection (9). The limit of quantitation for paclitaxel using this assay was 5 ng/mL, and the range of reliable response was 5 to 1,000 ng/mL. The standards used were ±15% of nominal concentration, and quality control samples (15, 400, and 800 ng/mL) were also within 15% of nominal concentration.

Pharmacokinetic variables were determined from each patient's whole-blood paclitaxel concentration profile. Standard compartmental analysis cannot be applied to these data, as a different model would have been required for both ABI-007 and Taxol. In the absence of additional information, such as the quantity of unbound paclitaxel and Cremophor levels for the Taxol cohort, the use of noncompartmental analysis was considered the most appropriate choice. Thus, noncompartmental analysis was done using WinNonlin Software version 4.1. Pharmacokinetic variables included AUC_∞, C_{max}, CL, $t_{1/2}$, T_{max}, V_z, dose-adjusted AUC_∞ ($AUC_{\infty da}$), $AUC_{\infty\%extrap}$, dose-adjusted C_{max} (C_{maxda}), volume of distribution at steady state (V_{ss}), and rate constant of the terminal phase (λ_z). A linear-up/log-down method of estimation was used for the calculation of AUC_∞. A weighting factor of $1/Y^2$ was used for the estimation of λ_z. $AUC_{\infty\%extrap}$ was estimated as the C_{last} divided by λ_z, and AUC_{last} was added to $AUC_{\infty\%extrap}$ to estimate AUC_∞. CL was calculated as dose divided by AUC_∞ and adjusted for BSA. V_z was calculated as CL divided by λ_z and adjusted for BSA; $t_{1/2}$ was calculated as In2 divided by λ_z. V_{ss} was calculated as the mean residence time multiplied by CL and adjusted for BSA. For statistical comparison and equivalence testing, variables were log transformed and hypothesis testing was done on the log-transformed variable. Student *t* test and one-way ANOVA were done using Prism (GraphPad Software, San Diego, CA). All tests were two sided, and the cutoff level for statistical significance was set at $P < 0.05$.

Results

Animal studies

Comparative paclitaxel pharmacokinetic variables. We compared the paclitaxel pharmacokinetic variables of [^{3}H]Taxol and [^{3}H]ABI-007 at a paclitaxel dose of 5 mg/kg using pooled blood from 10 rats. As shown in Table 1, the pharmacokinetic characteristics of the two paclitaxel formulations were different. Notably, the CL and V_z of paclitaxel were ~50% higher for ABI-007 compared with Taxol. This was true whether blood paclitaxel was quantitated by total radioactivity or HPLC for parent paclitaxel. Pharmacokinetic variables derived from total radioactivity understandably were somewhat different from pharmacokinetic variables derived from HPLC quantitation of paclitaxel in blood.

Dose escalation of Taxol beyond 10 mg/kg was not possible due to toxicity; 5 of 14 (36%) rats died at the 10 mg/kg dose

Table 1. Blood pharmacokinetic variables of paclitaxel formulated as either ABI-007 or Taxol

Variable	ABI-007*		Taxol*		
	5 mg/kg (Radioactivity)	5 mg/kg (HPLC)	5 mg/kg (Radioactivity)	5 mg/kg (HPLC)	10 mg/kg (Radioactivity)
$t_{1/2}$ (h)	19.01	11.42	20.78	7.24	7.58
T_{max} (h)	0.033	0.033	0.033	0.033	0.033
C_{max} (μg/mL)	4.2	4.0	13.5	11.8	32.3
C_0† (μg/mL)	8.1	7.3	20.5	17.7	40.2
AUC_{last} (μg·h/mL)	6.14	3.78	10.44	5.60	36.43
AUC_∞ (μg·h/mL)	9.86	4.59	15.69	5.85	41.13
$AUC_{\infty\%extrap}$ (%)	37.80	17.6	33.4	4.3	11.4
V_z (L/kg)	14.18	18.33	9.36	8.75	2.66
CL (L/h·kg)	0.517	1.112	0.312	0.837	0.243

*An i.v. bolus of either [^{3}H]ABI-007 or [^{3}H]Taxol at a paclitaxel dose of 5 mg/kg was administered (columns 2-5). Taxol was also administered at 10 mg/kg; those data are presented in column 6. Blood paclitaxel concentration was determined from extracted blood pooled from 10 rats, plotted versus time, and fitted using noncompartmental analysis. Two methods were used for blood paclitaxel quantitation: radioactivity and HPLC.
†Concentration at $t = 0$.

level. The limited data available for doses of 5 and 10 mg/kg suggested nonlinearity of Taxol pharmacokinetic properties, with a 4.8-fold decrease in CL being associated with a 2-fold increase in dose. In contrast, a dose-escalation study using ABI-007 showed CL values of 0.52 ± 0.06, 0.65 ± 0.10, 0.43 ± 0.03, and 0.37 ± 0.05 L/h kg at doses of 9, 26, 117, and 148 mg/kg, respectively, indicating that CL was not altered at high doses of ABI-007.

Comparative paclitaxel metabolism. Either [^{3}H]Taxol or [3H]ABI-007 at a paclitaxel dose of 5 mg/kg was given to Harlan Sprague-Dawley rats, and blood was collected at serial time points and pooled. Pooled blood from each group was extracted and analyzed for paclitaxel or its metabolites using HPLC coupled with LSC to obtain a time course of metabolite formation. Both ABI-007 and Taxol showed a gradual buildup of circulating paclitaxel metabolites, indicating a similar rate of metabolite formation. Metabolites constituted 0%, 0% to 0.5%, 0%, 1% to 2%, 2% to 8%, 9% to 14%, 11% to 13%, 20%, 22% to 24%, 27% to 32%, 32% to 41%, 44% to 50%, and 56% to 72% of the total radioactivity at 2, 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours, respectively (ABI-007 versus Taxol; $P > 0.05$, ANOVA).

At increasing doses of [^{3}H]ABI-007, consistent with the dose-independent CL, paclitaxel metabolism of the ABI-007 formulation was not saturable. At 24 hours, paclitaxel metabolites remained high despite the increasing dose of paclitaxel (80% at 9 mg/kg, 93% at 26 mg/kg, 78% at 117 mg/kg, and 87% at 148 mg/kg).

Comparative paclitaxel biodistribution. Tissue radioactivity of rats treated with either [^{3}H]ABI-007 or [^{3}H]Taxol at a paclitaxel dose of 5 mg/kg was quantitated at 1 and 5 days after dosing; at 1 day, 16.46 ± 5.29% and 17.50 ± 4.16% of the radioactivity remained in the tissues of ABI-007-treated rats and Taxol-treated rats, respectively. As shown in Fig. 1, the distribution of paclitaxel in tissues was similar for both formulations. The tissues with the greatest percentage of tissue radioactivity at 1 day were the liver, gastrointestinal tract, and carcass. After 5 days, only 1.68 ± 0.57% and 2.05 ± 0.90% of the radioactivity remained in ABI-007-treated rats and Taxol-treated rats, respectively, with most of the radioactivity remaining in the liver. As shown in Fig. 1, specific activity (defined as μg paclitaxel/g tissue) at 5 days after dosing remained high in the liver, testes, and lungs. The amount of radioactivity in these tissues was similar for both formulations, except that in lung tissue, which was 3.6-fold higher in Taxol-treated rats than in ABI-007-treated rats ($P < 0.0001$).

Comparative paclitaxel elimination. Sprague-Dawley rats, five male and five female, were treated with [^{3}H]ABI-007 or [^{3}H]Taxol at paclitaxel doses of 5 mg/kg to evaluate the time course of excretion. Excretion of paclitaxel was primarily through the fecal route and was similar for both formulations (Fig. 2A). After 5 days, 77.76 ± 6.63% and 75.77 ± 6.07% of the total radioactivity were found in the feces of Taxol-treated male and female rats, respectively, whereas 82.09 ± 4.42% and 78.70 ± 5.15% of the total radioactivity were found in the feces of ABI-007-treated male and female rats, respectively. Fecal elimination was essentially complete by 48 hours after dosing for both formulations (Fig. 2A).

Unlike fecal excretion, renal excretion (Fig. 2B) exhibited significant sexual dimorphism. After 5 days, 8.10 ± 2.03% and 12.45 ± 0.74% of the total radioactivity were found in the urine of male and female rats treated with the Taxol formulation, respectively ($P < 0.0001$); 9.51 ± 1.82% and 14.07 ± 1.66% of the total radioactivity were found in the urine of male and female rats treated with the ABI-007 formulation, respectively ($P < 0.0001$). Like the fecal route, renal elimination was essentially complete by 48 hours after dosing for both formulations (Fig. 2B).

Human studies

Patients. Twenty-seven patients were enrolled in the trial, 26 of whom had complete data for pharmacokinetic analysis. Fourteen of these patients received ABI-007 at a dose of 260 mg/m^2 for 30 minutes and 12 patients received Taxol at a dose of 175 mg/m^2 as a 3-hour infusion with standard premedication. Patient characteristics are summarized in Table 2. No statistically significant differences were noted in these characteristics between the two groups, except that patients randomized to Taxol had a higher incidence of liver metastases.

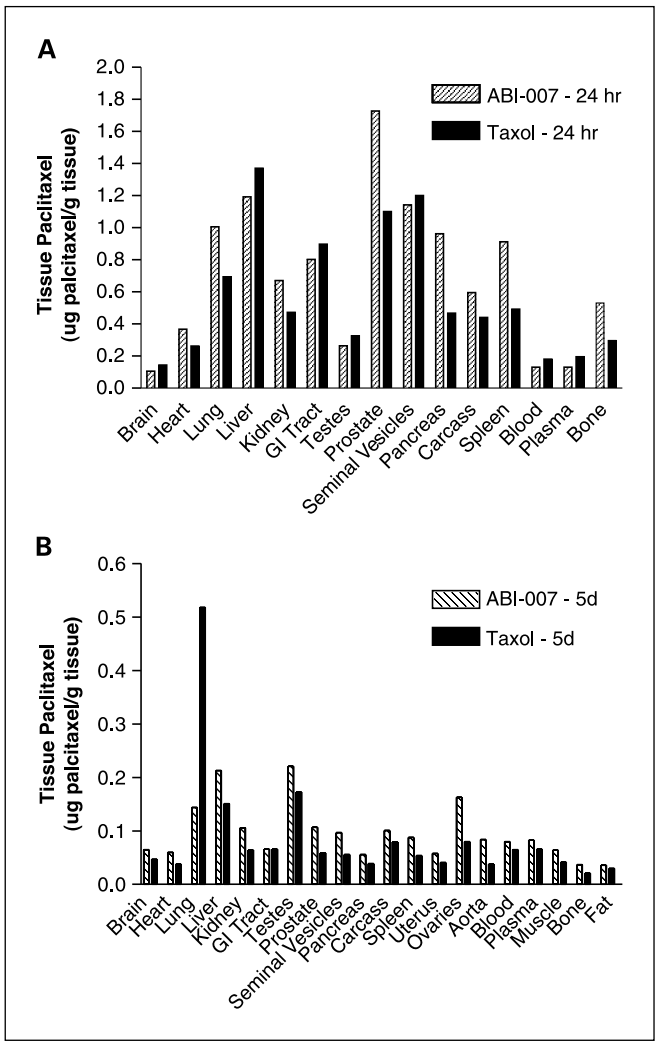

Fig. 1. Comparison of tissue radioactivity in rats receiving ABI-007 or Taxol at 24 hours (*A*) and 5 days (*B*). Radiolabeled paclitaxel formulations of ABI-007 (*hatched columns*) or Taxol (*solid columns*) were given i.v. at a paclitaxel dose of 5 mg/kg.

Pharmacokinetic studies. A semilogarithmic plot of the mean values of the whole-blood paclitaxel concentration for each paclitaxel formulation versus time is shown in Fig. 3A and B. A summary of the pharmacokinetic variables for paclitaxel administered as both ABI-007 and Taxol is presented in Table 3. As expected, the C_{max} for both drugs occurred at the end of infusion. C_{max} was 6.5-fold greater for ABI-007 than for Taxol (22,968.6 versus 3,543.3 ng/mL; $P < 0.001$); T_{max} was significantly less for ABI-007 compared with Taxol (0.36 versus 2.65 hours; $P < 0.001$), reflecting the shorter infusion duration. Mean paclitaxel AUC_{∞} for ABI-007 260 mg/m^2 (14,788.6 ng/h·mL) was similar to that for Taxol 175 mg/m^2 (12,602.7 ng/h·mL) despite the difference in dose. Likewise, the mean λ_z for ABI-007 was nearly identical to that for Taxol (0.033 versus 0.034 h^{-1}), resulting in similar half-lives of paclitaxel in the two groups (21.6 versus 20.5 hours, respectively). However, the mean CL and V_z of paclitaxel after the administration of ABI-007 were ~50% higher than those observed after administration of Taxol [21.13 versus 14.76 L/h/m^2 ($P = 0.048$) and 663.8 versus 433.4 L/m^2 ($P = 0.040$), respectively].

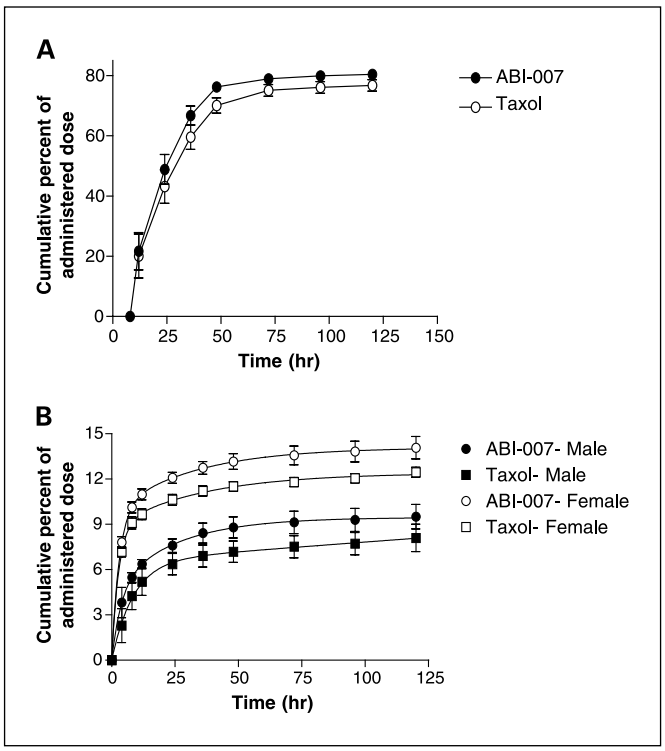

Fig. 2. Cumulative excretion rate of paclitaxel. ABI-007 and Taxol formulations were given at a paclitaxel dose of 5 mg/kg. The cumulative percent of given dose eliminated via the feces (*A*) and via urine (*B*).

Discussion

In the present study, we have described for the first time the comparative pharmacokinetic properties of paclitaxel following the administration of Cremophor-free, nanoparticle, albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in a mixture of Cremophor-ethanol (Taxol). The data complement previous knowledge on the preclinical and clinical pharmacology of paclitaxel and have important practical implications for the optimal use of this agent.

The administration of ABI-007 to Sprague-Dawley rats was associated with significantly higher CL and V_z of paclitaxel compared with Taxol. The fact that the initial dilution volume and the central V_z were higher for paclitaxel formulated as ABI-007 than for paclitaxel formulated as Taxol suggests that Cremophor prevented the distribution of paclitaxel out of the circulation and into the tissues. The mechanistic reasons for this difference in distribution are currently unclear. However, it is generally acknowledged that the unbound drug fraction of paclitaxel is the pharmacologically active form, which is capable of diffusing across biological barriers and interacting with receptor sites in the circulation or extravascular compartment. *In vitro* studies have shown that Cremophor can decrease the fraction of unbound paclitaxel by trapping it in micelles (8). Encapsulation of paclitaxel within the hydrophobic interior of Cremophor micelles takes place in a concentration-dependent manner, causing changes in cellular partitioning and blood/plasma concentration ratios of paclitaxel *in vitro* (13). Moreover, two studies with clinical data have shown that the fraction of unbound paclitaxel is inversely correlated to the circulating concentration of Cremophor (14, 15).

Table 2. Patient demographic and other baseline characteristics (intent-to-treat population)

Characteristics	ABI-007 260 mg/m^2 (n = 14)	Taxol 175 mg/m^2 (n = 13)	P^*
Age (y)			
Median	53.5	51.0	0.5764
Range	34-71	36-63	
<65	10 (71)	13 (100)	0.0978
≥65	4 (29)	0	
Sex			
Female	12 (80)	10 (77)	0.6483
Male	2 (14)	3 (23)[†]	
Race			
Caucasian, non-Hispanic, and non-Latino	14 (100)	13 (100)	0.4815
Eastern Cooperative Oncology Group performance score			1.0000
1	9 (64)	8 (62)	0.2968
0	5 (36)	5 (38)	
Primary diagnosis			
Time from diagnosis (y)			
Median	1.3	2.5	0.2968
Range	0-3	0-8	
Stage			
I	0	0	0.2354
II	2 (14)	4 (31)	
III	7 (50)	8 (62)	
IV	5 (36)	1 (8)	
Histology			
n	14	12	0.4615
Carcinoma/adenocarcinoma	14 (100)	11 (92)	
Squamous cell carcinoma	0	1 (8)	
Site			
Breast	8 (57)	8 (62)	1.0000
Lung and bronchus	4 (29)	3 (23)	
Ovary	2 (14)	2 (15)	
Metastatic disease			
Time from first documented metastatic disease (y)			
n	12	13	
Median	0.3	0.5	0.2533
Range	0-2	0-2	
Site of metastasis/relapse for disease			
Lung	11 (79)	7 (54)	0.2365
Lymph nodes	7 (50)	7 (54)	1.0000
Bone	4 (29)	4 (31)	1.0000
Skin/soft tissue/breast	3 (21)	5 (38)	0.4197
Liver	1 (7)	6 (46)	0.0329
Peritoneal	1 (7)	1 (8)	1.0000
Other visceral	1 (7)	1 (8)	1.0000
Other	0	1 (8)	0.4815
Dominant site of metastasis/relapse for disease			
Visceral	11 (79)	13 (100)	0.2222
Nonvisceral	3 (21)	0	

Note: Numbers in parentheses represent percentages.

*Ps for categorical and continuous measures are obtained from Fisher's exact test and Wilcoxon's rank-sum test, respectively.

†Pharmacokinetic population: ABI-007, 12 women and 2 men; Taxol, 10 women and 2 men.

Preclinical data on the metabolism, elimination, and distribution of radiolabeled paclitaxel in Sprague-Dawley rats showed that the extent of drug metabolism and excretion was similar for both formulations. After 24 hours, the quantity of radiolabeled paclitaxel was greatest in the liver, gastrointestinal tract, and carcass, which is consistent with previous studies done in rats (16, 17) and mice (18, 19). Likewise, the limited access of paclitaxel to brain tissue observed here is in line with

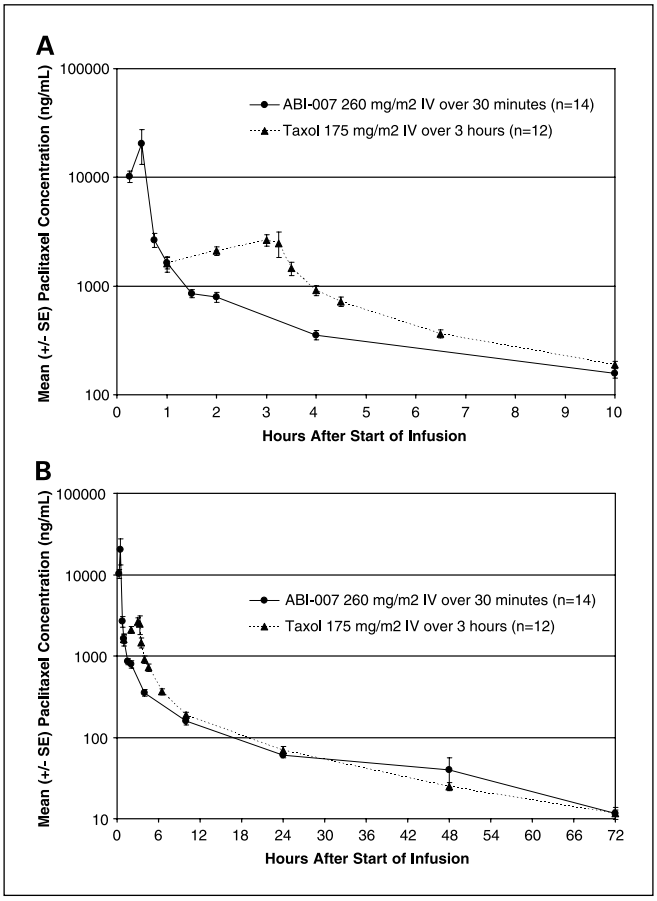

Fig. 3. Mean paclitaxel concentration versus time 0 to 10 hours after the start of the infusion (*A*) and 0 to 72 hours after the start of the infusion (*B*). Bars, SE for both ABI-007 and Taxol.

an earlier observation (20). One limitation of the current investigation is that tissues were sampled at two time points only—24 hours and 5 days after drug administration. Earlier sampling might have shown a difference in distribution between the two formulations that is undetectable at 24 hours or 5 days after dosing.

The initial rate of elimination of paclitaxel was slightly impaired in the rats that received Taxol compared with those that received ABI-007, although no substantial differences were noted over the entire time course. This finding suggests that inhibition of hepatic elimination of paclitaxel by Cremophor, which was reported previously in an isolated perfused rat liver (21), is probably a relatively unimportant factor in the interaction between Cremophor and paclitaxel in rats.

Of greatest importance for the antitumor activity of paclitaxel is the disposition of paclitaxel in plasma. Pharmacokinetic assessment of paclitaxel in both formulations showed ~50% greater CL and V_z with ABI-007 than with Taxol, which is consistent with results of the preclinical studies. The current observation also is in keeping with results of an earlier study comparing the administration of a tracer dose of [^{3}H]paclitaxel formulated in ethanol, with or without Cremophor, which showed a mean CL of 10.2 and 22.8 L/h m^2, respectively (22).

In patients, the disappearance of paclitaxel from the central compartment was characterized by a terminal disposition half-life of ~20 hours regardless of the formulation used. The near-parallel decline of paclitaxel concentrations in the two formulations during the terminal phase again suggests that the altered CL is associated with a change in the initial drug distribution immediately following administration. This is consistent with the postulated concept that the interference in paclitaxel pharmacokinetics caused by Cremophor is related to a disproportional accumulation process in plasma (13). However, other possible mechanisms for the increased CL of paclitaxel after administration of ABI-007 in patients, including increased metabolism or excretion, cannot be excluded.

Despite the significantly faster CL of paclitaxel after ABI-007 administration and the different infusion durations and total doses administered in patients, the resulting AUC values of paclitaxel for the two formulations were not significantly different statistically. This finding seems to be at odds with earlier observations that the AUC of total paclitaxel (i.e., bound

Table 3. Summary of estimated paclitaxel blood pharmacokinetic variables for ABI-007 and Taxol (pharmacokinetic population)

Variable	ABI-007 260 mg/m^2, 30 min (n = 14)			Taxol 175 mg/m^2, 3 h (n = 12)			P
	Mean	% Coefficient of variation	Range	Mean	% Coefficient of variation	Range	
CL (L/h·m^2)	21.13	43.8	8.72-43.41	14.76	31.8	10.20-28.75	0.048
V_{ss} (L/m^2)	230.7	54.3	53.2-492.9	156.3	43.2	99.7-346.0	0.211
V_z (L/m^2)	663.8	48.1	296.3-1,347.3	433.4	31.1	308.7-809.7	0.040
AUC_∞ (ng/h·mL)	14,788.6	45.3	5,981.7-28,680.2	12,602.7	21.0	6,087.1-17,081.2	0.524
$AUC_{\infty da}$ (ng/h·mL)	56.84	46.3	23.04-114.7	71.90	21.1	34.78-98.00	0.049
C_{max} (ng/mL)	22,968.6	112.5	4,060-86,700	3,543.3	57.2	1,540-9,380	<0.001
C_{maxda} (ng/mL)	88.69	114.2	15.64-346.8	20.14	55.8	8.8-52.4	<0.001
T_{max} (h)	0.36	45.2	0-0.5	2.65	27.6	1.0-3.5	<0.001
λ_z (h^{-1})	0.033	16.9	0.023-0.042	0.034	13.0	0.026-0.040	0.477
$t_{1/2}$ (h)	21.6	17.2	16.5-29.6	20.5	14.6	17.5-26.3	0.479
$AUC_{\infty\%extrap}$ (%)	2.8	41.3	1.0-5.0	2.8	52.6	1.4-6.8	0.983

and unbound) is not a predictor of pharmacodynamic effects related to paclitaxel treatment (23). To gain further insight into the comparative clinical pharmacology of ABI-007 and Taxol, a clinical study has been initiated using a randomized crossover design to examine both intrapatient and interpatient variability in both total and unbound paclitaxel concentrations, with simultaneous assessment of relationships between pharmacokinetic measures and pharmacodynamic outcome.

One intriguing observation is that patients receiving ABI-007 showed somewhat greater interindividual variation in BSA-corrected CL of paclitaxel compared with patients receiving Taxol (43.8% versus 31.8% coefficient of variation, respectively). As mentioned previously, the distribution of paclitaxel in patients receiving Taxol is dependent on the duration of infusion and the dose- and time-varying concentrations of Cremophor because of a preferential affinity of paclitaxel for Cremophor in blood (13). In a large group of patients, BSA was shown previously to be a significant covariate on CL in a population model for Cremophor pharmacokinetics (24). Because total blood volume is related to BSA (25), it has been hypothesized that the effect of BSA on variability in paclitaxel CL is caused by the association of paclitaxel in the systemic circulation with Cremophor micelles, of which the distribution is linked to total blood volume and thus to BSA (26). Consequently, Cremophor might obscure the influence of other (physiologic, environmental, and inherited) factors affecting the pharmacokinetic variability of paclitaxel in patients receiving Taxol.

In a phase III comparative trial, the safety profile of ABI-007 was improved by the removal of Cremophor and the observed increase in antitumor activity compared with Taxol could be explained by the increased dose of paclitaxel that could be safely administered (12). However, the current pharmacokinetic data provide another potential mechanistic explanation for the improved efficacy of ABI-007. Collectively, this study shows for the first time that the clinical pharmacokinetic properties of paclitaxel are markedly affected by the composition of the pharmaceutical preparation. Specifically, a more rapid CL and greater V_z was observed for ABI-007 compared with Taxol. Based on the available data from simultaneously performed animal disposition studies, the most likely explanation for the differences is temporary inhibition of paclitaxel distribution by Cremophor early after Taxol administration, thereby preventing the drug from reaching primary sites of action. These differences in pharmacokinetic properties may be associated with the higher intratumoral concentrations observed for ABI-007 compared with equal doses of Taxol.

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