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REVIEW ARTICLE

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Clinical pharmacology of thalidomide

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Abstract *Background*: Thalidomide has a chiral centre, and the racemate of (*R*)- and (*S*)-thalidomide was introduced as a sedative drug in the late 1950s. In 1961, it was withdrawn due to teratogenicity and neuropathy. There is now a growing clinical interest in thalidomide due to its unique anti-inflammatory and immunomodulatory effects.
Objective: To critically review pharmacokinetic studies and briefly review pharmacodynamic effects and studies of thalidomide in consideration of its chemical and stereochemical properties and metabolism.
Methods: Literature search and computer simulations of pharmacokinetics.
Results: Rational use of thalidomide is problematic due to lack of basic knowledge of its mechanism of action, effects of the separate enantiomers and metabolites and dose- and concentration-effect relationships. Due to its inhibition of tumour necrosis factor-α and angiogenesis, racemic thalidomide has been tested with good effect in a variety of skin and mucous membrane disorders, Crohn's disease, graft-versus-host disease, complications to human immunodeficiency virus and, recently, in multiple myeloma. Adverse reactions are often related to the sedative effects. Irreversible toxic peripheral neuropathy and foetal malformations are serious complications that can be prevented. The results of several published pharmacokinetic studies can be questioned due to poor methodology and the use of non-stereospecific assays. The enantiomers of thalidomide undergo spontaneous hydrolysis and fast chiral interconversion at physiological pH. The oral bioavailability of thalidomide has not been unequivocally determined, but available data suggest that it is high. Absorption is slow, with a time to maximum plasma concentration of at least 2 h, and may also be dose-dependent; however, that of the separate enantiomers may be faster due to higher aqueous solubility. Estimation of the volume of distribution is complicated by probable hydrolysis and chiral inversion also in peripheral compartments. A value of around 1 l/kg is however plausible. Plasma protein binding is low with little difference between the enantiomers. Elimination of thalidomide is mainly by pH-dependent spontaneous hydrolysis in all body fluids with an apparent mean clearance of 10 l/h for the (*R*)- and 21 l/h for the (*S*)-enantiomer in adult subjects. Blood concentrations of the (*R*)-enantiomer are consequently higher than those of the (*S*)-enantiomer at pseudoequilibrium. The mean elimination half-life of both enantiomers is 5 h. One hydroxylated metabolite has been found in low concentrations in the blood. Since both enzymatic metabolism and renal excretion play minor roles in the elimination of thalidomide, the risk of drug interactions seems to be low.
Conclusions: The interest in and use of thalidomide is increasing due to its potential as an immunomodulating and antiangiogenic agent. The inter-individual variability in distribution and elimination is low. Apart from this, its use is complicated by the lack of knowledge of dose– or concentration–effect relationships, possible dose-dependent oral absorption and of course by its well-known serious adverse effects.

Keywords Thalidomide · Stereoisomers · Pharmacokinetics

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Historical perspective

The story of thalidomide is a tragic chapter in the generally progressive development of drug therapy. It has

been described as a turning point, an end of innocence and the beginning of a new and greater sense of responsibility in clinical pharmacology, in clinical investigation and in medicolegal relationships (Curran 1971). It also had a profound effect on the drug regulatory process (Kelsey 1988).

Thalidomide was synthesised in 1954 by Kunz, a chemist at Chemie Grünenthal GmbH (Kunz 1956). Whilst the postulated antihistaminic properties for which it was synthesised were weak, it produced marked sedation. Doses of thalidomide in excess of 10 g/kg failed to show lethality in rodents. As a result it was regarded as a particularly safe drug. Thalidomide was launched as a sedative in 1957 and in 1960 it was marketed in 20 countries. In 1960 the sales in Germany amounted to 14.6 tons and it was sold free of prescription. Reports about neuro-pathogenicity after prolonged use of thalidomide began to appear in 1960. In 1961 McBride and Lenz, two physicians working independently of each other, started to suspect a link between births of children with severe malformations and consumption of thalidomide during the first trimester of pregnancy. The drug was withdrawn from the market but its use had resulted in more than 10,000 victims of malformation with abnormalities such as phocomelia (short limbs), amelia (absence of limbs), ear, eye, heart and gastrointestinal abnormalities (McBride 1961; Lenz 1988; Zwingenberger and Wnendt 1996).

In 1965 there was a report of remarkable effects in the treatment of the debilitating and disfiguring lesions associated with erythema nodosum leprosum (ENL), a complication of leprosy (Hansen's disease, Sheskin 1965). After this finding there was a renewed clinical interest in thalidomide, due to its anti-inflammatory and immunomodulating effects (for reviews see Schuler et al. 1995 and Zwingenberger and Wnendt 1996). Recently, the Food and Drug Administration of the United States approved thalidomide for use in patients with ENL (Nightinggale 1998).

Chemistry and chirality

Thalidomide (α-phthalimidoglutarimide, Fig. 1) has a chiral centre and is used as a racemate (1:1 mixture) of dextrorotatory (*R*)- and levorotatory (*S*)-thalidomide. The aqueous solubility of racemic (*rac*) thalidomide has been reported to be about 50 μg/ml, with a five-times higher solubility of the separate enantiomers (Hague and Smith 1988; Krenn et al. 1992; Eriksson et al. 2000a).

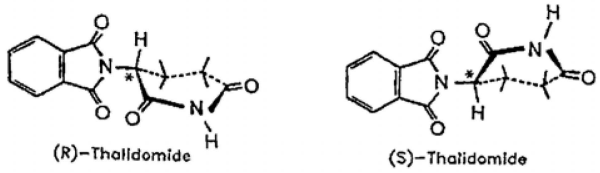

Fig. 1 Stereochemical structures of (*R*)- and (*S*)-thalidomide

Thalidomide is rapidly degraded by spontaneous hydrolysis in any aqueous medium at physiological pH (Schumacher et al. 1965a; Eriksson et al. 1992, 1997; Boughton et al. 1995; Huupponen et al. 1995; Lyon et al. 1995). All the substituted amide bonds are sensitive to hydrolysis and at pH 7.4 twelve hydrolysis products are formed by splitting these bonds. From pH 6 to pH 7 only the phthalimide ring undergoes cleavage, whereas at pH 7 and above the glutarimide moiety also undergoes hydrolysis (Schumacher et al. 1965a). The rates of inversion and hydrolysis of the enantiomers increase with pH in the interval 7.0–7.5 (Eriksson et al. 1998a).

Proper handling of solutions and biological samples of thalidomide and its enantiomers is crucial to avoid hydrolysis and chiral inversion. Various techniques have been described for handling of plasma samples, such as acidification with HCl (Boughton et al. 1995) or fast chilling and transportation for centrifugation and storing of plasma at –25°C (Lyon et al. 1995). These methods do not completely inhibit hydrolysis of thalidomide (some 4–10% degradation is reported) and do not address the problem of racemisation if one wishes to measure the concentrations of the separate enantiomers (Eriksson et al. 1997). In the latter case both procedures will probably be unacceptable, since enantiomeric inversion is twice as fast as hydrolysis in blood as well as in plasma (Eriksson et al. 1998a). In contrast, with the use of the protocol outlined in the appendix there was no detectable degradation or racemisation in blood/buffer mixtures stored at –25 °C for 75 days and 100 days, respectively (Eriksson et al. 1997).

Pharmacokinetics

There is fast chiral interconversion between the enantiomers of thalidomide after intravenous and oral administration of the separate enantiomers as shown in two subjects from our studies (Fig. 2). Since thalidomide is in reality two different molecules with different pharmacokinetic and pharmacodynamic profiles, pharmacokinetic data should be given for the separate enantiomers. However, since *rac*-thalidomide, in capsules or tablets, is the only form of thalidomide in clinical use, and since our group alone has performed human studies on the enantiomers, a summary of studies in which calculated pharmacokinetic parameters are based on total thalidomide concentrations will also be presented.

Oral absorption of the racemate

Pharmacokinetic parameters for absorption of oral doses of *rac*-thalidomide have been determined in healthy volunteers (Beckmann and Kampf 1961; Green

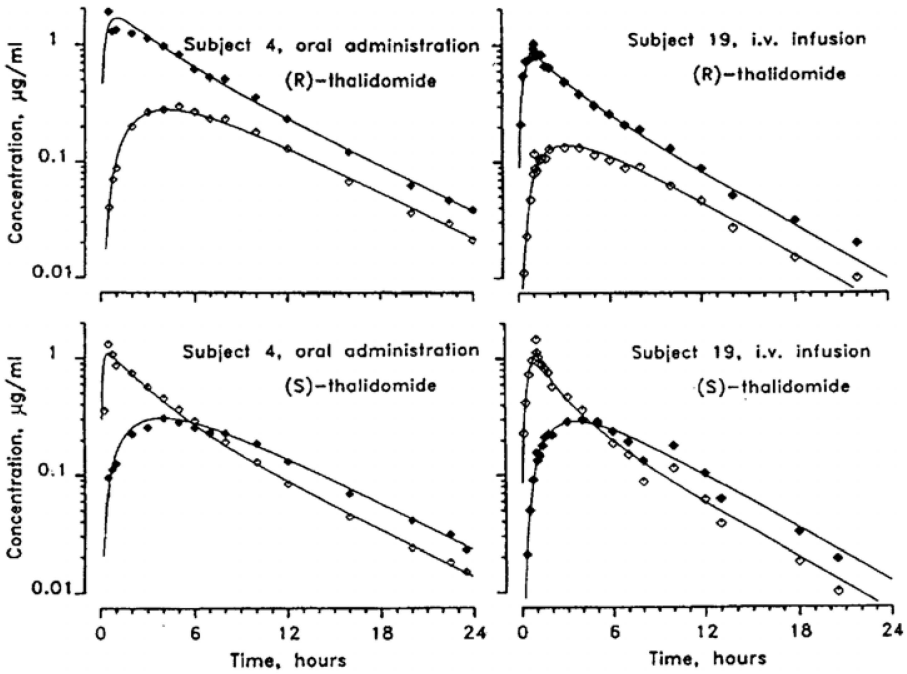

Fig. 2 Blood–concentration curves of observed (*R*)-thalidomide (*filled symbols*) and (*S*)-thalidomide (*open symbols*) and fitted concentrations (*curves*) after oral (1 mg/kg) or intravenous (i.v., 50 mg over 60 min) administration of the indicated enantiomer to two subjects

and Benson 1961; Chen et al. 1989; Boughton et al. 1995; Trapnell et al. 1999; Teo et al. 1999, 2000b; Celgene Corp. 2000), in patients suffering from graft-versus-host disease (GVHD) after bone marrow transplantation (Heney et al. 1991), in patients with human immunodeficiency virus (HIV) infection (Piscitelli et al. 1997; Noormohamed et al. 1999), in elderly patients with prostate cancer (Figg et al. 1999), in patients with leprosy (Celgene Corp. 2000) and in patients with gliomas (Fine et al. 2000). In these studies, the pharmacokinetics describing total thalidomide concentrations were presented. Their results are summarised in Table 1. However, as shown in Table 2, methodological weaknesses cast doubt on some of the findings. In addition to this, we have presented pharmacokinetic data for the separate enantiomers of thalidomide after oral administration of the racemate to healthy volunteers (Eriksson et al. 1995).

Table 1 demonstrates that the different studies on oral absorption of a low dose (typically 100 mg) of *rac*-thalidomide in healthy volunteers have yielded consistent results. Absorption is slow, with time to maximum plasma concentration (t_{max}) normally at 2–4 h and maximum plasma concentration (C_{max}) around 1 µg/ml. With larger doses, the poor solubility of thalidomide in intestinal fluids may decrease the rate of absorption (Celgene Corp. 2000). Rate of absorption may consequently be dose-dependent. Co-administration of thalidomide with a high-fat meal was reported to cause minor (< 10%) changes in the observed area under the curve (AUC) and C_{max} values but an increase in t_{max} to approximately 6 h (Teo et al. 2000b).

A large inter-individual variation in plasma concentrations after oral administration of thalidomide was found in patients with GVHD (Heney et al. 1991). Two of the four patients differed markedly from the profiles obtained in volunteers and in HIV-infected patients. The differences were stated to be due mainly to a slow absorption rate. The same pattern was described in three of five patients with GVHD and chronic malabsorption syndrome (Boughton et al. 1995). Ten hours after an oral thalidomide dose of 400 mg the plasma concentrations in these patients were 0.7, 0.7 and 0.8 µg/ml. In two patients with normal gastrointestinal function corresponding plasma concentrations were 5.0 µg/ml and 6.0 µg/ml. We have monitored blood concentrations of thalidomide in five children (0.5–15 years, 5–57 kg) with GVHD and possible chronic malabsorption syndrome (unpublished data). Duplicate blood samples were taken before the morning dose and the measured blood concentrations were compared with expected concentrations from a computer simulation based on our previous data (see below). Two of the five children had lower thalidomide concentrations than expected. In one boy (13 years, 36 kg) the blood concentrations in two samples separated by 7 days showed 0.7 µg/ml and 1.1 µg/ml when 3.0 µg/ml was expected. In another boy (9 years, 27 kg) the blood concentration was 0.2 µg/ml when 1.3 µg/ml was expected. In contrast to these findings it has been suggested that patients with leprosy may have an increased bioavailability of thalidomide compared with healthy subjects (Celgene Corp. 2000). This suggestion seems speculative since we have proposed a very high

Table 1 Pharmacokinetic parameters for oral absorption of *rac*-thalidomide [total, or (*R*)- and (*S*)-enantiomer concentrations], obtained in different studies (mean ± SD or median, range). C_{max} maximum plasma concentration, t_{max} time to reach C_{max}, $t_{1/2}$ half-life, t_{lag} absorption lag time, *"Saft"* syrup, *"Tropfen"* drops

	No. of patients (P) or healthy volunteers (Hv)	Administration form and dose (mg)	C_{max} (μg/ml)	t_{max} (h)	$t_{1/2abs}$ (h)	t_{lag} (h)
Beckmann and Kampf 1961	5 Hv	Tablet 100	0.9	4		
	7 Hv	"Saft" 100	1.2	2		
	7 Hv	"Tropfen" 100	1.8	2		
Green and Benson 1961	2 Hv	Tablet 150	1.3	4		
Chen et al. 1989	8 Hv, fasting	Tablet, chewed, 200	1.2 ± 0.2	4.4 ± 1.3	1.7 ± 1.1	0.4 ± 0.6 in 6/8
Heney et al. 1991	4 P, fasting	100	0.5–1.5	2		
Boughton et al. 1995	3 Hv	200	1.9 (1.7–2.1)	3 (2–4)		
Eriksson et al. 1995	6 Hv, fasting	Capsule 100[a]	[a](*R*):0.7 (0.6–0.9) [a](S):0.5 (0.4–0.6)	[a](*R*):4 (3–5) [a](S):4 (3–5)		0–0.7 in 3/6
Piscitelli et al. 1997	5 P	Capsule 100	1.2 ± 0.2	3.4 ± 1.8	1.5 ± 0.9	0.3 ± 0.1
	4 P	Capsule 300	3.5 ± 1.1	3.4 ± 1.5	1.2 ± 0.7	0.3 ± 0.2
Eriksson et al. 1998b	6 Hv, fasting	Tablet 100	(*R*):0.5 (0.4–0.6) (S):0.3 (0.3–0.4)	(*R*):3.5 (3–6) (*S*):4 (2–6)		
Noormohamed et al. 1999	14 P, fasting	Capsule 100	1.15 ± 0.2	2.5 ± 1.5	0.95 ± 0.96	0.2 ± 0.2 in 7/14
		Capsule 200	1.9 ± 0.5	3.3 ± 1.4	1.2 ± 1.2	0.1 ± 0.2 in 4/14
Figg et al. 1999	13 P	200	2.0 (1.2–3.8)	3.3 (2.0–7.1)		
	11 P	800	4.4 (2.4–8.4)	4.4 (1.4–7.1)		
Trapnell et al. 1999	9 Hv, fasting	200, Day 1	3.2 ± 1.0	5.8		
		200, Day 21	4.2 ± 2.0	5.8		
Teo et al. 2000a	17 Hv, fasting	3 Different capsules	2.0 ± 0.5	3.2 ± 1.4		
			2.1 ± 0.5	3.5 ± 1.6		
			1.0 ± 0.3	3.4 ± 1.4		
Teo et al. 2000b	13 Hv, fasting	Tablet 200	1.05 ± 0.3	6.2 ± 1.9		
	Fasting	Capsule 200	2.0 ± 0.4	4.0 ± 1.1		
	High-fat meal	Capsule 200	2.2 ± 0.5	6.1 ± 2.3		
Celgene Corp. 2000	14 Hv	Capsule 50	0.6 ± 0.3	2.9 ± 1.9		
		Capsule 200	1.7 ± 0.5	3.5 ± 2.0		
		Capsule 400	2.8 ± 0.8	4.3 ± 1.6		
	6 P	Capsule 400	3.4 ± 1.8	5.7 ± 1.6		
Fine et al. 2000	34 P	800	4.1 (0.9–12)	4.7 (1.7–8.8)		

[a]Recalculated from a dose of 1.5 mg/kg

bioavailability in healthy subjects as described below (Eriksson et al. 2000a).

All of these studies are small and some of the findings might be explained by the methodological problems shown in Table 2. However, they do suggest that in some patients thalidomide may have a lower bioavailability than expected due to general malabsorption, nonlinear absorption of high doses or other reasons. If a high systemic exposure is crucial for disease control, then therapeutic drug monitoring could be of value.

Oral absorption of the separate enantiomers

Our group investigated the oral absorption of the separate enantiomers and the racemate in six healthy volunteers in a crossover study (Eriksson et al. 1995). The doses were 1.0 mg/kg (*R*)- or (*S*)-thalidomide or 1.5 mg/kg *rac*-thalidomide, given as capsules. There was a faster absorption of (*R*)- and (*S*)-thalidomide when given separately than when they were given as the racemate. This was probably due to a faster dissolution of the more water-soluble separate enantiomers. The AUC values from this oral study were compared with AUC values from a similar study in which the thalidomide enantiomers were given separately as an infusion (Eriksson et al. 2000a). This comparison suggested that the oral bioavailability of the enantiomers is high, possibly around 100% and 80% for (*R*)- and (*S*)-thalidomide, respectively.

Rectal absorption of *rac*-thalidomide

We investigated the rectal absorption of racemic thalidomide in healthy male volunteers (Eriksson et al.

Table 2 Background information for judgement of relevance of results from studies presented in Table 1

	Adequate precautions taken against hydrolysis of thalidomide in blood or plasma samples	Full description of used drugs and/or food	Relevant data on subjects and intake	Assay fully described and acceptable
Beckmann and Kampf 1961	?	No	No	Yes
Green and Benson 1961	?	No	No	Yes
Chen et al. 1989	No	Yes	Yes	Yes
Heney et al. 1991	?	Yes	Yes	No
Boughton et al. 1995	Yes	No	No	Yes
Eriksson et al. 1995, 1998b	Yes	Yes	Yes	Yes
Piscitelli et al. 1997	No	No	No	Yes
Noormohamed et al. 1999	Yes	Yes	Yes	Yes
Figg et al. 1999	No	No	No	Yes
Trapnell et al. 1999	Yes	Yes	Yes	Yes
Teo et al. 2000a, 2000b	Yes	Yes	Yes	Yes
Celgene Corp. 2000	?	No	No	No
Fine et al. 2000	Yes?	No	No	Yes

2000b). The drug was micronised, and hard fat suppositories and eldexomer rectal gel were tested compared with tablets produced by Grünenthal GmbH (Stolberg, Germany). The rectal absorption was slow and variable. The mean bioavailability relative to oral administration was below 40%. We concluded that rectal administration is not suitable for clinical use.

Distribution and elimination data referring to total concentrations of thalidomide

Pharmacokinetic parameters for distribution and elimination of thalidomide are available from several sources (Chen et al. 1989; Piscitelli et al. 1997; Figg et al. 1999; Noormohamed et al. 1999; Trapnell et al. 1999; Celgene Corp. 2000; Fine et al. 2000; Teo et al. 1999, 2000b) and are presented in Table 3. In most studies, thalidomide showed an apparent volume of distribution after oral administration (V/F) of approximately 1 l/kg bodyweight. Values of apparent oral clearance (CL/F) are also fairly consistent between studies. However, these numbers represent a composite of the distribution and elimination of both enantiomers (where distribution processes also include reversible inversion to the other enantiomer, see Eriksson et al. 2000a) and also assume complete bioavailability. They are therefore very "apparent" in nature. Thalidomide is eliminated almost exclusively by spontaneous hydrolysis in vivo. Hepatic metabolism and renal excretion play very minor roles in animals (Beckmann 1962; Williams et al. 1965; Schumacher et al. 1965b, 1968, 1970) and in man (Williams et al. 1965; Chen et al. 1989; Teo et al. 2000a). Animal experiments demonstrated that hydrolysis takes place in plasma and in all examined tissues (Schumacher et al. 1965b, 1968, 1970). From in vitro findings we have also suggested that hydrolysis would occur in the entire distribution space of the drug (Eriksson et al. 1998a).

As shown in Table 2 the handling of the blood samples in the first study (Chen et al. 1989) can be questioned. An additional problem in the assessment of distribution and elimination data is the blood-sampling protocol, with frequent samples taken over 12 h followed by only a single sample after 24 h. The range of apparent terminal half-lives of thalidomide in the subjects was 3.0–14.6 h. This might reflect experimental uncertainty rather than actual inter-individual variation. The finding of a low urinary excretion seems more reliable. Urine is normally slightly acidic and thalidomide would therefore be protected from hydrolysis in the samples. Moreover, in a previous study the amount excreted unchanged in the urine was 1, 2.2 and 1.8% in man, rats and dogs, respectively (Williams et al. 1965).

In the study of Piscitelli et al. (1997) the sampling schedule was better, but only three samples were taken after the 6-h sample (at 23, 27 and 31 h) and the range of the terminal half-lives was also very wide, 3.7–11.5 h. The same sampling schedule was used by Figg et al. (1999), yielding a similar wide range of measured terminal half-lives, 2.0–18.3 h after a 200 mg dose and 4.9–55.4 h after 800 mg. Similar problems apply for the study by Fine et al. (2000) with half-lives varying from 2.7 h to 27.9 h after a single oral dose of 800 mg and being 0.75–31.9 h after multiple daily doses of 800–1200 mg.

The variation in half-lives was generally not as pronounced in the later studies (Noormohamed et al. 1999; Trapnell et al. 1999; Teo et al. 1999, 2000b), in which the blood sampling can be judged to have been appropriate. The Thalomid product monograph (Celgene Corp. 2000) reports similar terminal half-lives at three dose levels (50, 200 and 400 mg) of thalidomide. Slow dissolution of thalidomide in the intestine can, however, apparently give rise to flip-flop pharmacokinetics, i.e. the observed terminal half-life represents absorption instead of elimination of thalidomide. This was observed by Figg et al. (1999) for a high dose (800 mg) of thalidomide and also by Teo et al. (1999, 2000b) for one of the three studied products (as a consequence, the calculations of V/F are

Table 3 Pharmacokinetic parameters for distribution and elimination of total concentrations or the separate enantiomers of thalidomide, obtained in different studies. *V/F* volume of distribution, *CL/F* apparent oral clearance, $t_{1/2}$ half-life, *MRT* mean residence time, *i.v.* intravenous

	Route, dose	V/F (l)	CL/F (l/h)	Renal CL/F (l/h)	$t_{1/2}$ (h)	MRT (h)
Chen et al. 1989	Oral, 200 mg	121 ± 45.4	10 ± 2.0	0.08 ± 0.03	8.7 ± 4.1	
Eriksson et al. 1995	Oral, 1 mg/kg	(*R*):48 ± 8.8 (*S*):72 ± 14			4.7 ± 0.4	
Piscitelli et al. 1997	Oral 100 mg 300 mg	88 ± 13 78 ± 22	9.2 ± 1.2 7.8 ± 1.8		6.5 ± 3.4 5.7 ± 0.6	
Noormohamed et al. 1999	Oral 100 mg 200 mg	70 ± 16 83 ± 35	10.4 ± 2.1 10.8 ± 1.7		4.6 ± 1.2 5.3 ± 2.2	
Figg et al. 1999	Oral 200 mg 800 mg	67 ± 34 166 ± 84[b]	7.4 ± 2.0 7.2 ± 2.9		6.5 ± 3.8 18 ± 14	
Trapnell et al. 1999	Oral 200 mg		5.4 ± 1.9[c] 4.1 ± 2.0[c]		6.7 ± 1.7[c] 6.8 ± 3.1[c]	
Teo et al. 1999	Oral, 3 Different capsules, 200 mg	89 ± 26 77 ± 13 (240 ± 79)[b]	10.5 ± 2.1 10 ± 1.4 11.4 ± 3.05		6.2 ± 2.6 5.4 ± 1.3 15 ± 6.0	
Celgene Corp. 2000	Oral 50 mg 200 mg 400 mg[a]				5.5 ± 2.0 5.5 ± 1.4 7.3 ± 2.6, 6.8 ± 1.2	
Fine et al. 2000	Oral 800–1200 mg[d]	(146 ± 92)[e] (124 ± 73)[e]	13.3 ± 7.8 12.6 ± 6.6		8.3 ± 6.0 8.3 ± 7.1	
Teo et al. 2000b	Oral 200 mg				13.5 ± 6.8[g] 5.8 ± 1.7[g] 5.1 ± 1.0[g]	21.4 ± 8.2[g] 10.4 ± 2.3[g] 10.9 ± 2.0[g]
Eriksson et al. 2000a	1-h i.v. infusion 50 mg		(*R*):10 ± 2.1[f] (*S*):21 ± 4.6[f]		4.7 ± 0.5	R:4.7 ± 0.7, S:3.9 ± 0.6

[a]Healthy subjects and patients, respectively
[b]Not a valid estimate, due to flip-flop pharmacokinetics (see text)
[c]During 21 days of treatment, day 1 and day 21, respectively
[d]After a single dose of 800 mg, and after multiple daily doses of 800–1200 mg, respectively
[e]Possibility of flip-flop pharmacokinetics after these high doses
[f]Apparent clearance from the central compartment, see Eriksson et al. 2000a for details
[g]Tablet fasting, capsule fasting and capsule after a high-fat meal, respectively

not valid in these cases). The study by Fine et al. (2000) also seems to suffer from these problems.

We found a lower inter-individual variability in half-lives than any of the other studies (Eriksson et al. 1995, 2000a). From a mechanistic point of view, a very low variability is expected.

Since, as discussed above, only pH and temperature affect the rate of hydrolysis of thalidomide it should be very similar between individuals. Provided that hydrolysis takes place uniformly in the body one would even expect that the in vivo half-life should be close to the value obtained with incubations in blood or plasma in vitro at 37 °C, pH 7.4, as well as to half-lives in animal studies. This has also been confirmed experimentally; the half-life of thalidomide was virtually the same in buffer at pH 7.4, in human blood and plasma and in rabbit liver homogenates as in vivo (Eriksson et al. 1995, 1998a, 1998b). It also corresponded well with apparent terminal half-life in rats, rabbits and monkeys (Schumacher et al. 1968, 1970).

In a multiple-dose study, 200 mg thalidomide was given daily for 21 days to ten healthy female patients. The pharmacokinetic profiles were similar on the first and the last days of dosing, which indicates that thalidomide does not induce or inhibit its own metabolism (Trapnell et al. 1999). This study also demonstrated a lack of drug-drug interaction between thalidomide and ethinyl estradiol or norethindrone.

Distribution and elimination of the enantiomers

We have found that the enantiomers of thalidomide are not extensively bound to blood or plasma components (Eriksson et al. 1998a). The geometric means (95% confidence limits) of plasma protein binding were 55% (53–58%) and 66% (63–69%), respectively, for (*R*)- and (*S*)-thalidomide. The corresponding blood:plasma distribution ratios were 0.86 (0.84–0.89) and 0.95 (0.92–0.98). Serum albumin, and to a lesser extent human plasma, catalysed the inversion but not the degradation at pH 7.4. Thus, we suggested that chiral inversion takes place chiefly in the circulation and in extravascular (interstitial) sites with a high concentration of albumin while it is slower in more peripheral sites of distribution. Rates of hydrolysis, however, were apparently only dependent on pH, giving us a rationale for the suggestion that hydrolysis would take place more uniformly in the entire distribution space of the drug.

Table 4 Relevant clinical pharmacokinetic data (median values) for (*R*)-and (*S*)-thalidomide. Volumes refer to central volumes after intravenous infusions (Eriksson et al. 2000a). C_{max} maximum plasma concentration, t_{max} time to C_{max}, GHVD graft-versus-host disease, CL_{app} apparent clearance, $t_{1/2}$ half-life, *MRT* mean residence time, *F* oral bioavailability, V_c central volumes

Absorption[a]	C_{max}: (*R*) 0.6 μg/ml, (*S*) 0.4 μg/ml
	t_{max} 4 h
	F: Probably high (80–100% at low doses)
	Presumably variable and delayed at high doses and in some patients with GVHD[e]
Distribution	V_c: (*R*) 18 l, (*S*) 24 l
	Plasma protein binding: (*R*) 56%, (*S*) 63%
	Blood: plasma distribution ratio (*R*) 0.84, (*S*) 0.96
Elimination	Metabolism: spontaneous degradation to 12 hydrolysis products[b]
	Low concentrations of hydroxylated metabolites (low ng range)
	No induction or inhibition of its own metabolism[d]
	Urinary excretion: presumably around 1%[c]
	CL_{app}: (*R*) 10 l/h, (*S*) 21 l/h
	MRT: (*R*) 4.7 h, (*S*) 3.9 h
	$t_{1/2}$ 5 h
	Effects of decreased hepatic or renal function: unlikely due to mechanism of elimination
Interactions	Affecting distribution: unlikely due to low binding to plasma and blood components
	Affecting elimination: unlikely due to mechanism of elimination. Shown not to occur with ethinyl estradiol or norethindrone[d]

[a]After an oral dose of 100 mg *rac*-thalidomide as tablets or capsules to fasting healthy volunteers, with a weight of approximately 70 kg
All data from Eriksson et al. except
[b]Schumacher et al. 1965a
[c]Chen et al.1989
[d]Trapnell et al. 1999
[e]Boughton et al. 1995 and Heney et al. 1991

Pharmacokinetic parameters for distribution and elimination of the enantiomers of thalidomide are available from our two human studies (Eriksson et al. 1995, 2000a), which are presented in Table 3. The (*R*)-enantiomer predominated at pseudoequilibrium [(*R*)/(*S*) ratio 1.7] irrespective of administered enantiomer or route. There was excellent agreement between the fitted terminal half-lives in the oral and the intravenous study (an example of this is shown in Fig. 2). This unequivocally confirms that the terminal half-lives found after oral administration represent elimination and not absorption of thalidomide. The volume of the central compartment and apparent clearance were significantly higher for (*S*)-thalidomide than for (*R*)-thalidomide.

Formation of hydrolysis products and metabolites

Twelve hydrolysis products have been identified in humans and as enzymatic hydroxylation is theoretically possible on five different carbon atoms more than 100 metabolites and degradation products (including stereoisomers) could be formed (Schumacher et al. 1965b). We detected 5′-hydroxythalidomide in low concentrations in plasma from eight healthy male volunteers who had received 100–200 mg thalidomide orally. However, 5-hydroxy-, 5,6-dihydroxy- or 4,5-dihydroxythalidomide could not be found using high-performance liquid chromatography (HPLC) with a detection limit of 1–2 ng/ml. 5-Hydroxy- and 5′-hydroxy- but not 4,5-dihydroxy- or 5,6-dihydroxy-thalidomide could be identified after in vitro incubation of thalidomide with human S9 liver homogenates (Eriksson et al. 1998b). Teo et al. (2000a) found 5-hydroxythalidomide (mostly concentrations below the limit of quantification, 50 ng/ml) but not 4- or *N*-hydroxythalidomide in urine from patients with leprosy who had received thalidomide as a single 400-mg dose. No metabolites could be detected in plasma, however, with a much higher limit of detection than in our study. They also studied metabolism of thalidomide in vitro, by incubation with pooled microsomes containing cloned human cytochrome P450 isoenzymes. It was concluded that thalidomide does not undergo significant metabolism by human cytochrome P_{450} and that clinically important interactions between thalidomide and drugs that are metabolised by this enzyme system are therefore unlikely. A summary of the relevant clinical pharmacokinetic data for the enantiomers of thalidomide, after administration of the racemate, is presented in Table 4.

Pharmacodynamics

Mechanism of action

The molecular mechanism for the effects of thalidomide still remains unclear (Günzler 1992; Calabrese and Fleischer 2000). Multiple anti-inflammatory and immunomodulatory effects have been shown both in vivo and in vitro (for reviews see Tseng et al. 1996 and Koch 1986). After the finding that thalidomide reduces tumour necrosis factor (TNF)-α production by enhancing the degradation of TNF-α mRNA (Moreira et al. 1993) with other cytokines remaining unaffected (Sampaio et al. 1991), several studies have focused on the effect of thalidomide on this cytokine. Elevated serum TNF-α levels

were reduced and clinical symptoms including wasting were improved after thalidomide treatment of patients with tuberculosis and HIV (Tramontana et al. 1995; Klausner et al. 1996) or ENL (Sampaio et al. 1993). However, doses of thalidomide that healed the oral aphthous ulcers in HIV-infected patients caused increased plasma TNF-α levels (Jacobson et al. 1997). In patients with minimally symptomatic HIV disease thalidomide induced weight gain. Plasma TNF-α levels were not remarkably elevated at baseline but there was a slight, but significant, upward trend in response to thalidomide (Haslett et al. 1997b). However, the authors stated that TNF-α may exert its influence on metabolic responses in an autocrine or paracrine manner in metabolically important tissues, and therefore plasma concentrations may not reflect concentrations at the site(s) of action.

Analogues of thalidomide with a high potency to inhibit TNF-α and a suggested potential to treat a number of inflammatory and autoimmune diseases have been synthesised (Muller 1997). These analogues have chiral centres which do not carry an acidic hydrogen and they are reported to be chirally stable in human plasma. Some of them were postulated to be nonteratogenic.

Effects of the separate enantiomers

The (*S*)-enantiomer has been reported to be the active form in the biological response-modifying effects of methylthalidomide (a stable thalidomide analogue, Nishimura et al. 1994) and (*S*)-thalidomide inhibits the TNF-α release from stimulated mononuclear blood cells, in vitro, significantly more than (*R*)-thalidomide at higher concentrations (Wnendt et al. 1996). Our group has reported that sedative effects in healthy volunteers correlated with (*R*)- but not with (*S*)-thalidomide concentrations after oral (Höglund et al. 1998) and intravenous doses (Eriksson et al. 2000a) of the separate enantiomers.

Effects of metabolites

There has been much speculation about metabolism being the basis for activation of thalidomide and the effects of *rac*-thalidomide compared with hydrolysed and hydroxylated species have been investigated in vitro and in vivo. Various effects on lymphocytes and on some tumour cells have been studied by means of in vitro incubations. It has been shown that presumably formed hydroxylated metabolites (from *rac*-thalidomide incubated with liver homogenates) are active whereas thalidomide (Gordon et al. 1981; Östraat et al. 1996) and hydrolysed products (Braun and Weinreb 1985; Shannon et al. 1997) are not. There is also evidence for a toxic arene oxide metabolite of thalidomide (Gordon et al. 1981). Although limb defects could not be produced in vivo in the rat foetus by thalidomide, limb buds were affected in vitro when a liver enzyme system from a thalidomide-sensitive animal (monkey) was present in the system (Shepard and Shiota 1983). This has been confirmed in later studies in which inhibition of angiogenesis by thalidomide required metabolic activation by human and rabbit microsomes and no effects were seen using rat microsomes (Bauer et al. 1998). Previously it was shown that in contrast to thalidomide none of the hydrolysed compounds appeared to be significantly embryotoxic in rabbits (Fabro et al. 1965). However, there is no proof that the hydrolysis products are not teratogenic. Rather, in view of their high polarity they may not be able to penetrate into the embryo (Williams et al. 1965) but might still be toxic after formation from thalidomide in situ.

Clinical use

Rac-thalidomide has shown good therapeutic effects, in multiple studies, in a variety of skin and mucous membrane disorders such as ENL, prurigo nodularis, actinic prurigo, discoid lupus erythematosus, aphthous stomatitis and Behçets disease (for a review see Tseng et al. 1996). Efficacy has also been shown in Crohn's disease (Ehrenpreis et al. 1999; Vasiliauskas et al. 1999) and in chronic and acute GVHD after bone marrow transplantations (Heney et al. 1991; Vogelsang et al. 1992; Cole et al. 1994; Parker et al. 1995). However, it was also demonstrated that prophylaxis of chronic GVHD with thalidomide resulted in a higher incidence of chronic GVHD and lower overall survival (Chao et al. 1996). Efficacy has been seen in single studies or case reports in a number of diseases related to immunodysregulation and inflammation (for a review see Tseng et al. 1996).

Recently thalidomide has been documented in randomised, double blind, placebo-controlled studies for the treatment of wasting (Klausner et al. 1996; Reyes-Terán et al. 1996; Kaplan et al. 2000) and aphthous ulcerations (Jacobson et al. 1997, 1999; Ramirez-Amador et al. 2000) in advanced HIV infection.

Thalidomide also has antiangiogenic properties (D'Amato et al. 1994) and was tested against a variety of solid tumours such as metastatic breast cancer, astrocytomas, Kaposi's sarcoma and prostate cancer in clinical trials sponsored by the National Cancer Institute of the United States (Phillips et al. 1996). Some of the studies published recently show promising results but are lacking control groups. In a study on AIDS-related Kaposi's sarcoma, 7 of 18 patients had partial response (Little et al. 2000). A study on metastatic breast cancer patients comparing low and high dose showed no true partial or complete response (Baidas et al. 2000). Among 39 patients with recurrent high-grade glioma, four responded (Fine et al. 2000). Continuous low-dose thalidomide treatment (100 mg) gave partial response in 3 of 18 patients with renal cancer, but no objective response in advanced melanoma, ovarian or breast cancer

(Eisen et al. 2000). In refractory multiple myeloma 25 of 84 patients responded (Singhal et al. 1999). It has been suggested that thalidomide represents an important advance in the treatment of myeloma, and a review of the angiogenesis and antiangiogenic therapy with thalidomide in multiple myelomas has recently been published (Rajkumar and Witzig 2000).

Adverse effects

According to a very recent review of the first 18 months of spontaneous post-marketing surveillance, the adverse event pattern was as expected from previous experiences. The most common adverse events were somnolence, asthenia, rash, peripheral oedema, paresthesia, dizziness, constipation, dyspnoea and leucopenia (Clarke et al. 2001). The most frequently observed adverse effects are related to the sedative action which appears to be dose-related. This is in keeping with the observation that these effects correlate with (*R*)- but not with (*S*)-thalidomide concentrations (Höglund et al. 1998; Eriksson et al. 2000a). Drowsiness, dizziness and mood changes occurred in 33–100% of all patients. Loss of libido, nausea, pruritus, hypothyroidism, serious dermatological reactions including Steven-Johnson syndrome and menstruation abnormalities have been occasionally observed (Günzler 1992). Also possible thromboembolic adverse events, risk of seizure activity, neuropsychiatric events, impaired wound healing (possibly related to antiangiogenesis) could cause problems in special patient groups (Clarke et al. 2001).

There is an increased potential for toxicity in patients with HIV infection and 20 of 56 patients developed cutaneous and/or febrile reactions after a mean of 10 days of treatment with thalidomide. Forty-three percent of the patients discontinued therapy within 2–3 weeks (Haslett et al. 1997a).

Thalidomide can cause toxic peripheral neuropathy, which can sometimes be irreversible (Wulff et al. 1985). Incidences of 21–50% have been reported in recent studies after treatment of up to 5 years (Ochonisky et al. 1994b; Harland et al. 1995). It is not clear whether the development of neuropathy is dose dependent (Ochonisky et al. 1994b) although some reports indicate a relationship to total dose (Wulff et al. 1985). Changes in nerve conductivity are frequent and unpredictable adverse effects of thalidomide. Nerve conduction studies are required before and during the treatment, irrespective of prescribed dose (Harland et al. 1995).

Known or possible pregnancy is of course an absolute contraindication to the use of thalidomide. The period during which the embryo is susceptible to the teratogenic effect of thalidomide was determined to be from day 34 to day 50 after the beginning of the last menstrual period. A single dose of thalidomide may be sufficient for inducing malformation (Neubert and Neubert 1997).

Dosage and administration

Concentration–effect studies for thalidomide are lacking and dosing regimens have been based on early clinical studies and case reports, rather than on its pharmacokinetic or pharmacodynamic behaviour. The therapeutic dose of *rac*-thalidomide is normally 50–400 mg/day divided into one or two doses (Ochonisky et al. 1994; Tseng et al. 1996). In GVHD, doses of up to 1600 mg/day (divided into four doses) were used when aiming for peak plasma concentrations of at least 5 μg/ml, 2 h after dosing. The rationale for this dosing regimen was an animal model in which this concentration was necessary to produce a maximum response (Vogelsang et al. 1992). Another author aimed at concentrations of 1.5–3.0 μg/ml without giving a rationale for the schedule or stating to which time point after drug administration the target concentration refers (Cole et al. 1994).

The dose–effect relationship for thalidomide in man has been described in only two studies. In one study (Hamauryudan et al. 1998) patients with mucocutaneous lesions of the Behçet syndrome were treated with thalidomide 100 mg, 300 mg or placebo in a double-blind fashion over 24 weeks. It was concluded that the thalidomide treatment was effective and that a dosage of 100 mg/day was as effective as a dosage of 300 mg/day. In the second study (Kaplan et al. 2000) a total of 105 patients with HIV-associated wasting were treated with thalidomide 100 mg, 200 mg or placebo for 8 weeks using a double-blind protocol. A dose of 100 mg induced more weight gain than a 200-mg dose. However, the comparisons were hampered by drug intolerance (somnolence, fever and rashes) and a high level of drop-outs especially in the 200-mg thalidomide group.

We computer-simulated blood concentration curves for total thalidomide after various oral doses of *rac*-thalidomide using the SAS software (SAS Institute, Cary, N.C., USA). A one-compartment model was used and rate of absorption (k_a), CL/F and V/F were set at 1.18/h, 0.120 l/h×kg and 1.05 l/kg, respectively. Simulated blood concentrations using different dosing schedules are shown in Table 5. These data are based on results obtained in our study (Eriksson et al. 2000b) in which *rac*-thalidomide 100 mg (tablets from Grünenthal GmbH, Germany) were given to fasting healthy male subjects (70–94 kg). They may not be immediately applicable to other preparations, to very high doses where

Table 5 Predicted blood concentrations (minimum and maximum at steady state) of thalidomide (μg/ml) with different dosing schedules for a 70-kg person

Dose	1 Daily dose	2 Daily doses	3 Daily doses	4 Daily doses
50 mg	0.05, 0.6	0.2, 0.8	0.5, 1.0	0.7, 1.2
100 mg	0.1, 1.2	0.5, 1.5	1.0, 1.9	1.5, 2.3
200 mg	0.2, 2.3	1.0, 2.9	2.0, 3.7	3.0, 4.6
400 mg	0.3, 3.4	2.0, 5.8	4.0, 7.5	6.1, 9.2

the low solubility of thalidomide could affect the rate and extent of oral absorption and to some disease states with general malabsorption. However, the table can be used as a guide to assess whether the systemic exposure of thalidomide is as expected based on the dose and the patient's weight.

Especially due to the risk of neuropathogenicity the lowest possible dose of thalidomide is often given and preferably once daily at night because of the sedative effect. Once-daily dosing has been used successfully during maintenance therapy in several disease states (Tseng et al. 1996).

Thalidomide is available only as tablets or capsules of *rac*-thalidomide. As described above, rectal administration forms have not been found suitable for clinical use. An intravenous preparation of thalidomide would be of clinical interest due to the sometimes variable absorption described above (Krenn et al. 1992; Ehninger et al. 1993; Boughton et al. 1995) and in disease states where the patients need an alternative to oral formulations due to nausea, oral pain or other swallowing problems (Krenn et al. 1992; Jacobson et al. 1999). The development of an intravenous formulation of *rac*-thalidomide is problematic due to its poor solubility and rapid degradation in aqueous media (Krenn et al. 1992). Recently we developed a chemically stable solution for intravenous infusion of the separate enantiomers of thalidomide (Eriksson et al. 2000a). The solution consists of 200 mg/l of either thalidomide enantiomer in a 5% glucose solution of pH 4–5.

Putative benefits of using a separate enantiomer

Putative differences between the enantiomers in therapeutic or adverse effects would to a large extent be abolished by their fast chiral inversion in vivo. The teratogenic effect could therefore not have been avoided with the use of the pure (*R*)-enantiomer. However, if the anti-inflammatory and immunomodulating effects of thalidomide are due to the (*S*)-enantiomer, as suggested by some findings (Nishimura et al. 1994; Wnendt et al. 1996) but definitely not proved in clinical studies, use of this single enantiomer can be suggested for the following reasons:

1. The enantiomers have a higher aqueous solubility than the racemate, which would give a faster and probably more reliable oral absorption (Eriksson et al. 1995, 2000a).
2. (*R*)-thalidomide is responsible for the sedative effects (Höglund et al. 1998; Eriksson et al. 2000a), which constitute an important problem especially among patients prescribed high and/or multiple daily doses of *rac*-thalidomide (Günzler 1992; Parker et al. 1995).

The exposure to (*R*)-thalidomide was reduced by about 50% when (*S*)-thalidomide was given, compared with when the racemate was given (Eriksson et al. 1995).

Suggested need for future studies

Since administration of the presumably active (*S*)-enantiomer would probably reduce the problems with sedation it would seem logical to study (*S*)-thalidomide with the racemate as a comparator. This would apply in particular to patients taking multiple daily doses and to those with possible problems with oral absorption, e.g. patients suffering from chronic GVHD.

There is a need to identify the active disease-modifying component or components after administration of thalidomide to humans. There is also a need for traditional basic dose–effect studies, including low doses, for various disease states. Therapeutic drug monitoring of individual patient and concentration–effect studies of thalidomide (and the disease-modifying components) could possibly explain why some patients respond, some experience adverse reactions and some experience very limited effects.

Appendix

Handling of blood samples for determination of thalidomide or its enantiomers (Eriksson et al. 1997)

1. Add 2.00 ml 25 mmol/l citrate buffer (pH 1.5) to 10-ml glass-stoppered extraction tubes.
2. Collect blood in evacuated tubes containing an anticoagulant agent (heparin).
3. Without delay, transfer 2.00 ml blood to each extraction tube, and mix immediately.
4. As soon as possible freeze and store at –25 °C.
5. Analyse all samples within 75 days.

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