Taxol Metabolism by Human Liver Microsomes: Identification of Cytochrome P450 Isozymes Involved in Its Biotransformation

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ABSTRACT

The biotransformation of taxol by human liver was investigated in vitro with microsomes isolated from adult and developing human tissues. In vitro, no metabolism was detected with kidney microsomes, whereas two metabolites were generated by liver microsomes. The most prominent metabolite, termed M5, corresponded to an hydroxylation at the C6 position on the taxane ring, while the other metabolite, termed M4, corresponded to an hydroxylation at the para-position on the phenyl ring at the C3′-position of the C13 side chain. These two taxol derivatives have been shown to be the major metabolites recovered in bile from a patient infused with taxol. Several approaches have been used to identify the cytochrome P450 (CYP) isozymes involved in these reactions. No positive correlation was observed between the in vitro synthesis of these two metabolites, suggesting that two taxol P450 isozymes could be involved, although they could not be distinguished by their apparent affinities (Km ≈ 15 μM). The formation of metabolite M4 was substantially reduced both by antibody directed against CYP3A and by the addition of CYP3A substrates such as orphenadrine, erythromycin, troleandomycin, and testosteron. Conversely, the formation of metabolite M5 remained unaffected by antibodies against CYP3A and by CYP3A substrates but was sensitive to diazepam inhibition, a preferential substrate of CYP2C. Correlation between CYP2C content or diazepam demethylation and the synthesis of metabolite M5 was highly positive. The formation of metabolite M4 developed during the early postnatal period. In contrast, the synthesis of metabolite M5 rose only after 3 months of age. These data clearly implicated CYP3A in the formation of metabolite M4 and CYP2C in the synthesis of metabolite M5. Microsomes from patients treated with barbiturates or diethylstilbestrol increased the formation of metabolite M4 to the level of metabolite M5, demonstrating that drug interactions could modify the human metabolism of taxol.

INTRODUCTION

Taxol, a prototypical new anticancer agent, exhibits clinical activity in ovarian, breast, and lung cancers (1). Although the disposition of taxol has been investigated in both animals and humans (2–4), it is not yet clear whether modulation of taxol metabolism by other drugs and pathological situations could modify the therapeutic effects of this new promising compound (3).

The metabolism of taxol has been studied in both rats and human patients (2–4). In both cases, the parent drug was detected in plasma, urine, and bile. In contrast, taxol metabolites were observed only in bile (2–4). Investigation of human hepatic taxol metabolism is obviously restricted to a few exceptional clinical cases, because it involves the collection of bile through a percutaneous catheter. Our results showed that taxol metabolites observed in the bile of a human patient were mostly different from those observed in rat bile (3, 4). Nine and five taxol metabolites were detected in rat bile (2) and in the bile of a patient with metastatic cholangiocarcinoma (3, 4), respectively. Chemical structural studies of purified metabolites by mass spectrometry and nuclear magnetic resonance spectroscopy demonstrated that, of the five metabolites present in human bile, only one taxol derivative was present in rat bile (2, 4). In both cases, incubation of bile samples with glucuronidase and sulfatase did not modify the chromatographic pattern of these metabolites, suggesting that the formation of conjugates did not play a central role in the hepatic elimination of taxol. We demonstrated that the major metabolites found in both rats and the human patient corresponded to mono- and dihydroxylated compounds. Thus, hepatic metabolism of taxol is mediated through the monoxygenase system, mainly supported by cytochrome P450 isozymes.

About 35 isozymes of cytochrome P450 have been identified, purified, and/or cloned from the human liver (5). They display overlapping substrate specificity and are differently regulated by exogenous chemicals and during ontogenesis (6, 7). The in vitro biotransformation of taxol by human liver microsomes constitutes an alternative and powerful strategy to assess the validity of observations made with a very limited number of patients. Moreover, it could lead to the identification of the cytochrome P450 isozymes involved in taxol metabolism and could allow the understanding of the possible effects of other drugs on the anticancer action of taxol. First, by using human liver microsomes, we characterized the taxol metabolites synthesized in vitro. The two taxol metabolites generated by human liver microsomes corresponded to the two major taxol derivatives previously characterized in human bile (3, 4). Then, we defined the optimal kinetic parameters of their in vitro formation and we examined the possible inhibition of their synthesis by various antibodies and by several chemicals known to be substrates of some cytochrome P450 isozymes. Finally, we correlated the variations of taxol metabolism with other monooxygenases in adult and developing livers. These observations strongly suggest the involvement of members of two subfamilies of cytochromes P450 (CYP3A3 and CYP2C) in the formation of the two major hydroxylated taxol metabolites observed in humans. This in vitro metabolism system may be used to investigate the action of drug pretreatment or pathological situations on taxol metabolism, to explore their effects in cancer therapy.

MATERIALS AND METHODS

Chemicals. Taxol was kindly provided by Bristol-Myers Squibb (Wallingford, CT). Hexobarbital, diazepam, tolbutamide, troleandomycin, testosterone, and orphenadrine were purchased from Sigma. Erythromycin was provided by Abbott (Rungis, France) and racemic mephenytoin was generously supplied by Sandoz (Switzerland).

Tissue Collection. All protocols received the approval of the Ethical Committee of Institut National de la Santé et de la Recherche Médicale. Adult liver samples were collected from donors for kidney transplantation. Occasionally, one kidney was obtained under the same conditions. In most cases, donors had no drug history and died from traffic accidents. No information was available about smoking habits, but it is generally assumed that smoking does not modify hepatic drug metabolism (8), with the exception of CYP1A2-dependent activities (9). Liver samples were obtained from fetuses (age 22, 26, and 27 weeks) aborted for therapeutic purposes (Down syndrome). Postmortem post-
nant samples were obtained from children (age 12 h to 6 months) suffering from severe hypotrophy, malformations, or sudden infant death syndrome. In some cases, samples were obtained from children (age 6 days to 9 years) who had been subjected to drug treatments (barbiturates, benzodiazepines, or steroids). Usually hepatic samples were removed within the first hour after death, immediately frozen in liquid nitrogen, and kept at −80°C until use.

**Microsome Preparation and Determination of Individual P450 Protein Content.** After thawing in ice-cold isotonic saline to remove excess hemoglobin, tissues were homogenized and microsomes were prepared as described previously (10). Cytochrome P450 content was estimated by the procedure of Lowry et al. (11), and protein concentration was measured according to the procedure of Lowry et al. (12). The presence of individual P450 proteins was immunologically determined in liver microsomes: 50 μg microsomal proteins were applied to a sodium dodecyl sulfate-9% polyacrylamide gel (13) and, after migration, proteins were transferred overnight to nitrocellulose membranes, to achieve a complete transfer (14), and were further immunodetected with corresponding antibodies. Antibody-antigen complexes were visualized after addition of peroxidase-conjugated anti-human or anti-rabbit IgG antibodies (Dako, Denmark), using 4-chloronaphthol, and the amount of reacting material was measured by scanning. Reference adult samples were routinely incorporated in each experiment to calibrate determinations.

**Antibodies.** Rat CYP1A1 was purified from rat liver, and antibodies were prepared as described previously (15), and antibodies were raised in rabbits. Serum raised against rat CYP1A1 recognized both rat and human CYP1A1 and CYP1A2. As observed by us and others (16), no CYP1A1 was present in human liver. CYP2C (formerly termed P450-8) and CYP3A4 (formerly termed P450N or P450-5) were purified from adult human liver, and polyclonal antibodies were raised in rabbits (17). Serum raised against rat CYP1A recognized no CYP1A1 in human liver. CYP2D6 protein was immunochemically detected with serum from a patient (18). CYP4A1 was purified from rat liver, and antibodies were prepared as reported (19). The CYP2D6 protein was immunochemically detected with serum from a patient with chronic active autoimmune hepatitis, containing anti-LKM1 antibodies (20). Anti-rat CYP2E1 was purchased from Oxxygen (Dallas, TX) and recognized a single band in human liver microsomes.

**Monooxygenase Activities.** Monooxygenase activities were measured using 0.3 nmol total P450, as reported elsewhere (20). Methoxy- and ethoxyresorufin dealkylations were estimated by spectrophotometry according to the method of Burke et al. (21). The formation of 6-hydroxychlorzoxazone was quantitated after separation by HPLC (22), and diazepam demethylation was assayed as described by Reilly et al. (23). Separation of desmethyldiazepam from other derivatives was carried out at a flow rate of 0.9 ml/min, with a mixture of methanol and water (53:47, v/v) adjusted to pH 5 with phosphoric acid.

**Metabolism of Taxol.** Microsomal proteins (0.25-1.5 mg), corresponding to 0.3 nmol P450, were incubated in a final volume of 1 ml of 100 mM sodium phosphate buffer, pH 7.4, 10 mM MgCl2, 20% glycerol, containing 0.1 mM NADP and 1 mM glucose-6-phosphate. Taxol (10 μM, dissolved in methanol) was added to a final concentration of 100 μM, except when otherwise indicated, and the reaction was started by addition of glucose-6-phosphate dehydrogenase. After 30 min at 37°C, 2.5 ml ethyl acetate were added to recover unmodified taxol and taxol metabolites in the organic phase. For kinetic measurements, taxol concentrations ranged from 5 to 100 μM. Inhibition studies were performed in the presence of 20 μM orphenadrine, 400 μM erythromycin, 160 μM testosterone, or 500 μM hexobarbital, tolbutamide, diazepam, or racemic mephenytoin in the incubation mixture. Troleandomycin (10 μM) was preincubated for 15 min at 37°C with the microsomes in the presence of the NADPH-generating system prior to the addition of taxol. Immunoinhibition was performed as described previously (15); microsomal proteins containing 0.3 nmol P450 were preincubated for 10 min at 23°C with increasing amounts of preimmune or anti-CYP3A4 IgG. Tubes were then chilled on ice before the subsequent addition of all other reagents required to start the reaction.

**Characterization and Quantification of Taxol Metabolites.** The ethyl acetate extract was evaporated to dryness under a nitrogen stream. Residues were then dissolved in 200 μl methanol:water (65:35, v/v) and analyzed directly by HPLC. Detection and quantitation of the parent compound and metabolites were performed as described previously (2, 4). The HPLC system included a Waters model M680 chromatograph equipped with a model 510 pump and a U6K injector and linked to a Waters M991 photodiode array and 235-nm wavelength M481 detector. Injections of 20 μl were made onto the analytical column (0.39 x 25-cm Beckman ODS 5-μm C18 column) and eluted with a mixture of methanol and water (65:35, v/v) at a flow rate of 1 ml/min. The concentrations of taxol and of the main taxol metabolites (M5 and M4) were quantitated using linear calibration curves made with the corresponding pure compounds. Under the experimental conditions used, 10-20 pmol of either taxol or its major metabolites could be easily detected by HPLC.

**RESULTS**

**In Vitro Formation of Taxol Metabolites by Human Microsomes.** Taxol (Fig. 1) was incubated with human microsomes in the presence of NADPH. When the incubation was performed with microsomes isolated from human kidney, even in the presence of large amounts of protein (4 mg protein) taxol remained totally unmodified and no taxol metabolites could be detected by HPLC analysis of the ethyl acetate extract of the reaction mixture. In contrast, when human liver microsomes were used, the HPLC profile demonstrated two new peaks (Fig. 2A), which were undetectable when NADPH was omitted from the reaction mixture (data not shown). In a typical HPLC profile, taxol constituted a prominent absorption peak eluting at 20.3 min, while the two taxol metabolites eluted at 15.5 and 8.9 min. These two peaks exhibited the characteristic UV spectra of taxol derivatives (2, 4). Their retention times corresponded exactly to those of the two reference metabolites M5 and M4 (Fig. 2B), two taxol metabolites chemically characterized by mass spectrometry and nuclear magnetic resonance spectroscopy and previously purified from the bile of a human patient subjected to taxol treatment (metabolites VIII’ and VII’, respectively) (2, 4). Both taxol metabolites resulted from monoxygenation reactions; the M5 derivative was hydroxylated at the C6 α-position of the taxane ring, while the M4 derivative was hydroxylated at the para-position of the phenyl ring at the C3’-position on the C13 side chain (Fig. 1). Both in the bile of the human patient and in the in vitro assay with human liver microsomes, the amount of metabolite M5 greatly exceeded the amount of metabolite M4, indicating that the in vivo data reflected the in vitro situation. In contrast, three minor taxol metabolites that we previously detected in human bile (3, 4) remained undetectable in the in vitro assay.

Kinetin determinations performed in vitro with human hepatic microsomes allowed determination of the time and dose dependence of taxol biotransformation. The rate of formation of metabolite M5 was linear up to 30 min, while the rate of formation of metabolite M4 was linear up to 60 min. When the taxol concentration was increased from 5 to 100 μM, the rate of formation of both metabolites increased following typical Michaelis-Menten kinetics (Fig. 3). Although velocities of the synthesis of the two derivatives were quite different, the
Interindividual Variability of Taxol Metabolism. The formation of metabolite M4 remained extremely low in all hepatic samples tested, 5.3 ± 1.4 pmol/min/mg microsomal protein (n = 11), with values varying from 1 to 15 pmol/min/mg. The formation of metabolite M5 was considerably greater, 120 ± 30 pmol/min/mg protein, and exhibited rather disparate values ranging from 24 to 347 pmol/min/mg. These data demonstrated a large interindividual variability in the formation of the two main taxol metabolites. However, when the formation of metabolite M4 was plotted versus the formation of metabolite M5, no correlation was observed (r = 0.64). This could be explained by the involvement of different P450 isozymes in the two reactions.

Correlation between P450 Content, Monooxygenase Activities, and Taxol Metabolism. We studied the relationships between the rates of formation of metabolites M5 and M4, total P450 content, immunochemically determined levels of individual P450 isozymes (CYP2C, -2E1, -1A2, -3A, -4A1, and -2D6), and monooxygenase activities supported by CYP2C (diazepam demethylation), CYP2E1 (chlorzoxazone hydroxylation), and CYP1A2 (methoxy- and ethoxyresorufin dealkylations) (Table 1). Regarding the formation of the major metabolite produced by human liver microsomes (metabolite M5), a positive correlation was observed with the relative amount of CYP2C (r = 0.72), as well as with the demethylation of diazepam (r = 0.89), which is believed to be supported by CYP2C (24). The better correlation reported with diazepam demethylation was related to the fact that enzymatic assays required the full active protein (protein plus heme), in contrast to immunochemical determinations, in which only the protein moiety was detected. Conversely, correlations were negative between the formation of metabolite M5 and total P450 content, individual CYP1A2, -2D6, -2E1, -3A4/5, and -4A1 isozyme content, and related monooxygenase activities. This clearly assigned CYP2C as the site for metabolite M5 formation. As expected from the absence of correlation between the formation of metabolites M4 and M5, the formation of metabolite M4 was not correlated with CYP2C content (r = 0.42). All other correlations were negative except in two cases; a high correlation was observed with CYP3A content (r = 0.82) and a low correlation was observed with total P450 concentration (r = 0.73). This is not surprising, because CYP3A is a major P450 subfamily in adult human liver, accounting for about 40% of the total P450 content (25).

Inhibition of Taxol Metabolism. We investigated by immunoinhibition and substrate inhibition the respective roles of CYP3A and O

apparent affinity of taxol towards human liver microsomes was identical for the formation of both metabolites, with an apparent K_m of approximately 15 μM. Taking these results in account, we routinely incubated 0.3 nmol P450 (~1 mg protein) with 100 μM taxol for 30 min.
CYP2C in the formation of metabolites M4 and M5. To confirm the involvement of CYP3A in the formation of metabolite M4, human liver microsomes were incubated with immunoglobulins purified from serum of a rabbit given injections of pure CYP3A (Fig. 4). Increasing amounts of anti-CYP3A IgG demonstrated that the formation of metabolite M5 was clearly unaffected, while potent (80%) and dose-dependent inhibition of the formation of metabolite M4 was observed. The formation of metabolite M4 was almost completely inhibited in the presence of 2 mg IgG/nmol P450. Under the same conditions, preimmune IgG did not elicit a reduction in metabolite production.

Substrate inhibition studies (Fig. 5) were carried out with two groups of chemicals, i.e., orphenadrine, erythromycin, testosterone, and troleandomycin, which substantially reduced CYP3A-dependent monooxygenase activities, and hexobarbital, tolbutamide, diazepam, and mephenytoin, which are substrates for different CYP2C members. Chemicals in the first group (orphenadrine, erythromycin, testosterone, and troleandomycin) are potent inhibitors of the biotransformation of taxol into metabolite M4, producing 50–80% reduction of enzyme activity (Fig. 5). Conversely, these molecules had no effect on the formation of metabolite M5. Interferences between testosterone and metabolite M5 prevented any accurate measurements of taxol derivatives. Among the substrates of CYP2C, diazepam was the most potent inhibitor of metabolite M5 formation, whereas mephenytoin was totally ineffective. Tolbutamide, hexobarbital, and mephenytoin did not affect metabolite M4 formation. In the case of diazepam, the elution profile of taxol metabolites was perturbed by diazepam itself or one of its metabolites, preventing the quantitation of metabolite M4. All together, these data indicate that CYP3A inhibitors acted...
liver microsomes from fetuses, newborns, and adults, as indicated in "Materials and Methods." Results are the mean ± SE for fetuses (n = 3), 1-7-day-old newborns (n = 5), 3-6-month-old newborns (n = 4), and adults (n = 11) and are expressed as pmol metabolites produced in 1 min by 1 mg microsomal protein.


selectively on the formation of metabolite M4, whereas CYP2C substrates (especially diazepam) reduced the formation of metabolite M5 by adult human liver microsomes.

**Ontogenic Profile of Taxol Biotransformation.** The investigation of the metabolism of taxol by liver microsomes from fetuses, newborns, and adults confirmed previous results. It has been demonstrated that P450 subfamilies develop asynchronously during the perinatal period (25); CYP2C is absent from human fetal liver and increases during the first month after birth. In contrast, CYP3A7, which is present and active in human fetal liver (26), is replaced by CYP3A4/5 in the first week after birth. The production of metabolite M5 remained barely detectable with microsomes isolated from newborns younger than 3 months of age (<1 pmol/min/mg of protein) and was maximal in adults (Fig. 6). The rise in the formation of metabolite M4 occurred earlier, because its level was readily measurable during the first week after birth (~1 pmol/min/mg of protein) and was higher in 3-6-month-old newborns than in adults. These observations confirm the involvement of CYP3A in the formation of metabolite M4 and of CYP2C in the formation of metabolite M5.

**Effect of Drug Intake on Taxol Metabolism.** Information obtained about the drug history or pathological status of some patients allowed us to classify some of the hepatic biopsies as "induced" or "treated" samples. Individual examination of drug intake and taxol metabolism is detailed in Table 2. After viral infection, no important modifications in the formation of metabolites M4 and M5 occurred. Interestingly, long term treatment with corticoids (1 year of treatment with 1 mg/kg/day) for medulla aplasia did not notably increase taxol biotransformation. A different picture was obtained after treatment with barbiturates. Treatment for several days with phenobarbital (Garden, 5 mg/kg/day) and/or pentobarbital (2–3 mg/kg/h) resulted in selective stimulation (6–9-fold) of the formation of metabolite M4. In one case of multiple dosages with barbiturates, benzodiazepine, and steroid, the formation of both metabolites M4 and M5 was increased. However, while the formation of metabolite M4 was increased 26-fold, that of metabolite M5 was increased by only 2-fold.

**DISCUSSION**

In humans, taxol is eliminated from the body through the biliary pathway, and up to 20% of the dose infused into a patient has been calculated to be excreted in bile during the first 24 h following taxol infusion (2, 3). Two major derivatives have been isolated from bile, i.e., metabolite M5 and metabolite M4, which account for 60% and 10%, respectively, of the total excreted taxol. These two metabolites resulted from hydroxylation of the native molecule either on the phenyl ring or on the taxane ring. Their hydroxylation is likely due to the action of cytochromes P450. Consequently, disposition and steady state concentrations of taxol in the body should depend on the metabolism and rate of biotransformation by human liver microsomes. However, determination of the real significance of these results is severely hampered by the small number of patients for whom there has been a detailed characterization of biliary metabolism (2, 3). In *vitro* biotransformation of taxol by human microsomes constitutes an efficient alternative strategy. We demonstrate for the first time that, in *vitro*, taxol is metabolized by human liver microsomes but that no metabolites could be detected using human kidney microsomes. Moreover, as was the case in human bile, the quantity of metabolite M5 greatly exceeded the quantity of metabolite M4. However, none of the three minor metabolites chemically characterized in human bile could be detected after incubation of taxol in the presence of human liver microsomes. Despite this limitation, biotransformation of taxol by human liver microsomes offers the possibility of identifying the P450 isozymes involved in the hepatic elimination pathway and of predicting and evaluating drug interactions that are able to modify taxol biotransformation and excretion in *vivo*.

The characterization of the cytochrome P450 isozymes responsible for the formation of the major taxol metabolites relied on correlations with various monoxygenase activities, quantitative variations of taxol biotransformation during human ontogeny, inhibitory effects of antibodies directed against CYP3A, and competitive actions of exogenous chemicals used as substrates by either CYP3A or CYP2C. All observations strongly suggest that metabolite M4 is produced by CYP3A, whereas the formation of metabolite M5 is catalyzed by CYP2C (Fig. 7). In *vivo*, metabolites M4 and M5 could be further oxidized to form the dihydroxy derivative recovered in human bile (metabolite VI') (3, 4). These two cytochromes P450 are the major P450 isozymes detected in adult human liver and are known to play an important role in hepatic drug metabolism. With the exception of CYP3A, which is present in relatively small quantities in the intestine, the content of cytochromes P450 in extrahepatic tissues is extremely low (27), accounting for the absence of taxol biotransformation by kidney microsomes. The specific involvement of CYP3A and CYP2C could explain the minor role of extrahepatic tissues in the overall metabolism of taxol, in agreement with *in vivo* observations (1), and should exclude any effect of cigarette smoking (restricted to CYP1A2) (9) on the rate of formation of taxol metabolites.

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4 T. Cresteil, unpublished observations.
Although CYP3A and -2C are present in comparable amounts in human liver (25) and exhibit similar affinities for taxol, the formation of metabolite M5 greatly exceeds the formation of metabolite M4 with all samples studied (11 adults and 8 children). There is no obvious explanation for this observation, but it is possible that, among the bulk of CYP3A (CYP3A4 and -3A5) detected with our antibody preparation, only one isoform, present in low concentrations, could carry out the reaction. This could be resolved only by using highly specific antibodies that are able to discriminate between isozymes or by studying the metabolism of taxol with microsomes from genetically engineered cell lines expressing a single human P450 after transfection of the respective complementary DNA (V79 cells, COS cells, etc.).

A crucial question which cannot be adressed in human patients concerns a possible influence of drug coadministration upon taxol biotransformation. First, drugs could inhibit taxol metabolism. Thus, CYP3A substrates like cyclosporin, steroids, erythromycin, macrolide antibiotics, and anticancer agents like Vinca alkaloids and tamoxifen (28–32) could substantially reduce the formation of metabolite M4. Similarly, benzo diazepines, barbiturates, and antiepileptic drugs could be competitive inhibitors of the formation of metabolite M5 (23, 33–35). Second, repeated coadministration of these drugs could increase the level of CYP3A and -2C isozymes (30, 36) and consequently modify the metabolism and elimination of taxol. In this respect, samples from patients treated with a combination of barbiturates, steroid, and/or benzo diazepines showed a considerable increase in the formation of metabolite M4 and a smaller increase in the formation of metabolite M5. This clearly emphasizes the role of drug interactions in taxol metabolism. These observations have clear implications when taxol is administered after or concommitantly with other drugs which could modify its hepatic metabolism and thus influence the extent of biliary elimination. This might be related to the lowered taxol clearance observed in patients treated successively with cisplatin and taxol versus patients treated successively with taxol and cisplatin (37). One could hypothesize that cisplatin acts by repressing the synthesis of CYP2C members, as it does in rats with respect to the CYP2C11 mRNA level (38). Further studies are required to refine multidrug treatment including taxol dosage during cancer therapy.

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**REFERENCES**


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