JPP Journal of Pharmacy and Pharmacology

JPP 2003 55: 1701–1706

Received May 6, 2003
Accepted July 22, 2003
DOI 10.1211/0022357022241
ISSN 0022-3573

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Acknowledgement and funding: We thank Bodil Roth for determination of thalidomide concentrations from blood samples. We also thank all physicians, nurses and laboratory technicians involved in planning, collecting and delivering samples in the myeloma study. The myeloma and dialysis study was sponsored by Grünethal GmbH (Aschen Germany) and Celgene Corp. (Warren, NJ), respectively. TE and PH have no sponsoring or funding from the companies involved.

Communication

Pharmacokinetics of thalidomide in patients with impaired renal function and while on and off dialysis

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Abstract

There is a renewed interest in thalidomide for use in malignancies and systemic inflammatory diseases. Reduced renal function is not uncommon among patients with these disease states but the pharmacokinetics has not been fully investigated. The aim of this study was to investigate the pharmacokinetics of thalidomide in haemodialysis patients while on and off dialysis and in myeloma patients with varying degrees of renal function.

Two studies were performed. To establish the pharmacokinetics of thalidomide in patients with mild to moderate renal failure, blood samples were taken over 12 weeks from 40 patients with multiple myeloma. A second study was performed in six patients with end-stage renal disease both on a non-dialysis day and before and during a haemodialysis session. Thalidomide concentration was determined by HPLC. A one-compartment open model with first-order absorption and elimination was used to fit total thalidomide concentration to population pharmacokinetics and statistical models using the NONMEM program. Clearance and volumes were slightly below $10\,L\,h^{-1}$ and $1\,L\,kg^{-1}$, respectively, in both patient groups. The inter- and intra-patient variability was low. Clearance was doubled during dialysis. There was no correlation between thalidomide clearance and renal function. In conclusion, the pharmacokinetics of thalidomide in patients with renal failure are very similar to values reported by others for patients with normal renal function. Although clearance during dialysis is doubled, thalidomide dose need not be changed for patients with decreased kidney function. There is also no need for a supplementary dose due to haemodialysis.

Introduction

Thalidomide was initially introduced over 40 years ago as a non-barbiturate hypnotic. It became known for its severe teratogenic effects on foetal development and the subsequent changes throughout the world in governmental regulation of new drugs. More recently, its immunomodulating properties have renewed interest in the use of thalidomide in various inflammatory and immunological diseases (Zwingenberger & Wnendt 1996). It has been approved for use in the USA for treating erythema nodosum leprosum, a complication of Hansen's disease. Thalidomide is currently being investigated for use in a variety of other inflammatory disease (e.g. systemic lupus, rheumatoid arthritis, inflammatory bowel disease, and graft-vs-host disease) as well as malignancies (Calabrese & Fleischer 2000), including gliomas and multiple myeloma (Rajkumar et al 2002).

The clinical pharmacology of thalidomide has recently been reviewed (Eriksson et al 2001). In brief, the enantiomers of thalidomide undergo spontaneous hydrolysis and fast chiral interconversion at physiological pH. The oral bioavailability is probably high. Absorption is slow, with a time to maximum concentration of at least 2 h, and may also be dependent on dose. The volume of distribution is around $1\,L\,kg^{-1}$ and the plasma protein binding is low, 56 and 63% for the (*R*)- and (*S*)-enantiomers, respectively. Elimination of thalidomide is mainly by pH-dependent spontaneous hydrolysis in all body fluids, with an apparent mean clearance of $10\,L\,h^{-1}$ for the (*R*)- and $21\,L\,h^{-1}$ for the (*S*)-enantiomers in adult subjects. Blood concentrations of the (*R*)-enantiomer are consequently higher than those of the (*S*)-enantiomer at

pseudoequilibrium. Very low amounts of hydroxylated metabolites have been detected in human blood and urine. The mean elimination half-life of both enantiomers is 5 h. The inter-individual variability in distribution and elimination is low.

Patients with end-stage renal disease (ESRD) have increased levels of acute-phase proteins (CRP, SAA) and cytokines suggesting the presence of an inflammatory state (Kaysen 2001), which may be predictive of death (Yeun et al 2000, Wanner et al 2002). It is possible that suppression of inflammation might be of use in reducing cardiovascular risk in these patients. Thalidomide can reduce elevated levels of TNFα, an important mediator in the cytokine cascade. The anti-inflammatory effect of thalidomide is thought to be effected by decreasing TNFα mRNA levels by increasing its rate of degradation (Moreira et al 1993). For this reason it may be useful to use thalidomide in ESRD patients with inflammation to improve both nutritional status and potentially to protect against the cardiovascular risks of inflammation. To proceed further to investigate the utility of thalidomide for this purpose, it is first necessary to understand the effects of both dialysis and ESRD on thalidomide metabolism.

There are some data indicating low renal excretion in man and animals (Williams et al 1965; Chen et al 1989) but it is unknown whether the pharmacokinetic profile of thalidomide is altered in patients with renal failure and to what extent the drug is removed during haemodialysis.

The aim of this study was to investigate the pharmacokinetics of thalidomide in multiple myeloma patients with reduced renal function and also in haemodialysis patients on and off dialysis. With this knowledge, it may be possible to safely conduct studies in ESRD patients with increased levels of CRP, SAA and cytokines suggesting presence of an inflammatory state.

Patients and Methods

The studies were approved by the national official medicines authorities and ethical commitees in each of the institutions.

The US Food and Drug Administration have prepared guidance for pharmacokinetic studies in patients with impaired renal function (US Department of Health and Human Services, Food and Drug Administration 1999). The main goal of this study was to determine whether pharmacokinetics were altered in patients with renal impairment and to establish what additional clearance, if any, was imparted by haemodialysis. We chose to conduct a population pharmacokinetic study using a non-linear mixed-effects model. NONMEM is a computer program that can use routine retrospective data as well as prospective experimental clinical pharmacokinetic data to estimate population pharmacokinetic parameters. This approach treats the population as the unit of analysis, rather than the individual, and in general requires fewer data points per individual (but more individuals) than are normally required in an experimental study. By adopting this method, a much more representative sample of the target population can be obtained and quantitative relationships between pharmacokinetic parameters and pathophysiological features (age, weight, gender, kidney function, etc) can be investigated in a single step. These relationships may then explain a considerable amount of the inter-subject variability present in the population (Whiting et al 1986).

Myeloma study

The multiple myeloma patients were included in a study conducted by the Nordic Myeloma Study Group and will be presented elsewhere. In brief, we included sixty-five patients with multiple myeloma of 1–16 years duration (median 4.2 years) refractory to treatment with chemotherapy or who relapsed within 6 months after high-dose therapy with peripheral blood stem cell support. Patients were recruited from hospitals in Denmark, Sweden and Norway from November 1999 to February 2000. Thalidomide (Grunenthal GmbH, Aachen Germany) was given as a single agent in a dose of 100 mg twice daily, was escalated to 400 mg twice daily during 7 weeks, and treated according to the initial protocol for 24 weeks. Blood samples for the determintion of thalidomide pharmacokinetics were collected before the morning dose at weeks 3, 5, 7 and 9 and blood samples for a concentration–time profile were collected at weeks 1 and 12 before the morning dose and at approximately 1, 3 and 5 h after dosing. Dosing was after fasting conditions for about 10 h.

Dialysis study

Six patients with ESRD who had been on chronic haemodialysis for at least 3 months were recruited from the Renal Clinic at the University of California Medical Center, Sacramento, CA, from April to July 2001. The patients were administered thalidomide (Celgene Corp.Warren, NJ) 200 mg, with a full glass of water on an empty stomach, in the evenings for a total of 5 days. The day after taking the 4^{th} evening dose, the patients were admitted to the renal clinic for collection of blood samples on a non-dialysis day. Four samples were collected over 3 h. On the next day, after taking the 5^{th} evening dose, the patients were admitted to the renal clinic for collection of blood samples on a day when dialysis was performed. Three blood samples were taken over 2 h before dialysis and four during the 3–4 h of dialysis treatment (a total of 7 samples on the dialysis day). Patients were dialysed using Fresenius 2008 machines and F-80 dialysers (Fresenius, Walnut Creek, CA)

Sampling

All samples where taken in duplicate. Whole blood (1.0 mL) was transferred to tubes that had been pre-filled with citrate buffer-given pH and pre-weighed. Samples were then frozen ($-25\,^{\circ}C$) within 15 min. The exact times for thalidomide administration on the day before and on the study day, as well as for each sampling time, were recorded. Samples were transported to the Hospital Pharmacy Research Unit at Malmö University Hospital on dry-ice for determination of thalidomide concentrations by a high-performance

liquid chromatography method, described previously by Eriksson & colleagues (Eriksson et al 1992; Eriksson & Björkman 1997). The between-day coefficient of variation of the assay was 8.9% at 0.25 μg mL^{-1} (n = 8) and 6% at 1.0 μg mL^{-1} (n = 35) for the dialysis and myeloma study, respectively.

Pharmacokinetic and statistic analysis

Based on previous experiences, we chose a one-compartment open model with first-order absorption and elimination and used this to fit total thalidomide concentration data to the population pharmacokinetic and statistical models. This was achieved by non-linear mixed-effect modelling software (NONMEM, version 5.0; University of California, San Francisco, SA). Simulations with incomplete data sets and extreme patient characteristics, based on previous experiences, were carried out when planning the number of patients and data points needed for the studies. In the myeloma study, the rate of absorption (Ka), rate of elimination (K) and volume of distribution (V) of thalidomide was determined. In the dialysis study, clearance (CL), on and off dialysis, and volume of distribution of thalidomide was determined. In both models, potential covariates were added sequentially to the regression model. Covariates that significantly improved the NONMEM objective function (decrease more than 5 units) were used to build the final model. Tested covariates in the dialysis study were weight and dialysis, and in the myeloma study weight, age, serum creatinine and creatinine clearance. Creatinine clearance was calculated using the Cockroft and Gault equation (Cockroft & Gault 1976). Random inter-individual variability and residual intra-patient variability were statistically modelled. The dialysis study was not designed to investigate absorption kinetics and we fixed the rate of absorption at the value obtained in the myeloma study (0.200 h^{-1}).

In the dialysis study, a supplementary dose required to replace the drug removed by dialysis was calculated according to Equation 1 (Rowland & Tozer 1995).

$$\text{Supplementary dose} = V * C(0)\ (e^{-K\tau} - e^{-KD\tau}) \qquad (1)$$

V is the volume of distribution, C(0) is the thalidomide concentration at the start of dialysis, K is the elimination rate constant without dialysis, KD is the elimination rate constant during dialysis and τ is the duration of dialysis.

Linear regression was used to estimate the influence of patient mean creatinine clearance on their thalidomide clearance (Proc REG, SAS version 8.2; SAS Institute, Cary, NC).

Results

Myeloma study

Study details such as clinical response, side effect and reasons for termination the study will be presented elsewhere. A total of 381 concentration determinations from 40 patients (13 female, weight 44–161 kg, mean 72 kg) were available to evaluate the thalidomide pharmacokinetics. Full data sets (12 concentration determinations) were obtained for 23 patients. The final regression model used is described in Table 1.

Estimated pharmacokinetic parameters (calculated from individual estimates) are shown in Table 2. Inter-individual variability in population values for Ka, K and V were 16, 14 and 19%, respectively. Residual intra-patient variability was 28%. Introduction of renal function (serum creatinine or creatinine clearance) into the regression model did not improve the NONMEM objective function. We could calculate creatinine clearance for 35 patients. A plot of thalidomide clearance and mean creatinine clearance is shown in Figure 1. It is clear from this figure that creatinine clearance among these 35 multiple myeloma patients had no significant effect on thalidomide clearance ($P = 0.515$), indicating no effect of renal impairment on the pharmacokinetics of thalidomide.

Dialysis study

Six patients (all male, range 28–69 years, median 50.5) completed the study. Four of the six patients had no residual renal function and the other two had a urea clearance of approximately 1 mL min^{-1}. Full data sets were obtained from every patient and 66 concentration determinations were used to evaluate the pharmacokinetics. The final regression model used is described in Table 1.

Obtained and predicted concentration versus time profiles during the sampling days are shown in Figure 2. Individual and mean values, and 95% confidence intervals (calculated from individual estimates) are shown in Table 3. As shown (mean values increased from 9.9 to 17.2 L h^{-1}), CL increased significantly during dialysis. Inter-individual variability in population values for CL and V were 11 and 14%, respectively. Residual intra-patient variability was 16%. Including dialysis as a covariate to volume in the regression model did not improve the NONMEM objective

Table 1 Regression models used in the myeloma and dialysis study.

Myeloma study	Dialysis study
TVKA = THETA(1)	TVKA = THETA(1)
KA = TVKA*EXP(ETA(1))	KA = TVKA
TVK = THETA(2)	TVCL = THETA(2)*WT + THETA(3)*DIA
K = TVK*EXP(ETA(2))	CL = TVCL*EXP(ETA(2))
TVV = THETA(3)*WT	TVV = THETA(4)*WT
V = TVV*EXP(ETA(3))	V = TVV*EXP(ETA(3))

TVKA is the typical absorption rate value (population value), WT is patient weight, DIA is dialysis, THETA is mean fixed effect parameters, ETA is the random effect variables. TVKA was set at 0.200 h^{-1} in the dialysis study.

Table 2 Mean values and 95% confidence intervals (CI) for empirical Bayes' estimates of pharmacokinetic parameters in the myeloma study (n = 40).

	Mean	95% CI
Ka (h^{-1})	0.200	0.196–0.204
K (h^{-1})	0.140	0.136–0.144
V (L)	63.8	58.8–68.7
CL ($L\,h^{-1}$)	8.98	8.22–9.74
V ($L\,kg^{-1}$)	0.886	0.847–0.924
CL ($L\,h^{-1}kg^{-1}$)	0.126	0.117–0.134
$t_{1/2}$ (h)	4.98	4.83–5.12

function significantly. The mean extra volume was estimated at 483 mL.

During the 48-h test period, the mean total amount of thalidomide cleared was 474 L ($48\,h \times 9.9\,L\,h^{-1}$). During a 3-h dialysis session, an additional 22 L ($3\,h \times 7.3\,(17.2 - 9.9)\,L\,h^{-1}$) was cleared, an increase of 4.6% during 48 h.

Therefore, using Equation 1, the calculated supplementary dose was 10 mg (based on data from Table 3, a 200-mg once daily dose and a 3- h dialysis session 10–15 h after dosing). Thalidomide concentration at the start of dialysis was approximately $1\,mg\,L^{-1}$ (Figure 2). This concentration can also be obtained from computer-simulated concentrations at steady state described by Eriksson et al (2001). If dialysis is performed at the peak thalidomide concentration (i.e. 2–4 h after dosing) or just before the next dose, a supplementary dose of 23 and 2 mg, respectively, can be calculated from the simulated concentrations 2.3 and $0.2\,mg\,L^{-1}$ using Equation 1.

Discussion

This study shows, as expected from other indirect evidence (Williams et al 1965; Chen et al 1989), that distribution and elimination of thalidomide are not dependent on renal function. This is demonstrated in Figure 1, which shows that there is no correlation between thalidomide clearance and renal function in myeloma and dialysis patients. The study also shows that clearance is doubled during haemodialysis.

The NONMEM approach estimated the extra loss of thalidomide during dialysis with good accuracy and low inter- and residual intra-individual variability. The pharmacokinetic parameters obtained for distribution and elimination in myeloma patients and in dialysis patients off-dialysis correspond well to studies conducted with satisfactory methodology (Eriksson et al 2001). In these studies the inter-patient variations in terminal half-lives were low and the mean values were in the range 4.7–6.8 h (Eriksson et al 1995; 2000; Trapnell et al 1999; Noormohamed et al 1999; Teo et al 1999). In other studies the variations in terminal half-lives were higher (3.0–14.6 h

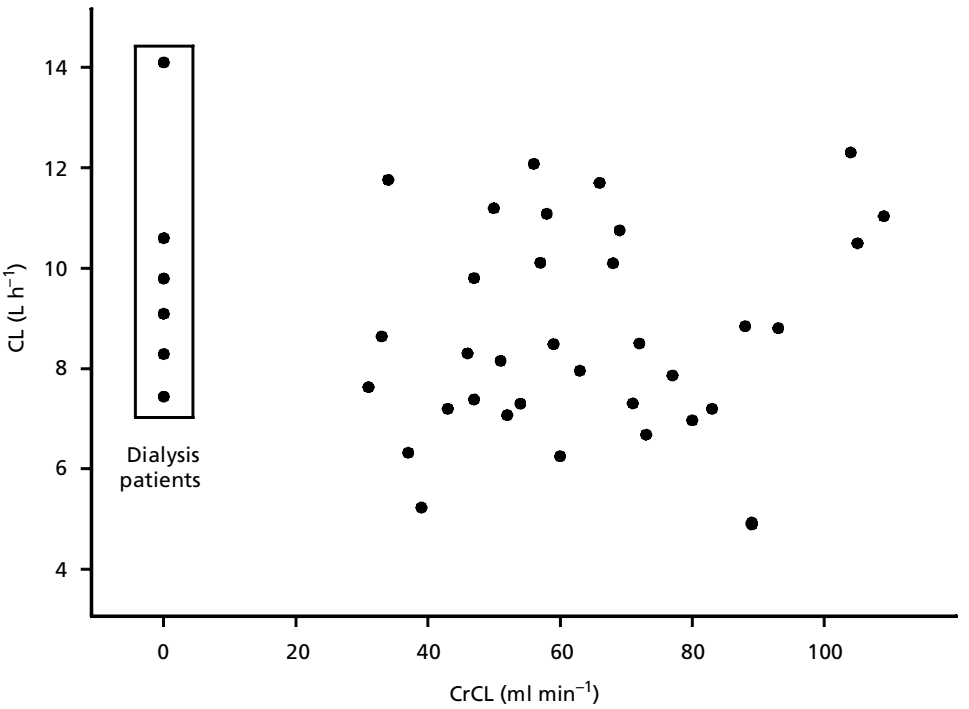

Figure 1 Each patient's estimated thalidomide clearance (CL) and their mean observed creatinine clearance (CrCL) in the myeloma and dialysis (box) study. Severe, moderate, mild renal impairment, and normal renal function is < 30, 30–50, 50–80 and > $80\,mL\,min^{-1}$, respectively. Among the dialysis patients, four of the six had no residual renal function and the other two had a urea clearance of approximately $1\,mL\,min^{-1}$.

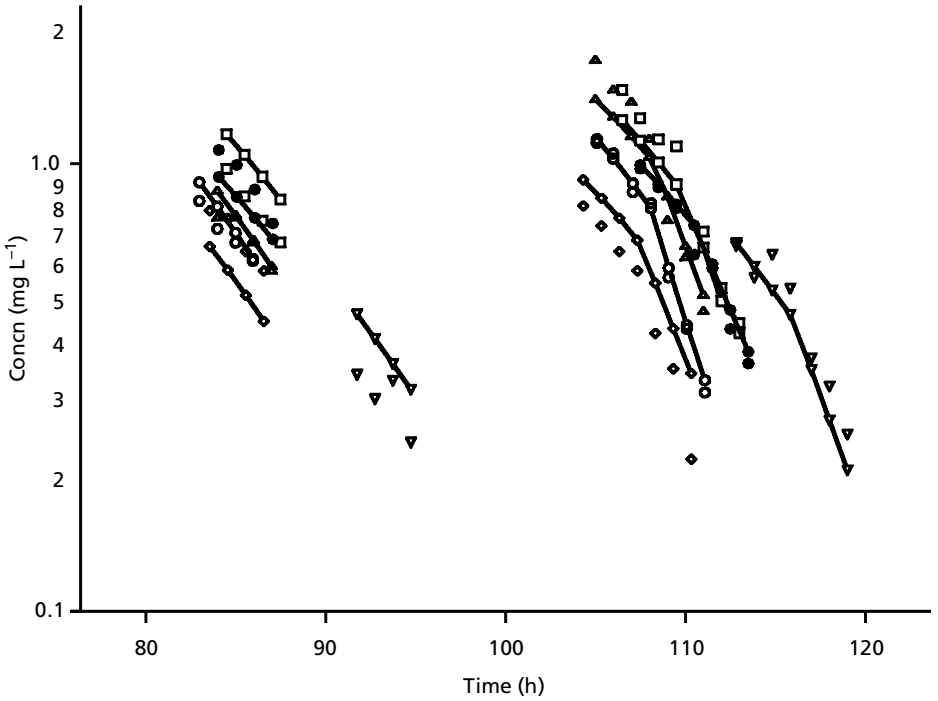

Figure 2 Obtained (symbols only) and predicted (symbols with curves) thalidomide concentration–time profiles during the sampling days in the dialysis study. The symbols represent thalidomide concentrations for each patient 10–15 h after the 4th evening dose (non-dialysis day) and after the 5th evening dose (dialysis day, first off and then on dialysis). The time-scale starts when the first dose is given on day1.

(Chen et al 1989), 3.7–11.5 h (Piscitelli et al 1997), 2.7–27.9 h and 0.75–31.9 h (Fine et al 2000)). This might more reflect experimental uncertainty than actual inter-individual variation. From a mechanistic point of view, since only pH (and temperature) affects the rate of hydrolysis of thalidomide, a very low variability between individuals is expected (Eriksson et al 2001).

Mean total CL increased by a factor of 2 during dialysis. In our setting, a supplementary dose of 10 mg was calculated to replace the drug removed. Using Equation 1, supplementary doses for different dialysis and dosing schedules can be calculated. To estimate thalidomide concentration during the dialysis session, Table 5 in Eriksson et al (2001) can be of use. As an example, a dialysis session 22–24 h after a 50-mg once-daily dose would require a supplementary dose of less than 1 mg. A dialysis session 2–4 h after a 400-mg four-times-daily dose would require a supplementary dose of 90 mg. Since basic knowledge on mechanism of action, effects of the separate enantiomers and metabolites and dose– and concentration–effect relationships is lacking (Eriksson et al 2001), it seems very ambitious to routinely administer a supplementary dose, since thalidomide obviously is not a drug with a narrow therapeutic range.

Table 3 Individual and mean values, and 95% confidence intervals (CI), for empirical Bayes' estimates of pharmacokinetic parameters off and on dialysis.

Patient no.	Weight (kg)	V (L)	Off dialysis			On dialysis		
			K (h^{-1})	CL (L h^{-1})	t½ (h)	K (h^{-1})	CL (L h^{-1})	t½ (h)
1	81	47.1	0.226	10.6	3.06	0.407	19.2	1.70
2	86	46.4	0.196	9.09	3.54	0.343	15.9	2.02
3	68	44.4	0.168	7.44	4.13	0.327	14.5	2.12
4	112	67.6	0.208	14.1	3.32	0.329	22.2	2.11
5	75	52.6	0.158	8.29	4.39	0.293	15.4	2.37
6	100	60.3	0.162	9.79	4.27	0.267	16.1	2.60
Mean	87	53.1	0.186	9.89	3.79	0.328	17.2	2.15
95% CI		43.5–62.7	0.156–0.216	7.43–12.35	3.21–4.37	0.277–0.378	14.2–20.3	1.83–2.47

Conclusions

The pharmacokinetics of thalidomide in this study were very similar to values obtained from other well-conducted studies. The inter- and intra-patient variability was low. This study supports the previous findings that there is no reason for dose changes with thalidomide in the presence of decreased kidney function. There is also normally no need for a supplementary dose due to haemodialysis, although clearance is doubled during dialysis.

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