Thalidomide Pharmacokinetics and Metabolite Formation in Mice, Rabbits, and Multiple Myeloma Patients

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ABSTRACT

Purpose: **Thalidomide has a variety of biological effects that vary considerably according to the species tested. We sought to establish whether differences in pharmacokinetics could form a basis for the species-specific effects of thalidomide.**

Experimental Design: **Mice and rabbits were administered thalidomide (2 mg/kg) p.o. or i.v., and plasma concentrations of thalidomide were measured after drug administration using high performance liquid chromotography. Plasma samples from five multiple myeloma patients over 24 hours after their first dose of thalidomide (200 mg) were similarly analyzed and all data were fitted to a one-compartment model. Metabolites of thalidomide in plasma were identified simultaneously using liquid chromatography-mass spectrometry.**

Results: **Plasma concentration-time profiles for the individual patients were very similar to each other, but widely different pharmacokinetic properties were found between patients compared with those in mice or rabbits. Area under the concentration curve values for mice, rabbits, and multiple myeloma patients were 4, 8, and 81 μmol/L · hour, respectively, and corresponding elimination half-lives were 0.5, 2.2, and 7.3 hours, respectively. Large differences were also observed between the metabolite profiles from the three species. Hydrolysis products were detected for all species, and the proportion of hydroxylated metabolites was higher in mice than in rabbits and undetectable in patients.**

Conclusions: **Our results show major interspecies differences in the pharmacokinetics of thalidomide that are related to the altered degree of metabolism. We suggest that the interspecies differences in biological effects of thalidomide may be attributable, at least in part, to the differences in its metabolism and hence pharmacokinetics.**

INTRODUCTION

Thalidomide has a number of biological activities that have led to its clinical application to a variety of diseases. After demonstration of its efficacy in the control of erythema nodosum leprosum (1), thalidomide was evaluated for the management of numerous inflammatory and autoimmune diseases, including Crohn's disease (2) and rheumatoid arthritis (3). Its application as an anti-inflammatory agent is thought to be derived from its ability to inhibit the biosynthesis of proinflammatory cytokines such as tumor necrosis factor-α (4). After the demonstration that it could inhibit angiogenesis in the rabbit cornea (5), it was also evaluated for the treatment of cancer. Although activity was modest against renal carcinomas (6), gliomas (7), and prostate cancers (8), it was outstanding against refractory multiple myeloma (9), and thalidomide has been put forward as a 1st line treatment for this disease (10). However, thalidomide has an unfavorable effect, *i.e.,* its teratogenicity (11, 12), which led to its withdrawal when it was first marketed in the 1950s as a sedative and antiemetic (13). The difficulties in determining thalidomide's teratogenic properties during its initial development were perhaps because of the widely disparate interspecies sensitivities to the action of thalidomide. Rodents appear resistant to the teratogenicity of thalidomide, whereas rabbits and humans were highly susceptible (14). It has been suggested that the antiangiogenic and teratogenic effects are caused by stable metabolites, and species specific differences in thalidomide metabolism form the basis for the interspecies differences in the action of thalidomide (15).

Biotransformation of thalidomide can occur by nonenzymatic hydrolysis (16, 17) or by hepatic cytochrome P450-catalyzed hydroxylation (18), with all products often referred to as metabolites. Considerable interspecies differences in the production of hydroxylated metabolites have been observed. A 20-fold higher production of hydroxylated metabolites was found with rodent liver microsomes than with human liver microsomes (18). Two hydroxylated products were obtained when thalidomide was incubated with human liver enzymes, but only one of these could be found in low concentrations in plasma samples from healthy male volunteers (19). In patients with Hansen's disease, no hydroxylated metabolites were detected in plasma whereas one was detected in urine by tandem mass spectrometry but mostly at levels below the limit of quantitation, and *in vitro* studies indicated that thalidomide was a poor substrate for human cytochrome P450 isoenzymes (20). Among patients with prostate cancer, *cis*-5′-hydroxythalido-

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mide and 5-hydroxythalidomide were detectable in only 48% and 32% of individuals, respectively (21). In a previous study, we have used liquid chromatography-mass spectrometry to show that whereas hydroxylated metabolites of thalidomide were present in the plasma and urine of mice, none were detectable in the urine of multiple myeloma patients on thalidomide therapy (22).

In this report we have extended those studies to compare thalidomide pharmacokinetics and metabolite formation in mice, rabbits, and multiple myeloma patients. Our results suggest that differences in the rates by which the drug is metabolized may provide a basis for interspecies differences in the response to thalidomide.

MATERIALS AND METHODS

Materials. Thalidomide for animal studies was kindly provided by Dr. George Muller (Celgene Corp., Warren, NJ). 2-Hydroxypropyl-β-cyclodextrin and trichloroacetic acid were purchased from Sigma-Aldrich. Acetonitrile was purchased from BDH Laboratory Supplies (Poole, United Kingdom). Glacial acetic acid was purchased from Panreac Quimica SA (Barcelona, Spain).

Authentic Standards. Phthaloylglutamic acid was purchased from Sigma-Aldrich (St. Louis, MO). Phthaloylisoglutamine, 4-hydroxyphthaloylisoglutamine, 5-hydroxyphthaloylisoglutamine, phthaloylglutamine, 4-hydroxyphthaloylglutamine, 5-hydroxyphthaloylglutamine, 4-hydroxythalidomide, 5-hydroxythalidomide, *N*-(*o*-carboxybenzoyl)glutamine, *N*-(*o*-carboxybenzoyl)isoglutamine, *N*-(*o*-carboxybenzoyl)glutamic acid imide, and 5-hydroxy-*N*-(*o*-carboxybenzoyl)glutamic acid imide were synthesized as described previously (22), and their structures were confirmed using 400 MHz ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry. 5′-Hydroxythalidomide was a generous gift from Professor Sven Bjorkman (Malmo University Hospital, Malmo, Sweden) and was a mixture of 5′-*cis*- and 5′-*trans* diastereomers.

Murine Studies. Female 8 to 12 week-old C57Bl/6 mice bred at the Animal Resources Unit, Faculty of Medical and Health Sciences, University of Auckland, were housed under conditions of constant temperature and humidity according to institutional ethical guidelines. Thalidomide was dissolved in 2-hydroxypropyl-β-cyclodextrin (1 mg/ml) and administered p.o. (gavage needle) or i.v. (tail-vein; 2 mg/kg, 2 μL/g body weight). In another set of experiments, thalidomide was administered p.o. or i.v. at a dose of 20 mg/kg dissolved in 30% dimethylsulfoxide in polypropylene glycol solution (8 mg/ml). Mice were bled at 5, 15, and 30 minutes, and 1, 2, 4, and 6 hours after treatment. Three mice were used for each time point plus an untreated control group. The mice used for the 6-hour time point were placed in metabolic cages with water and food, and urine was collected over the first 4 hours after treatment. Blood samples were collected into heparinized tubes during terminal halothane (NZ Pharmacology Ltd., Christchurch, New Zealand) anesthesia, centrifuged, and the plasma removed. Plasma (200 μL for pharmacokinetic studies and 300 μL for metabolite studies) and urine (100 μL) were acidified by adding 10% trichloroacetic acid up to 1 ml. Samples were centrifuged at 3000 × *g* for 10 minutes to remove precipitated protein and then processed using solid phase extraction as described previously (22). Dried plasma and urine residues were reconstituted in 100 μL and 1,000 μL mobile phase, respectively, for analysis.

Rabbit Studies. Three female New Zealand White rabbits supplied by Animal Resource Unit of the University of Auckland were used between 6 and 12 months-old for all of the experiments according to institutional ethical guidelines. Thalidomide was dissolved in 2-hydroxypropyl-β-cyclodextrin (1 mg/ml) and administered p.o. using a polyethylene plastic tube, or i.v. via ear-vein injection (2 mg/kg in a volume of 2 ml/kg). After drug administration, rabbits were placed in metabolic cages with water and food for urine collection over a 6-hour period. Blood samples were collected into heparinized tubes from the ear-vein at 15 and 30 minutes and 1, 2, 3, 4, 6, and 8 hours for the p.o. studies, and at 15 and 30 minutes and 1, 1.5, 2, 3, 4, and 8 hours for i.v. studies. Control urine and plasma samples for each rabbit were obtained before thalidomide administration. Plasma (200 and 300 μL for pharmacokinetics and metabolite studies, respectively) and urine (100 μL) were processed as described for the murine samples. Dried residues were reconstituted in 200 or 100 μL of mobile phase, respectively, for urine samples and plasma samples.

Clinical Studies. All clinical studies conformed to institutional ethical guidelines. Three male and two female Caucasian patients who were beginning their thalidomide therapy for refractory multiple myeloma at Auckland Hospital were recruited for these studies. Their ages ranged from 42 to 81 years, and their weights ranged from 52 to 105 kg. All patients had been instructed not to take nonprescription medications or drink alcohol. Blood was collected into heparinized tubes at 1, 2, 4, 6, 8, and 24 hours after the patients' first dose of thalidomide (2 × 100-mg tablets p.o.). Urine samples were collected whenever possible. A control sample of blood and urine was obtained from the patients before treatment. Blood samples were centrifuged and plasma collected and quickly stored at −80°C until analysis. Plasma (200 and 300 μL, respectively, for pharmacokinetics and metabolite studies) was acidified by adding 10% trichloroacetic acid up to 1 ml and centrifuged to remove precipitated protein. Urine samples (3.33-ml each) were acidified by adding 10% trichloroacetic acid up to 10 ml. All samples were processed as described for murine samples. Dried residues from plasma and urine samples were reconstituted in 100 and 1,000 μL mobile phase, respectively.

Pharmacokinetic Determination. Thalidomide concentrations were measured using a specific high performance liquid chromatography assay as described previously (23). Concentration-time data were analyzed using Pharsight WinNonlin 4.01 software (Mountain View, CA) and fitted either to a one-compartmental i.v. model or one-compartmental p.o. model with first-order absorption and elimination. C_{max} and T_{max} were determined visually from the plasma time-concentration profile. The elimination rate constant (λ) was determined from the terminal linear portion of the concentration *versus* time curve. The terminal $t_{1/2}$ was calculated as ln(2)/λ. The area under the plasma thalidomide concentration *versus* time curve (AUC_{0-t}) from time zero to the last quantifiable concentration (C_t) was calculated by trapezoidal rule. Area under the concentration-time curve (AUC) extrapolated to infinity was calculated from (AUC_{0-t}) + C_t/λ.

Metabolite Studies. Reconstituted samples were analyzed together with authentic standards using an Agilent 1100 series liquid chromatography-mass spectrometry system (Agilent Technologies, Avondale, PA) as described previously (22) with two modifications. The proportions of solution A (80% acetonitrile, 1% glacial acetic acid, and 19% Milli Q water) and solution B (9.5% acetonitrile, 1% glacial acetic acid, and 89.5% Milli Q water) in the mobile phase were altered slightly to improve resolution; all samples were analyzed using diode array UV detection at 230 nm and mass spectral detection set on negative-ion scan mode with a M_r range of 70 to 1,000 atomic mass units, negative single-ion monitoring mode, with the sensitivity of 1 pg, at the M_r 257, 273, 275, 276, 289, 291, 293, 294 and 449, and positive single-ion monitoring mode at the M_r 259, 275, 277, 278, 291, 293, 295, 296 and 451 (corresponding to each of the peaks) simultaneously.

Statistical Analysis. All pharmacokinetic data are presented as means ± SD, and because of limitations on the volume of blood samples obtainable from mice, murine pharmacokinetic parameters were calculated by modeling group mean data using Pharsight v4.01. Student's *t* test was used to calculate the statistical significance between groups, with a probability value $P < 0.05$ considered significant.

RESULTS

Thalidomide Pharmacokinetics in Mice. After p.o. administration of thalidomide at 2 mg/kg, the peak concentration was 4.3 ± 0.9 μmol/L after 0.5 hour (Fig. 1*A*). When given i.v., the highest concentration was 7.7 ± 0.3 μmol/L, observed after 5 minutes (Fig. 1*B*), and the $t_{1/2}$ was 0.5 to 0.8 hour. The AUC after p.o. administration (4.3 ± 0.8 μmol/L · hour) was significantly lower than that obtained with i.v. (8.7 ± 0.7 μmol/L · hour) administration (Table 1). The calculated bioavailability, based on AUC, was 50%. Thalidomide concentrations were also measured after a dose of 20 mg/kg, which was used previously in our *in vivo* studies (ref. 24; Fig. 1*A* and *B*). This 10-fold increase in dose resulted in a 10-fold increase in AUC after p.o. administration of thalidomide (Table 1). The C_{max} was increased only 3-fold (12 ± 3 μmol/L) and occurred after 1 hour

Table 1 Thalidomide pharmacokinetic parameters in plasma in mice, rabbits, and patients

Route	Dosage (mg/kg)	C_{max} (μmol/L)	T_{max} (h)	$AUC_{0-\infty}$ (μmol/L · h)	$t_{1/2}$ (h)
Mice					
p.o.	2	4.3 ± 0.9	0.50	4.3 ± 0.8	0.5 ± 0.20
	20	12.0 ± 3.0	1.00	44.0 ± 6.0	1.2 ± 0.05
i.v.	2	7.7 ± 0.3*	≤0.08*	8.7 ± 0.7	0.8 ± 0.10
	20	59 ± 7*	≤0.08*	60.0 ± 7.0	0.7 ± 0.10
Rabbits					
p.o.	2	1.8 ± 0.4	1.5 ± 0.9	8 ± 0.2	2.2 ± 0.3
i.v.	2	7.2 ± 0.6*	0.25*	8 ± 1.0	0.7 ± 0.1
Patients					
p.o.†					
P1	1.95	3.5	4	49	6.7
P2	2.11	3.8	4	69	7.7
P3	2.60	5.1	4	72	7.8
P4	3.51	7.2	6	107	7.7
P5	3.85	7.5	6	110	6.5
Mean ± SD		5.4 ± 1.9	4.8 ± 1	81 ± 26	7.3 ± 0.6

* C_{max} and T_{max} values limited by the first time-point of analysis.
† Patients were treated with 200-mg tablets, and the dose was normalized.

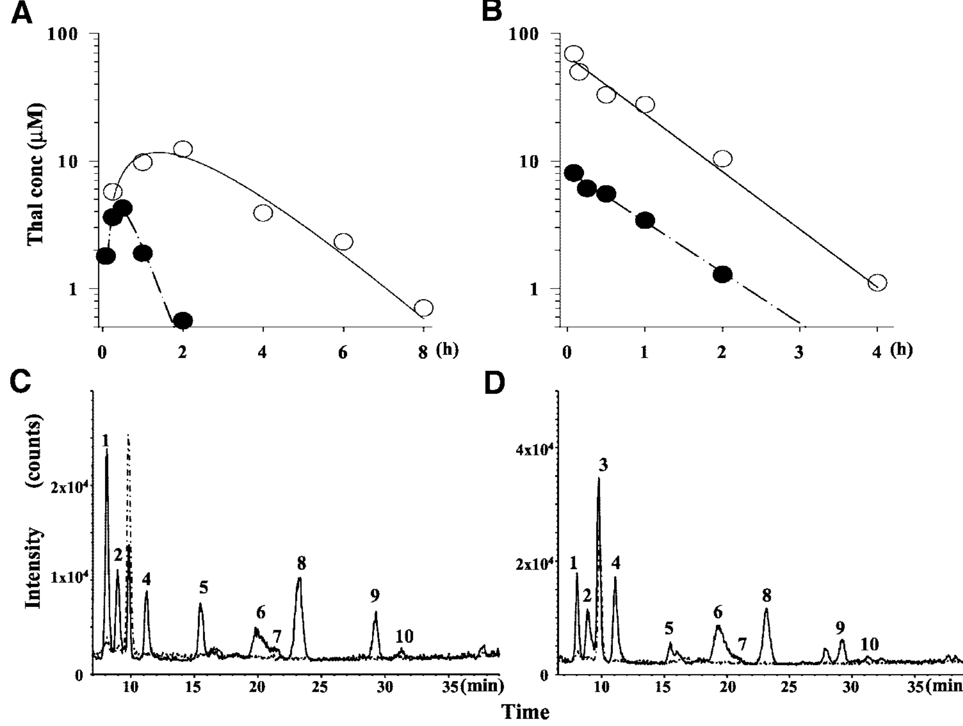


Fig. 1 *A* and *B*, plasma concentration-time profiles of thalidomide after p.o. (*A*) or i.v. (*B*) administration of 2 mg/kg (●–·-) or 20 mg/kg (○—) in mice. Data were fitted using Pharsight model. *C* and *D*, MS chromatograms detected on negative single-ion monitoring mode before treatment (*dashed lines*) or after (*solid lines*) thalidomide treatment (2 mg/kg) p.o. (*C*) or i.v. (*D*) treatment in plasma from mice (30 minutes time point).

(Table 1), and the $t_{1/2}$ increased by 3- and 2-fold respectively at 20 mg/kg compared with 2 mg/kg p.o. thalidomide. Intravenous administration of thalidomide at 20 mg/kg also produced a proportionate increase in AUC (60 ± 7 μmol/L · hour) but with no significant change in $t_{1/2}$ (0.7 ± 0.1 hour).

Thalidomide Pharmacokinetics in Rabbits. Rabbits were administered thalidomide 2 mg/kg either p.o. (Fig. 2*A*) or i.v. (Fig. 2*B*). The C_{max} after p.o. administration (1.8 μmol/L) was 4-fold lower than that observed after i.v. administration (7.2 μmol/L). The T_{max} was 1.5 hours, and the bioavailability of thalidomide was 100%. The $t_{1/2}$ of p.o. administered thalidomide was 3-fold higher than that for i.v. administration (Table 1).

Thalidomide Pharmacokinetics in Multiple Myeloma Patients. Thalidomide was absorbed slowly in patients (Fig. 3*A-E*), with the mean peak concentration (5.2 ± 1.9 μmol/L) achieved after 4.5 ± 1 hour. The elimination $t_{1/2}$ in patients was 7.6 ± 0.6 hours, 15- and 3-fold longer than that in mice and rabbits, respectively. The AUC, 83 ± 14 μmol/L · hour, was 20- and 10-fold higher than in mice and rabbits, respectively (Table 1). In two patients, total 24-hour urines were collected for analysis, and unchanged thalidomide was found to account for 0.9% of the administered dose.

Thalidomide Metabolites in Mice. Metabolite profiles were monitored by liquid chromatography-mass spectrometry as described previously (22), with a modification in the solvent allowing separation of phthaloylisoglutamine (peak 5) from phthaloylglutamine (peak 7), as well as separation of the *cis*- and *trans*-5′-hydroxy-*N*-(*o*-carboxybenzoyl)glutamic acid imides (peaks 2 and 4). On the basis of their relative polarities, peak 2 and peak 4 would be expected to be the *cis*- and the *trans*-isomer, respectively, but this has yet to be validated with authentic standards. The modification also provided a better resolution of *N*-(*o*-carboxybenzoyl)isoglutamine (peak 3). All plasma samples exhibited the same metabolite profile regardless of the route of administration (Fig. 1*C* and *D*), which contained peaks 1, 5, and 7 corresponding to hydrolysis products, plus peaks 2, 4, 6, 8, 9, and 10 corresponding to hydroxylated and glucuronidated metabolites (Table 2). Urine samples contained the same peaks with the addition of peak 3, *N*-(*o*-carboxybenzoyl)isoglutamine, which was masked in plasma samples by a background component present in untreated controls. Although i.v. (Fig. 1*D*) or p.o. (Fig. 1*C*) administration produced the same number of metabolite peaks, the plasma metabolite peaks at 2 hours or earlier were higher after i.v. administration compared with p.o. administration.

Thalidomide Metabolites in Rabbits. After p.o. administration to rabbits, two different metabolic profiles were observed in plasma, dependent on the concentration of the parent thalidomide present. At all time points when the concentration of thalidomide was below 1 μmol/L, the metabolite profile showed hydrolysis products only (peaks 1, 5, and 7; Fig. 2*D*). However, when the thalidomide plasma level was above 1 μmol/L, whether during the absorption or the elimination phase, hydroxylated metabolites (peaks 2, 4, 6, and 8) were detected in addition to the hydrolysis products (peaks 1, 3, and 5; Fig. 2*C*). The mass spectral peak areas of peaks 2, 4, 6, and 8 in rabbit samples were 26.8, 43.7, 3.6, and 6.2%, respectively, of their corresponding peak in murine samples, indicating a lower level of hydroxylation in rabbits compared with mice. Urine samples contained hydrolysis products (peaks 1, 3, and 5) only. After i.v. administration, plasma samples collected before 2 hours, when thalidomide concentration was above 1 μmol/L, hydrolysis

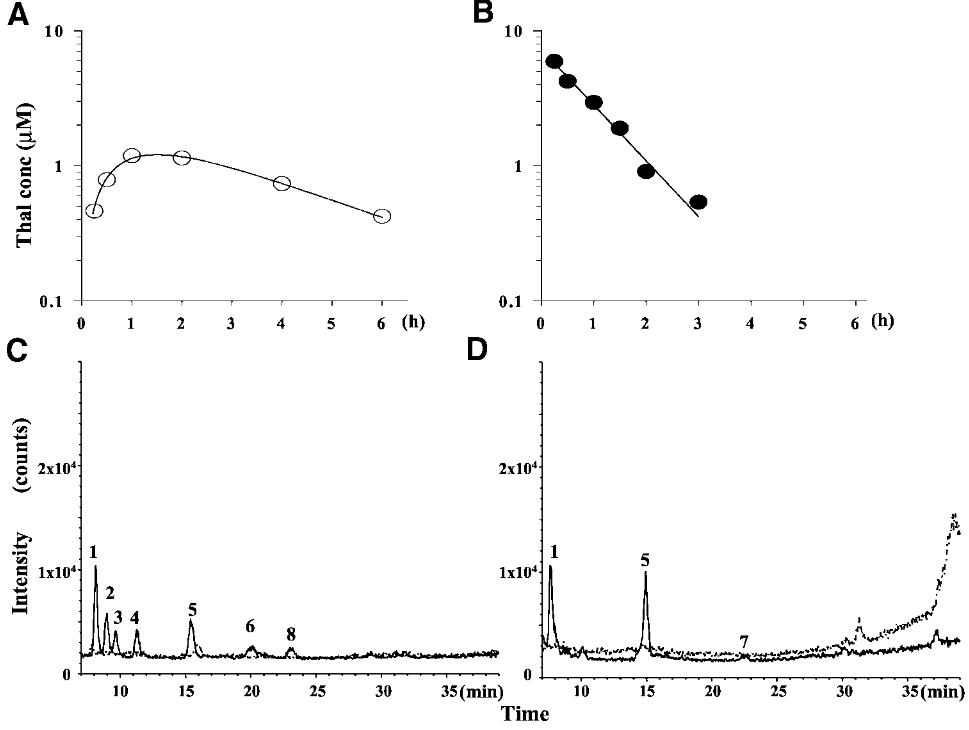
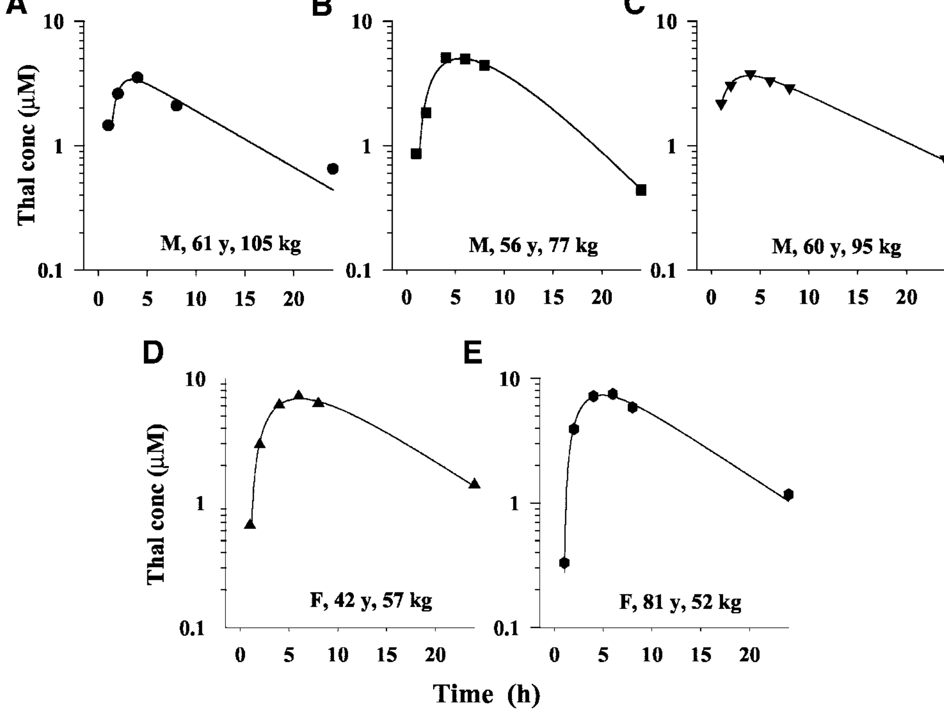


Fig. 2 *A* and *B*, plasma concentration-time profiles of thalidomide after p.o. (○; *A*) or i.v. administration (●; *B*) of 2 mg/kg to rabbits. Data were collected from three rabbits and fitted using Pharsight model. *C* and *D*, MS chromatograms detected on negative single-ion monitoring mode before (*dashed lines*) or after (*solid lines*) 2 hours (*C*) or 30 minutes (*D*) of thalidomide (2 mg/kg) p.o. treatment in plasma from rabbits.



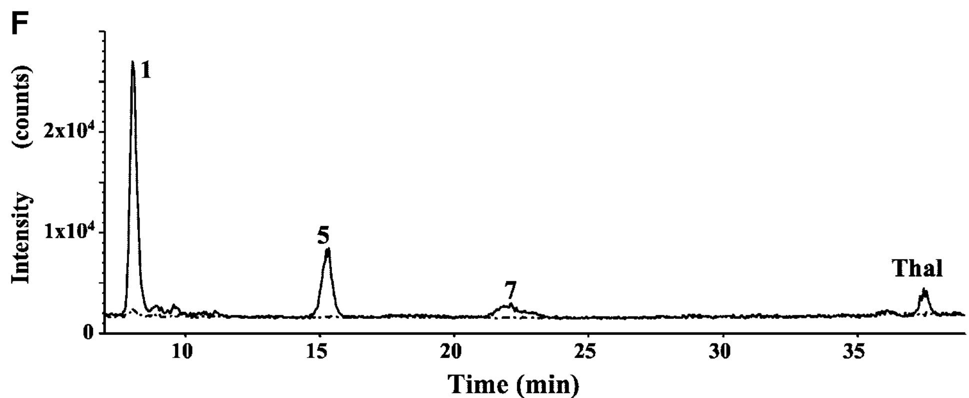


Fig. 3 *A–E*, plasma concentration-time profiles of thalidomide after an oral dose of 200 mg for each of five multiple myeloma patients ●, ■, ▲, ⬣, represent different patients. *F*, representative MS chromatogram detected on negative single-ion monitoring mode before (*dashed line*) or after (*solid line*) thalidomide (2 mg/kg p.o.) treatment in plasma from patient 2 (4-hour time point).

products (peaks 1, 3, and 5), and hydroxylated products (peaks 2, 4, 6, 8, 9, and 10) were detected. However, after 2 hours, when thalidomide concentrations had dropped below 1 µmol/L, the metabolite profiles showed only hydrolysis products (peaks 1, 5, and 7). Urine samples after i.v. administration showed two hydrolysis products (peaks 1 and 5) and one hydroxylation product (peak 10; data not shown).

Thalidomide Metabolites in Patients. All plasma and urine samples from multiple myeloma patients contained only peaks 1, 5, and 7, corresponding to the hydrolysis products; hydroxylated metabolites were not detected at any time point in urine or in plasma (Fig. 3*F*). Very little inter-individual variability in thalidomide pharmacokinetics and metabolite formation was seen in five patients despite differences in age (42–81 years), weight (52–105 kg), sex, and disease status (Fig. 3, Table 1).

DISCUSSION

This study, the first detailed comparison of thalidomide pharmacokinetics and metabolite formation in mice, rabbits, and patients with multiple myeloma, was carried out to determine whether thalidomide pharmacokinetics could explain the inter-species differences in biological response. Widely different pharmacokinetic parameters for thalidomide were found (Fig. 4; Table 1). In mice, bioavailability was 50%, and the elimination was rapid whereas in rabbits bioavailability was 100% and $t_{1/2}$ was longer, and in multiple myeloma patients the $t_{1/2}$ was even longer. We hypothesize that differences in metabolism are the principal cause of the observed interspecies differences in pharmacokinetics. Our observation in two multiple myeloma patients, that <1% of the administered thalidomide dose was excreted unchanged in urine, is in agreement with data for other species including mice and rabbits (25). In mice, 10 metabolite

Table 2 Metabolite peaks in UV and MS profiles of mouse urine after p.o. thalidomide

Peak No.	Molecular weight	Metabolite	Structure
1*	276	*N*-(*o*-carboxybenzoyl)glutamic acid imide	
2†,‡	292	*cis*-5′-Hydroxy-*N*-(*o*-carboxybenzoyl)glutamic acid imide	
3*	294	*N*-(*o*-carboxybenzoyl)isoglutamine	
4†,‡	292	*trans*-5′-Hydroxy-*N*-(*o*-carboxybenzoyl)glutamic acid imide	
5*	276	Phthaloylisoglutamine	
6†	450	Thalidomide-5-*O*-glucuronide	
7*	276	Phthaloylglutamine	
8†	274	*cis*-5′-Hydroxythalidomide	
9†	274	*trans*-5′-Hydroxythalidomide	
10†	274	5-Hydroxythalidomide	

* Hydrolysis product.
† Hydroxylation product.
‡ Not yet confirmed by comparison with authentic standard.

peaks corresponding to hydrolysis, hydroxylation, and glucuronidation products were detectable in urine and plasma within 30 minutes of i.v. (Fig. 1*D*) or p.o. (Fig. 1*C*) administration. Hydroxylation products were detectable in rabbits only if the thalidomide concentration was above 1 μmol/L in the plasma, irrespective of the route of administration and the phase of the pharmacokinetic profile (Fig. 2). In contrast, hydroxylated metabolites were not detected in any sample from the five multiple myeloma patients in this study (Fig. 3*F*). Thus, hydroxylation of thalidomide occurs extensively in mice, moderately in rabbits, and undetectably in patients. Because hydroxylated and glucuronidated metabolites are much more soluble than the parent drug, greater metabolism along this pathway would facilitate more rapid elimination of thalidomide from the system. Consistent with this, a reverse correlation between the rate of elimination and the amount of hydroxylation in the three species was obtained, suggesting that the interspecies differences in thalidomide pharmacokinetics are related to the rate at which it is hydroxylated.

The results confirm our previous finding that hydroxylated products are not detectable in multiple myeloma patients (22). If the parent drug, or one of its hydrolysis products, is responsible

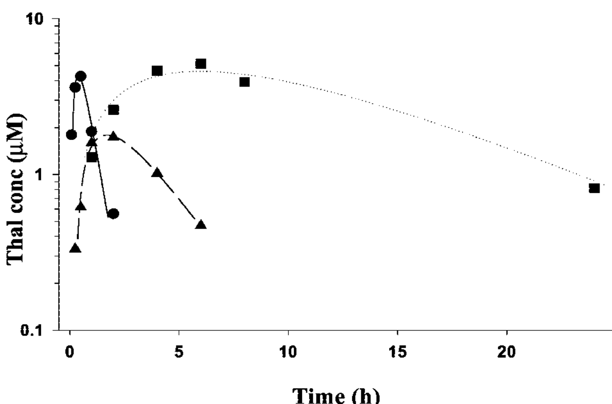


Fig. 4 Comparison of thalidomide pharmacokinetics in mice (2 mg/kg, ●), rabbits (2 mg/kg, ▲) and multiple myeloma patients (200 mg, combined data from five individuals, ■).

for the *in vivo* effects, thalidomide would be expected to be more effective in a species in which it is hydroxylated slowly. Consistent with this proposal, humans are more susceptible than rodents to many of the effects of thalidomide including antitumor effects. Although clinical responses have been reported for renal carcinomas (6), gliomas (7), prostate cancers (8), and in particular for multiple myeloma (9, 26), evidence for antitumor activity after single or multiple dose administration of thalidomide to mice has been difficult to obtain (27, 28). On the basis of the AUC values determined in the present study (Table 1), rabbits would be expected to be intermediate between humans and mice in their responsiveness to thalidomide, and there is a single report of daily high doses of thalidomide (200 mg/kg/day) achieving a 55% reduction in tumor volume of V2 carcinomas in rabbits (29). The teratogenicity of thalidomide in rabbits at high doses and in humans at low doses, as well as the resistance of rodents to teratogenicity (14), may also be related to the AUC and exposure to the parent drug (Table 1).

Thalidomide modulates the biosynthesis of a number of cytokines that are essential to the growth and survival of multiple myeloma cells, suggesting that its primary mechanism of action in multiple myeloma patients involves down-regulation of cytokine synthesis (30, 31). Consistent with this, a recent study has shown that multiple myeloma patients who are genetically high tumor necrosis factor-α producers respond better to thalidomide therapy (32). Inhibition of cytokine biosynthesis by thalidomide does not require hepatic activation (4) and we suggest that the long plasma half-life of thalidomide in multiple myeloma patients, which is a result of a low rate of metabolism, is important for such down-regulation. These considerations are relevant to the development of newer thalidomide analogs, some of which have been reported to have more consistent pharmacokinetic profiles than thalidomide and are currently undergoing clinical trial (33).

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