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ORIGINAL ARTICLE

Carlos A. Jamis-Dow · Raymond W. Klecker
Aspandiar G. Katki · Jerry M. Collins

Metabolism of taxol by human and rat liver in vitro: A screen for drug interactions and interspecies differences

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Abstract Human liver slices, human liver microsomes, and rat liver microsomes were used to investigate the metabolism of ^{3}H-taxol. The effects of drugs frequently coadministered with taxol and the effects of several cytochrome P450 system probes were studied. In all, 16 compounds were screened. After incubation with liver slices or with microsomal protein, ^{3}H-taxol was converted into several radioactive species resolved by HPLC. There were qualitative and quantitative species differences in the metabolism of taxol. The pattern of metabolism was similar for both human-derived preparations, with 6α-hydroxytaxol being the major metabolite peak. In drug interaction studies performed with human liver microsomes, cimetidine 80 μ*M*, and diphenhydramine 200 μ*M*, had little or no effect on 6α-hydroxytaxol formation. Quinidine, ketoconazole, dexamethasone and Cremophor EL inhibited 6α-hydroxytaxol formation with IC_{50} values of 36 μ*M*, 37 μ*M*, 16 μ*M* and 1 μl/ml, respectively, but these concentrations exceed the usual clinical range. Cremophor EL also inhibited microsomal metabolism of taxol, but at 2 μl/ml it had little or no effect on 6α-hydroxytaxol production by human liver slices. These results suggest that: (1) taxol is metabolized by the cytochrome P450 system; (2) taxol metabolism is different in humans than in rats; (3) taxol metabolism in humans is unlikely to be altered by cimetidine, dexamethasone, or diphenhydramine, drugs regularly coadministered with taxol; (4) taxol metabolism can be indirectly affected by Cremophor EL, the formulation vehicle; (5) taxol metabolism may be altered by concentrations of ketoconazole achievable in humans only at very high doses; and (6) taxol metabolism and drug interaction studies of clinical relevance can be performed in vitro with human liver microsomes and human liver slices, but not with rat liver preparations.

Key words Drug metabolism · Species differences
Drug interactions

Introduction

Taxol (Fig. 1), a natural product initially isolated from the stem bark of the western yew *Taxus brevifolia* [27], is an active agent against refractory ovarian cancer, breast cancer, lung cancer, and malignant melanoma [2, 8, 13, 20]. Taxol is currently approved for the treatment of platinum-refractory ovarian cancer, and it is formulated in a vehicle of 50% ethanol and 50% Cremophor EL (Cremophor), a polyethoxylated castor oil.

Taxol is readily metabolized by the liver, mainly by the cytochrome P450 (P450) system, and eliminated almost exclusively through the bile [16, 21, 22]. Patients with neoplastic liver involvement seem to have reduced taxol clearance [30]. Therefore, potential interactions may occur between taxol and drugs that impair hepatic metabolism.

Patients receiving taxol therapy are very likely to receive other medications for their neoplasia or concurrent illnesses. Taxol infusions can provoke severe hypersensitivity reactions possibly related to its vehicle, Cremophor [24, 29]. In order to decrease the incidence of such reactions, almost every patient on taxol therapy is premedicated with a regimen that frequently includes

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C.A. Jamis-Dow (✉) · R.W. Klecker · A.G. Katki · J.M. Collins
Division of Clinical Pharmacology, Office of Research Resources, Center for Drug Evaluation and Research, Food and Drug Administration, 4 Research Court, Room 314, Rockville, MD 20850, USA

C.A. Jamis-Dow
Medicine Branch, Clinical Oncology Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD, 20892, USA

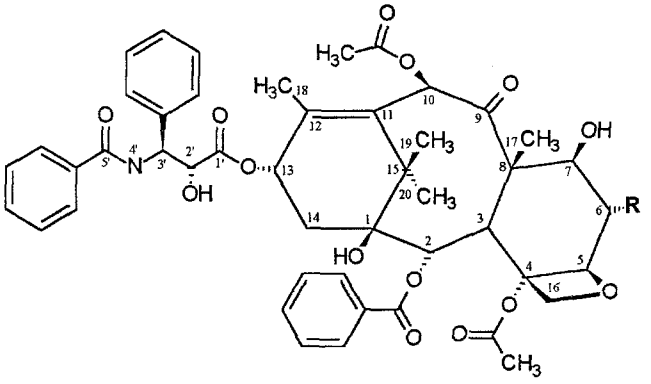

Fig. 1 Chemical structure of taxol (R = H) and 6α-hydroxytaxol (R = OH)

diphenhydramine, dexamethasone and cimetidine [24, 29]. Dexamethasone can induce certain P450 isoenzymes in primary cultures of human hepatocytes and inhibit their activities in human liver microsomes [25]. Cimetidine is a known inhibitor of several P450 isoenzymes [17].

We studied the metabolism of taxol in vitro by human liver slices and human liver microsomes. We examined the effect of drugs usually coadministered with taxol, as well as the effect of several P450 probe drugs, on the metabolism of this agent in vitro. The purpose of this study was to detect possible interactions between taxol and any of these drugs. A screen for potential interactions is of interest for safety and economic reasons. The major metabolite of taxol in humans, 6α-hydroxytaxol, is less cytotoxic to human cells in tissue culture than the parent drug [12]. Therefore, an inhibitor of taxol metabolism could increase the host toxicities, requiring adjustment of the taxol dose. It is also conceivable that such a drug could be purposely used to reduce the dose of taxol needed for treatment. There is a precedent for this kind of intervention. The inhibition of cyclosporin metabolism by ketoconazole has been used intentionally to considerably reduce the cost of cyclosporin treatment [9]. Although alternative sources of taxol are being explored, and methods for its total synthesis recently described [14, 15, 23], at the present time the bark of the yew tree is the only source of the drug approved for clinical use. It takes about one mature yew tree and a lengthy and costly process to produce a single dose of taxol, 400 mg [4].

Materials and methods

Materials

Human liver samples, medically unsuitable for transplantation, were obtained through the Washington Regional Area Transplant Consortium (Washington, D.C.). Human liver slices were prepared by In Vitro Technologies (Baltimore, Md.) from liver samples obtained from the International Institute for the Advancement of Medicine (Exton, Pa.). Quality control studies for the liver slices included phase II conjugation capabilities. Male Sprague-Dawley rats (300 g) were obtained from Taconic (Germantown, N.Y.). ^{3}H-taxol, 2.2 Ci/mmol, 74% pure by HPLC, and 23 Ci/mmol, 98% pure by HPLC, was purchased from Amersham Life Sciences (Buckinghamshire, UK) and Moravek Biochemicals (Brea, Calif.), respectively. Pure 6α-hydroxytaxol, characterized by proton nuclear magnetic resonance and secondary-ion mass spectrometry was provided by Dr. J. W. Harris, Food and Drug Administration [12]. Coomassie Blue reagent for protein determination was purchased from Bio-Rad (Hercules, Calif.). All other reagents were obtained from Sigma Chemical Co. (St. Louis, Mo.).

Preparation of liver microsomes

Human liver samples were obtained and immediately sectioned and stored at − 70° C until used. Rat livers were removed and stored at −70° C until used. Microsomes were prepared by tissue homogenization and differential centrifugation. Tissues were homogenized with a blender in 150 m*M* KCl, 100 m*M* sodium phosphate 1 m*M* EDTA, pH 7.4. After filtration through gauze, the preparation was homogenized with a Dounce homogenizer and centrifuged twice at 13 500 *g* for 20 min at 4° C, removing the pellet after the first centrifugation. The supernatant (S-9 fraction) was filtered through gauze and centrifuged at 105 000 *g* for 60 min at 4° C. The resulting pellet (microsomes) was resuspended in 5 m*M* $MgCl_2$, 100 m*M* sodium phosphate 1 m*M* EDTA, pH 7.4. The preparation was centrifuged at 105 000 *g* for 60 min at 4° C, for a second time and the pellet resuspended as above. The protein concentration of the microsomal fraction was determined by the Coomassie Blue method [1], and the preparation aliquoted into single-use vials and stored at − 70° C until used.

Metabolism of taxol by human liver and rat liver microsomes

Each 1 ml of incubation mixture contained 2.25% bovine serum albumin (BSA) in 5 m*M* $MgCl_2$, 100 m*M* sodium phosphate 1 m*M* EDTA, pH 7.4, NADPH-generating system (10 m*M* glucose-6-phosphate, 1 m*M* $NADP^+$, and 1 Sigma unit glucose-6-phosphate dehydrogenase), test drug in the concentration range 0.5–200 μ*M* (Cremophor in the range 0.05–20 μl/ml, cimetidine 20 and 200 μg/ml), and 0.5 μCi (0.23 μ*M*) ^{3}H-taxol. Reagents were added in the listed order. Some mixtures contained 1% ethanol or 0.5 m*M* HCl, required to solubilize some of the test drugs. At these concentrations, neither ethanol nor HCl interfered with taxol metabolism (data not shown). After a 10-min preincubation at 37° C, 0.3–1 mg microsomal protein was added to the mixtures and the reactions incubated for 10 min at 37° C in a shaking water bath. After stopping the reactions with the addition of 1 ml acetonitrile, and mixing, the reaction mixtures were centrifuged at 1900 *g* for 15 min at 4° C, and the supernatants analyzed for taxol and metabolites. Controls were run with 1% ethanol, with 0.5 m*M* HCl, without the NADPH-generating system, or with heat-inactivated microsomes. The concentration of drug that decreased metabolite formation to 50% of the untreated controls (IC_{50}) was calculated by fitting the experimental data to an Inhibitory Sigmoid Maximum Effect Model with the equation:

$$E = E_{max} - \frac{E_{max} C^n}{IC_{50}^n + C^n}$$

where E_{max} is the maximum metabolic conversion, C is the inhibitor concentration and n is a sigmoidicity factor.

Metabolism of taxol by human liver slices

Incubations were performed in 24-well cluster trays. Each well contained 1 ml of a mixture of 2.25% BSA in modified Krebs-Henseleit buffer, pH 7.55, two 8 × 0.3 mm human liver slices, 50 μ*M* ketoconazole or 2 or 20 μl/ml Cremophor, and 3 μCi (0.13 μ*M*) ^{3}H-taxol. Reagents were added in the listed order. Some mixtures contained 0.5 m*M* HCl, required to solubilize ketoconazole. At this concentration HCl did not interfere with taxol metabolism (data not shown). Incubations were carried out for 2 h at 37° C in a humidified incubator under an atmosphere of air containing 5% CO_2. Reactions were stopped by removing the slices. One slice from each incubation was rinsed twice with 2.25% BSA in Krebs-Henseleit buffer and counted for total radioactivity. The second slice was rinsed in the same way, transferred to a microfuge tube and frozen at − 70° C until analyzed. Controls were run with 0.5 m*M* HCl and with heat-inactivated slices.

Analysis of taxol and metabolites

^{3}H-taxol and its metabolites were analyzed by HPLC in liver slices, their incubation media, and in the microsomal mixtures. The liver slices were homogenized with a Dounce homogenizer and extracted with 1 ml acetonitrile. Each 100 μl aliquot of slice incubation medium was extracted with 1 ml acetonitrile. For the microsomal reactions, a 200-μl aliquot of the supernatant obtained from the initial acetonitrile precipitation was further extracted with 900 μl acetonitrile. All the samples were then mixed and centrifuged at 11 000 *g* for 4 min at 4° C. A 1-ml aliquot of the resulting supernatant was dried under vacuum, reconstituted with 20% acetonitrile in 10 m*M* ammonium acetate buffer, pH 4, and analyzed by HPLC with in-line radioactivity detection. The separation of taxol and its metabolites was accomplished on a Hewlett-Packard ODS Hypersyl 5 μm 100 × 4.6 mm column (Hewlett-Packard Co., Palo Alto, Calif.) and a 15-min linear gradient from 20 to 69% acetonitrile in 10 m*M* ammonium acetate buffer, pH 4. Radioactivity detection was performed on a Model A-140 Radiomatic Flo-One/βeta Radio-Chromatography Detector (Packard Instrument Co., Downers Grove, Ill.).

Results

Metabolism of taxol by rat and human liver microsomes

^{3}H-taxol was extensively metabolized by human microsomes (Fig. 2). The major peak had a retention time identical to that of pure 6α-hydroxytaxol. Rat microsomes also metabolized the drug into several species. None of the rat peaks coeluted with 6α-hydroxytaxol, and only one had a retention time equal to a peak generated by the human material (Fig. 2). The metabolism of taxol proceeded faster in human- than in rat-derived preparations. After a 10-min incubation with 1 mg of microsomal protein, the remaining parent drug peak (mean ± SD, $n = 3$) accounted for 32 ± 5% and 80 ± 1% of the total radioactivity found in the human and rat incubation mixtures, respectively. No metabolism was observed with heat-inactivated microsomal protein, without microsomal protein, or without the NADPH-generating system. Since preliminary studies in human liver microsomes, S-9 fractions, and human liver slices showed a similar pattern of taxol metabolism (data not shown), drug interaction studies were performed with human liver microsomes.

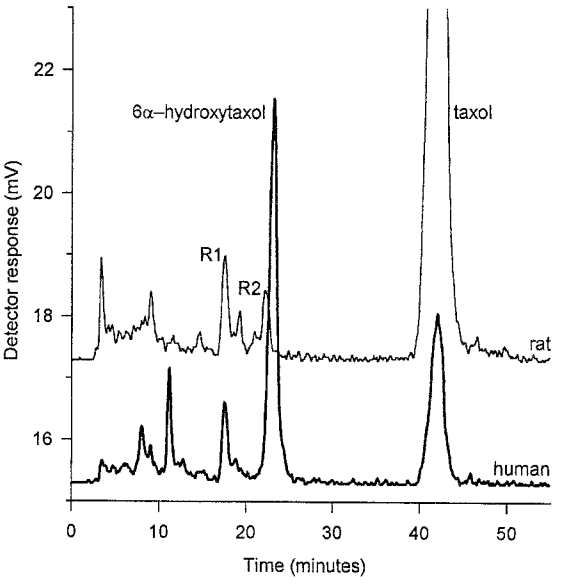

Fig. 2. Species differences in the metabolism of ^{3}H-taxol. Human (*lower trace*) and rat (*upper trace*) microsomes were incubated with ^{3}H-taxol. Incubation mixtures were extracted and analyzed by HPLC with in-line radiodetection. This separation was performed on a Beckman Ultrasphere ODS 5 μm 250 × 4.6 mm column (Beckman Instruments, Fullerton, Calif.) eluted isocratically with 41% acetonitrile in 10 m*M* ammonium acetate buffer, pH 4. (*R1* and *R2*: ^{3}H-taxol metabolites generated by rat microsomes that correspond to ones previously found in rat bile [16])

Effects of coadministered drugs on taxol metabolism

Cimetidine, dexamethasone, and diphenhydramine are given with taxol, to prevent hypersensitivity reactions due to the drug and/or its vehicle. The effect of these comedications on taxol metabolism was studied in human liver microsomes (Table 1). Diphenhydramine, 20 and 200 μ*M*, and cimetidine, 20 μg/ml (80 μ*M*), had little or no effect on 6α-hydroxytaxol formation, but dexamethasone, 20 and 200 μ*M*, was able to decrease it. Cremophor had the most impressive effect on taxol metabolism. At 20 μl/ml it completely prevented 6α-hydroxytaxol formation. Concentration-response curves of Cremophor and dexamethasone produced IC_{50} values of 1 μl/ml and 16 μ*M*, respectively (Fig. 3).

Effects of cytochrome P450 probes on taxol metabolism

In an attempt to identify the P450 isoenzyme(s) involved in taxol metabolism, several substrates/inhibitors of various P450 enzymes were screened (Table 2).

Table 1 Effect of clinically coadministered drugs on 6α-hydroxytaxol formation by human liver microsomes. Human liver microsomes were incubated with ^{3}H-taxol and clinically coadministered drugs at the concentrations indicated. After a 10-min incubation the samples were processed and analyzed by HPLC as described in Materials and methods. Values are mean ± SD of four observations. ND, not detected; NP, not performed

Target P450	Coadministered drug	Concentration	6α-Hydroxytaxol formation (% of control)
	Diphenhydramine	20 μ*M*	104 ± 5
		200 μ*M*	93 ± 2
Nonspecific	Cimetidine	20 μg/ml	98 ± 6
		200 μg/ml	60 ± 6
3A	Dexamethasone	20 μ*M*	48 ± 7
		200 μ*M*	5 ± 5
	Cremophor	20 μl/ml	ND
		200 μl/ml	NP

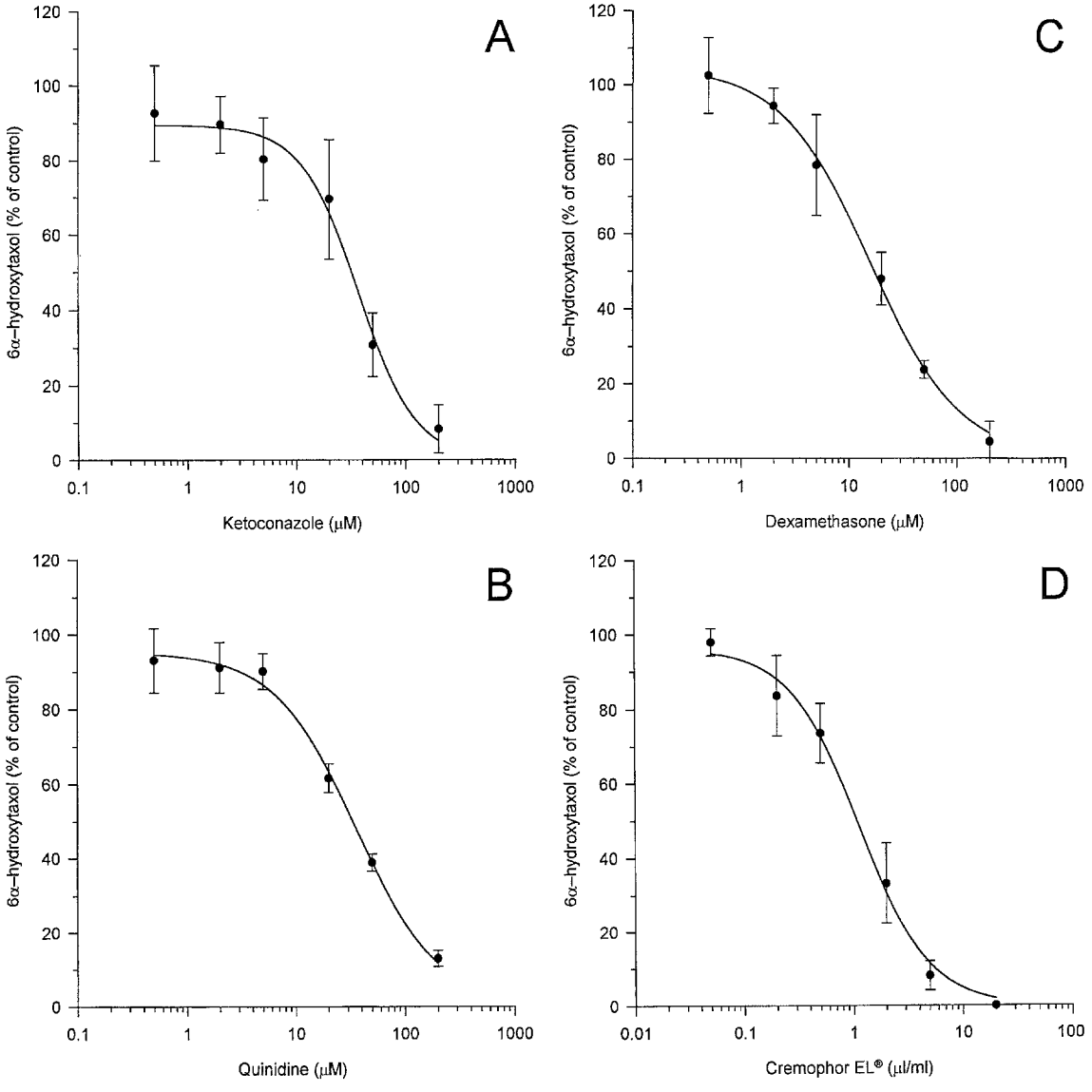

Fig. 3A–D Inhibition of in vitro microsomal ^{3}H-taxol metabolism. The curves of concentration of ketoconazole (**A**), quinidine (**B**) dexamethasone (**C**) and Cremophor (**D**) versus ^{3}H-taxol metabolism were constructed by measuring 6α-hydroxytaxol formation in human liver microsomal incubation extracts as described in Materials and methods. Values are the mean ± SD of eight (**A** and **B**), or four observations (**C** and **D**).

Table 2 Effect of P450 probe drugs on 6α-hydroxytaxol formation by human liver microsomes. Human liver microsomes were incubated with ^{3}H-taxol and P450 probe drugs at the concentrations indicated. After a 10-min incubation the samples were processed and analyzed by HPLC as described in Materials and methods. Values are mean ± SD of four observations

Target P450	Probe drug	Concentration (μ*M*)	6α-Hydroxytaxol formation (% of control)
1A1, 1A2, 3A	αNaphthoflavone	20	103 ± 5
		200	54 ± 20
1A2	Ciprofloxacin	20	105 ± 4
		200	105 ± 5
2A6	Coumarin	20	104 ± 3
		200	79 ± 4
2B, 3A	Benzphetamine	20	98 ± 5
		200	55 ± 2
2C, 4A	Lauric acid	20	106 ± 3
		200	88 ± 21
2C	Sulfinpyrazone	20	104 ± 4
		200	88 ± 2
2C	Tolbutamide	20	96[a]
		200	100[a]
2D6, 3A	Quinidine	20	62 ± 4
		200	13 ± 2
2E1	Chlorzoxazone	20	110 ± 6
		200	94 ± 4
2E1	Diethyldithiocarbamate	20	102 ± 3
		200	88 ± 7
3A	Ketoconazole	20	70 ± 16
		200	8 ± 7
3A	Erythromycin	100	107 ± 9

[a]Mean of two observations

Table 3 Effect of ketoconazole and Cremophor on the amount of 6α-hydroxytaxol found in the human liver slice incubation medium. Human liver slices were incubated with ^{3}H-taxol and ketoconazole or Cremophor. After a 2-h incubation the slices were removed and the incubation medium processed and analyzed as described in Materials and methods. The amounts of 6α-hydroxytaxol and taxol found in the slice incubation medium are expressed as the percentage of the total radioactivity present in the whole incubation mixture. Values are mean ± SD of three observations

Condition	6α-Hydroxytaxol	Taxol	Ratio (6α-hydroxytaxol/taxol)
Control	4 ± 1	66 ± 1	0.06 ± 0.02
Ketoconazole (50 μ*M*)	1 ± 0.2	64 ± 1	0.01 ± 0.004
Cremophor (2 μl/ml)	1 ± 0.2	86 ± 0.4	0.01 ± 0.002
Cremophor (20 μl/ml)	0.2 ± 0.3	98 ± 0.4	0.002 ± 0.003

At 20 μ*M*, only quinidine and ketoconazole were able to decrease 6α-hydroxytaxol formation to less than 80% of the control values. In order to further characterize the effect of these two drugs on taxol metabolism, we performed concentration–response studies (Fig. 3). Quinidine and ketoconazole inhibited 6α-hydroxytaxol formation with IC_{50} values of 36 and 37 μ*M*, respectively.

Metabolism of taxol by human liver slices

We used human liver slices to try to elucidate the mechanism by which Cremophor and ketoconazole inhibited 6α-hydroxytaxol formation. After a 2-h incubation, about a third of the total radioactivity found in the control incubations was associated with the liver slices. Cremophor at 2 and 20 μl/ml decreased the amount of total radioactivity associated with the slices by 58% and 93%, respectively. Ketoconazole at 50 μ*M* increased the amount of total radioactivity associated with the slices by about 17% of the control value.

The pattern of taxol metabolism by human liver slices was qualitatively very similar to that of human liver microsomes (data not shown). Under basal conditions, 6α-hydroxytaxol accounted for 30% and 6% of the radioactivity present in the liver slices and their incubation medium, respectively. Almost all the remaining radioactivity in both samples was parent drug. Compared to controls, treatment with ketoconazole or Cremophor decreased the total amount of 6α-hydroxytaxol as well as the ratio of 6α-hydroxytaxol to taxol present in the incubation medium (Table 3). Treatment with 50 μ*M* ketoconazole or 20 μl/ml Cremophor decreased the total amount of 6α-hydroxytaxol as well as the ratio of 6α-hydroxytaxol to taxol present in the liver slices (Table 4). Treatment with 2 μl/ml Cremophor also decreased the total

Table 4 Effect of ketoconazole and Cremophor on the amount of 6α-hydroxytaxol found in the human liver slices. Human liver slices were incubated with ^{3}H-taxol and ketoconazole or Cremophor. After a 2-h incubation the slices were removed, processed and analyzed as described in Materials and methods. The amounts of 6α-hydroxytaxol and taxol found in the slices are expressed as the percentage of the total radioactivity present in the whole incubation mixture. Values are mean ± SD of three observations

Condition	6α-Hydroxytaxol	Taxol	Ratio (6α-hydroxytaxol/taxol)
Control	9 ± 0.1	21 ± 0.8	0.42 ± 0.02
Ketoconazole (50 μ*M*)	6 ± 0.7	29 ± 1	0.19 ± 0.03
Cremophor (2 μl/ml)	3 ± 0.4	9 ± 0.6	0.36 ± 0.07
Cremophor (20 μl/ml)	0.2 ± 0.1	2 ± 0.2	0.13 ± 0.07

amount of 6α-hydroxytaxol found in the slices, but the ratio of 6α-hydroxytaxol to taxol was similar to that of the controls (Table 4).

Extracts from incubations with no liver slices or with heat-inactivated ones contained only unchanged parent drug.

Discussion

Taxol is extensively metabolized in the liver by the P450 system. Hence any compound that interferes with this system can potentially alter the pharmacokinetics of taxol [21, 22]. As its clinical use increases, so does the possibility that taxol will be coadministered with other drugs regularly used in cancer patients. Taxol metabolism in vitro by human liver microsomes closely resembles observed human metabolism in vivo [5, 21]. This makes it feasible to screen drugs in vitro for potential clinical interactions with taxol metabolism.

We found that taxol metabolism in vitro by rat microsomes, although similar to that reported for the intact animal [22], was different from the metabolism observed in humans (Fig. 2) [21]. These differences between taxol metabolism in rats and in humans are also consistent with the findings of Kumar et al [18]. This precludes the use of rats for the study of taxol metabolism and drug interactions. Consequently, we studied taxol metabolism in human liver slices and human liver microsomes. No new radioactive species were found in the human liver slice incubations as compared to the human microsomal incubations. Since the pattern of taxol metabolism was similar in human microsomes and liver slices, and microsomes are more stable and have higher P450 enzyme activities than liver slices, we performed all the drug interaction experiments in human microsomes.

In order to prevent the hypersensitivity reactions associated with taxol or its vehicle, patients usually receive a premedication regimen which includes diphenhydramine, cimetidine, and dexamethasone. In humans diphenhydramine is quickly metabolized, mainly in the liver. Effective antihistaminic diphenhydramine plasma concentrations are 0.1–0.2 μ*M* [3, 7]. In human microsomes, diphenhydramine at 20 and 200 μ*M* did not affect taxol metabolism (Table 1).

Cimetidine is an inhibitor of several P450 isoenzymes [17]. When given at maximal doses (2400 mg/24 h, i.v.), steady-state cimetidine plasma concentrations of 8 μ*M* are expected. In microsomal experiments, 80 μ*M* cimetidine (20 μg/ml) had no effect upon taxol metabolism, and at 800 μ*M* (i.e. 100-fold higher than maximum clinical concentrations) only a 40% decrease in metabolism was observed. This lack of metabolic interaction between cimetidine and taxol in vitro has been corroborated in a phase II clinical trial conducted at the National Cancer Institute [26].

Dexamethasone can induce P450 3A4 in primary cultures of human hepatocytes and can inhibit its activity in human liver microsomes [25]. Dexamethasone inhibited 6α-hydroxytaxol formation with an IC_{50} of 16 μ*M* (Fig. 3C). Patients undergoing taxol therapy are usually premedicated with 20 mg dexamethasone orally 14 and 7 h before the taxol infusion. Expected peak plasma dexamethasone concentrations in these patients are less than 1 μ*M*. Hence, dexamethasone should not inhibit taxol metabolism in vivo.

Cremophor is a polyethoxylated castor oil used to formulate taxol. In a group of 21 cancer patients treated with 135 or 175 mg/m^2 taxol given as a 3-h infusion, Cremophor plasma concentrations averaged 1.4 μl/ml [28]. In human microsomes Cremophor inhibits 6α-hydroxytaxol formation with an IC_{50} of 1 μl/ml (Fig. 3D). To further study this interaction we incubated human liver slices with ^{3}H-taxol and 2 and 20 μl/ml Cremophor. At both concentrations Cremophor decreased the amount of radioactivity associated with the liver slices, the total amount of 6α-hydroxytaxol, and the 6α-hydroxytaxol/taxol ratio found in the liver-slice incubation medium (Table 3), but only the highest concentration of Cremophor decreased the 6α-hydroxytaxol to taxol ratio present in the slices (Table 4). At 2 μl/ml, Cremophor had very little or no effect on the ratio of metabolite to parent drug found in the slices, suggesting that Cremophor should not interfere directly with taxol metabolism in vivo, but could indirectly decrease metabolism by reducing taxol uptake in the liver.

Several P450 probe drugs were screened in human liver microsomes. At 20 μ*M*, only quinidine and

ketoconazole seemed to decrease 6α-hydroxytaxol formation to less than 80% of the control values. Quinidine is a specific inhibitor of P450 2D6 at low concentrations (e.g. $< 1\ \mu M$), but at high concentrations it can be a substrate for P450 3A4 [11]. In human microsomes, quinidine inhibited 6α-hydroxytaxol formation with an IC_{50} of 36 μM (Fig. 3B). This result would suggest that 6α-hydroxytaxol formation is not mediated by P450 2D6. Since therapeutic concentrations of quinidine are 6–18 μM, with an overlapping range of toxic concentrations [10], it is not likely that standard clinical use of this drug would interfere with taxol metabolism in vivo.

Ketoconazole, an antifungal drug, is a potent inhibitor of P450 3A4 with a K_i of 1 μM or less [19]. In microsomes, ketoconazole inhibited the formation of 6α-hydroxytaxol with an IC_{50} of 37 μM (Fig. 3A). Further, 50 μM ketoconazole inhibited 6α-hydroxytaxol formation by 50–75% in liver slices. Thus, 6α-hydroxytaxol is not likely to be generated via P450 3A4. Nonetheless, since ketoconazole inhibits other metabolic pathways (less potently), high concentrations could still generate an interaction. With standard clinical doses, peak plasma concentrations of ketoconazole are 9–19 μM [6]. At higher doses of ketoconazole, there is a potential for inhibition of taxol metabolism. Cresteil et al. have shown a correlation between taxol metabolism and P450 2C activity in human liver [5]. However, diazepam was the only P450 2C substrate that they found would inhibit the metabolism of taxol, and it only did so at concentrations far in excess of those used clinically. Similarly, we found no inhibition of taxol metabolism with the P450 2C probe drugs sulfinpyrazone, tolbutamide or lauric acid at concentrations less than 200 μM.

In summary, taxol is metabolized in the liver of humans and rats, but with species variations that preclude the use of the rat as a model. Thus, careful attention to interspecies differences in metabolism is essential for the design and interpretation of drug–drug interaction studies. Since taxol is metabolized by the P450 system, studies of the metabolism of taxol and drug interactions can be carried out in vitro with the use of human microsomes or human liver slices. These systems should be useful for screening in vitro for potential clinical drug interactions between taxol and other agents that may be used in a combination treatment. We found metabolic interactions with dexamethasone, Cremophor, quinidine, and ketoconazole in vitro. However, under standard clinical use, none of these agents is likely to inhibit taxol metabolism.

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