Chapter A

Thalidomide in Mann’s Pharmacovigilance

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BACKGROUND AND SUMMARY

Thalidomide was marketed in 1957 as a very safe sedative drug. But the clinical safety documentation was very poor and more than 10,000 malformed children were born before withdrawal from the market in 1961. The lessons from the thalidomide story have had very strong impact on drug development, the drug regulatory process, and on the science and application of pharmacovigilance. Today, thalidomide is back on the market for treatment of specific life-threatening conditions and with a specific follow-up system to avoid malformations. The aim of this chapter is to tell the thalidomide story in a scientific perspective based on chemical and biomedical aspects of the molecule and on the pharmacology and use. This journey is documented in several hundred publications. Therefore, reviews are normally used instead of original references, except for the most paramount and recent publications.

HISTORICAL PERSPECTIVE

Thalidomide was synthesized in 1954 by Kunz, a chemist at Chemie Grünenthal (Kunz, 1956). Whilst the postulated antihistaminic properties for which it was synthesized 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. This is the background for the thalidomide story, by far the most frightening in the drug development and pharmacovigilance history. It contains initial high hopes of being able to replace barbiturates (a dangerous and at that time widely used class of drugs), approval without proof of efficacy and safety, “marketing patient experiments,” early suspicion of very serious side effects, neglect of these allegations from the pharmaceutical industry, poor communication between and within agencies and businesses, slow withdrawal of product from some markets, law suits and claims of victims,
safety and toxicity data for the application and insisted on this. About a year later, phocomelia, a severe birth defect in which infants are born without limbs or with severely deformed limbs, was linked to the use of thalidomide use during pregnancy. The drug was withdrawn from the market, but its use had resulted in more than 10000 victims of malformation with abnormalities such as phocomelia (short limbs), amelia (absence of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).

After the first suspicion of malformations, from Dr Lens’s case–control study and presentation at a national congress and Dr McBride’s report, Chemie Grünenthal finally took the drug from the German market in November 1961, after a few weeks’ heavy debate in scientific journals and newspapers (Lenz, 1988; Yllner, 2007). Still the company refused to accept the connection between the drug and malformations, and it was still sold in 30 countries. One reason for the slow withdrawal in some countries was that it was sold using different names. At least 60 different names were used worldwide. So when the reports from Germany and Australia came, some countries did not react since that drug name was not used in that country. In Germany, the best known name was Contergan, in the UK and Australia Distaval, and in USA and Canada Kevadon.

Thalidomide was not marketed in the USA but had been distributed to 1267 doctors, and was given to more than 20000 patients as an “experiment.” There are 17 confirmed and 9 likely cases of thalidomide phocomelia according to the FDA (Hilts, 2006). Dr Kelsey’s refusal to approve the application probably saved thousands of US children from malformation, and for this she has been honoured with several awards (Kuehn, 2010). It also had a profound effect on the drug regulatory process (Kelsey, 1988; Hilts, 2006).

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). After this finding there has been a renewed clinical interest in thalidomide, due to its anti-inflammatory, immunomodulatory, and anti-angiogenic effects, and it has been tested for several disease states during the last decades (Franks et al., 2004). Today, it is again marketed and used for specific conditions and with special

<p>| Box A.1 Important Historical Data for Thalidomide |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1954</td>
<td>Synthesized at Chemie Grünenthal GmbH, West-Germany</td>
</tr>
<tr>
<td>1957</td>
<td>Marketed as a sedative (and for morning sickness in pregnancy) in Europe</td>
</tr>
<tr>
<td>1960</td>
<td>Marketed in 46 countries The sales in Germany 290 million doses (50 mg), sold free of prescription (Lenz 1988) Report of neurotoxicity (Florence, 1960)</td>
</tr>
<tr>
<td>1961</td>
<td>Suspicion of link between births of children with severe malformations and consumption of thalidomide during the first trimester of pregnancy by Dr McBride in Australia and by Dr Lenz in Germany (McBride, 1961; Lenz, 1988) Withdrawn from most markets</td>
</tr>
<tr>
<td>1965</td>
<td>First report of remarkable effects in the treatment of ENL, a complication of leprosy (Sheskin, 1965)</td>
</tr>
<tr>
<td>1967–1970</td>
<td>National lawsuits and settlements for victims</td>
</tr>
<tr>
<td>1997</td>
<td>Approved for use in the USA for ENL</td>
</tr>
<tr>
<td>2006</td>
<td>Approved for use in the USA for multiple myeloma</td>
</tr>
<tr>
<td>2008</td>
<td>Approved for use in the EU for multiple myeloma (orphan medicinal product)</td>
</tr>
</tbody>
</table>
The mechanisms behind the multiple anti-inflammatory, immunomodulatory, and anti-angiogenic effects are also unclear (Eriksson, et al., 2001; Franks et al., 2004). Tumour necrosis factor alpha (TNF-\(\alpha\)) is a cytokine regulating inflammation. After the finding that thalidomide reduces TNF-\(\alpha\) production by enhancing the degradation of TNF-\(\alpha\) 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, but also on modulation of selected cell surface adhesion molecules involved in leukocyte migration.

**EFFECTS AND TOXICITIES**

**MECHANISM OF ACTION**

Researchers have been investigating the molecular mechanism of action for the teratogenic and therapeutic effects of thalidomide for 50 years. Still we do not have the answers. This is important for elimination of side effects in the development of new compounds, and for understanding of mechanisms of limb development.

More than 30 hypotheses have been proposed to explain how thalidomide causes limb defects (Stephens, 1988; Stephens and Fillmore, 2000; Vargesson, 2009; Ito et al., 2011). It includes the disruption of molecular pathways, including DNA intercalation, acetylation of macromolecules, interference of glutamate metabolism, and folic acid antagonism. In recent years the focus for teratogenesis has been on oxidative stress (mediated through NF-\(\kappa\)B induce programmed cell death) and anti-angiogenesis (mesenchymal loss due to downregulation of growth factors). Recently, it has been suggested that the anti-angiogenesis activity is the primary cause of chick limb malformations (Therapontos et al., 2009) and also that a thalidomide binding protein, cereblon, is the primary target for thalidomide teragenicity (Ito et al., 2010). However, the existing hypothesis cannot explain all aspects of thalidomide teragenicity (Vargesson, 2009; Ito et al., 2010).

Thalidomide (\(\alpha\)-phthalimidoglutaramide) (Figure A.1) has a chiral center and is used as a racemate (1:1 mixture) of dextrorotatory (\(R\))- and levorotatory (\(S\))-thalidomide. A chiral, or handed, molecule has a carbon atom that carries four different substituents. It does not have a plane of symmetry, and has two non-superimposable mirror images of the molecule, called enantiomers. The enantiomers possess identical physical properties, except that they rotate polarized light in opposite directions, as referred to by the nomenclature (+) and (−). The \(R\) (rectus = right) and \(S\) (sinister = left) nomenclature refer to the absolute configuration.

There have been several studies focusing on the search of the enantiomer or molecule responsible for therapeutic, teratogenic, or other effects. There is some evidence that \((S)\)-thalidomide is responsible for the therapeutic and teratogenic effects and that \((R)\)-thalidomide is responsible for the sedative effects. However, putative differences between the enantiomers in therapeutic or adverse effects would to a large

![Stereochemical structures of \((R)\)- and \((S)\)-thalidomide. (Eriksson 2001). Reproduced with permission of Springer.](image-url)
Multiple myeloma, over 65 years or ineligible for high-dose chemotherapy. In the USA it is also approved for ENL.

A recent systematic review of multiple myeloma treatment states that thalidomide is associated with improved survival when added to standard chemotherapy regimens as induction or maintenance therapy, but at the expense of an increased risk of serious adverse events, such as venous thromboembolism (Kumar et al., 2011). High-dose therapy with single autologous hematopoietic stem cell transplant (AHCT) is associated with superior event-free but not overall survival compared with chemotherapy. Tandem AHCT does not prolong survival but is associated with better event-free survival in comparison with single AHCT. In addition, combination treatment with bisphosphonates reduces pathological vertebral fractures and pain, but does not prolong survival (Kumar et al., 2011).

Thalidomide is first-line therapy for symptomatic, moderate-to-severe ENL, and can be used for the suppression and prevention of cutaneous disease (Teo et al., 2002). Thalidomide is also used off-label for aphthous stomatitis, Behçet’s disease, lupus erythematosus, prurigo nodularis, sarcoidosis, actinic prurigo, graft-versus-host disease (GVHD), Langerhans cell histiocytosis, erythema multiforme, lichen planus, Kaposi sarcoma, Jessner lymphocytic infiltrate, uremic pruritus, pyoderma gangrenosum, scleroderma, scleromyxedema, and necrobiosis lipoidica (Chen et al., 2010).

Several reviews of clinical applications and studies have been published (Tseng et al., 1996; Eriksson et al., 1992; Eriksson and Björkman, 1997). The rates of inversion and hydrolysis of the enantiomers increase with pH in the interval 7.0–7.5 (Eriksson et al., 1998a), and proper handling of solutions and biological samples of thalidomide and its enantiomers is crucial to avoid hydrolysis and chiral inversion (Eriksson and Björkman, 1997).

**TODAY’S CLINICAL USE**

**APPROVED AND EXPERIMENTAL USE**

Today, thalidomide is approved for use in the EU and USA in combination with melphalan and prednisone as first-line treatment of patients with untreated multiple myeloma, over 65 years or ineligible for high-dose chemotherapy. In the USA it is also approved for ENL.

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There has been much speculation about metabolism being the basis for activation of thalidomide and the effects of rac-thalidomide compared with hydrolyzed and hydroxylated species have been investigated in vitro and in vivo. It has been shown that presumably formed hydroxylated metabolites, are active whereas thalidomide and hydrolyzed products are not. There is also evidence for a toxic arene oxide metabolite of thalidomide. Although limb defects could not be produced in vivo in the rat fetus by thalidomide, limb buds were affected in vitro when a liver enzyme system from a thalidomide-sensitive animal (monkey) was present in the system. This has been confirmed in later studies where inhibition of angiogenesis by thalidomide required metabolic activation by human and rabbit microsomes and no effects were seen using rat microsomes. Very recently, thalidomide and two hydrolysis products demonstrated limb bud embryopathies in a mammalian embryo culture model of a species susceptible to thalidomide in vivo (Lee et al., 2011).

The (S)-enantiomer has been reported to be the active form in the biological response-modifying effects of methylthalidomide (a stable thalidomide analog) and (S)-thalidomide inhibited the TNF-α release from stimulated mononuclear blood cells, in vitro, significantly more than (R)-thalidomide at higher concentrations. There were similar teratogenic effects seen in rabbits given the separate enantiomers orally, and dose-dependent teratogenicity in mice and rats only from the (−)-(S)-enantiomer after intraperitoneal injection. In animal models of GVHD, (−)-(S)-thalidomide was superior to (+)-(R)-thalidomide in preventing splenomegaly in chicken embryos, but no differences were seen in rats between the enantiomers. The sedative effects in healthy volunteers correlated with (R) but not with (S)-thalidomide concentrations after oral and intravenous doses of the separate enantiomers (Eriksson et al., 2000a; Höglund et al., 1998).

The observed differences in species susceptibility to the teratogenic effects could result from differences in biotransformation, observed in vivo and in vitro, in liver homogenates. Low concentrations of 5′-hydroxy thalidomide have been found in human plasma, the 5-hydroxy metabolite in human urine, and both in human liver homogenates (Eriksson et al., 1998b; Teo et al., 2000).

The CYP450 enzymes responsible for thalidomide hydroxylation have been identified, and there is increasing evidence that interspecies differences in metabolism account for the species specific biological effects of thalidomide that have been observed (Lepper et al., 2004). There is evidence that 5′-OH-thalidomide produced by CYP2C19 may contribute to the antiangiogenic activity of the parent drug in vitro, albeit at high concentrations. However, since thalidomide appears to be a relatively poor CYP450 subtype and levels of 5′-OH in patients are low or undetectable, the question of whether this metabolite is solely or at all responsible for the clinical effects of thalidomide is debatable. Furthermore, all other currently known metabolites have proved to be inactive (Lepper et al., 2004).
normally 50–400 mg/day divided into one or two doses. In particular 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. If sedation is a problem, the dose is best given at night (Eriksson et al., 2001).

Commercially, thalidomide is available only as oral solid formulations (tablets or capsules). The rectal absorption was slow and variable (Eriksson et al., 2000b). The mean bioavailability relative to oral administration was below 40% and not suitable for clinical use. Also, in some patient groups oral absorption can be a problem (Eriksson et al., 2001). Stable intravenous formulations have been developed and given to humans (Eriksson et al., 2000a).

The clinical pharmacology of thalidomide has recently been extensively reviewed (Eriksson et al., 2001). The enantiomers of thalidomide undergo spontaneous hydrolysis and 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 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 for the (R)-enantiomer and 21 L/h for the (S)-enantiomer in adults. Blood concentrations of the (R)-enantiomer are consequently higher than those of the (S)-enantiomer at pseudo-equilibrium. 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 (Eriksson et al., 2001).

CYP2C19 has been shown to be primarily responsible for the active metabolism of thalidomide, and polymorphism in CYP does not dictate response to thalidomide (Lepper et al., 2004). There is no reason for dose changes with thalidomide in the presence of decreased kidney function (Eriksson et al., 2003). There is also normally no need for a supplementary dose due to hemodialysis, although clearance is doubled during dialysis.

ADVERSE EFFECTS

Side effects of thalidomide therapy have been extensively reviewed (Eriksson, 2006). According to a review of the first 18 months of spontaneous postmarketing surveillance after thalidomide’s approval for ENL in the USA, the adverse event pattern was as expected from earlier experiences. The most common adverse events were somnolence, asthenia, rash, peripheral edema, 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. Drowsiness, dizziness, and mood changes occurred in 33–100% of all patients. Loss of libido, nausea, pruritus, hypothyroidism, serious dermatological reactions, including Stevens–Johnson syndrome, and menstruation abnormalities have been occasionally observed previously (Günzler, 1992). Also, possible thromboembolic adverse events, risk of seizure activity, neuropsychiatric events, and impaired wound healing could cause problems in special patient groups (Clarke et al., 2001).

There is an increased potential for cutaneous and/or febrile reactions in patients with HIV infection (Haslett et al., 1997). Combination of thalidomide and some chemotherapies raises the risk of deep vein thrombosis (Franks et al., 2004). Patients with newly diagnosed multiple myeloma treated with thalidomide in combination with dexamethasone have a risk of 4.1 per 100 patient-cycles (Carrier et al., 2011). Rash is also potentiated when thalidomide and steroids are combined. Docetaxel and thalidomide use in patients with prostate cancer is associated with additional pulmonary toxicity. Complications with combination treatments have also been reported, such as toxic epidermal necrosis, severe hepatic toxicity hypothyroidism, bradycardia, and poor CD34+ cell mobilization with stem-cell procurement.

TERATOGENIC EFFECTS

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 (Neubert and Neubert, 1997). A single dose of thalidomide may be sufficient for malformation. The majority of malformations from tha-
There is a recent report that an individual’s risk of developing a peripheral neuropathy after thalidomide treatment can be mediated by polymorphisms in genes governing repair mechanisms and inflammation in the peripheral nervous system (Johnson et al., 2011). There are no reports on the relative activities of the separate enantiomers, or hydrolyzed or hydroxylated metabolites of thalidomide.

Nerve conduction studies are required before and during the treatment, irrespective of prescribed dose (Harland et al., 1995). Peripheral nerve function should be closely monitored through review of symptoms, regular neurologic examinations, and periodic screening of sensory nerve electrophysiology (Apfel and Zochodne, 2004). When evidence of neuropathy appears, consideration should be given to discontinuing thalidomide. The decision should be made on an individual basis and should consider the seriousness and severity of the underlying condition and the severity of the neuropathy (Apfel and Zochodne, 2004).

In recent years, thalidomide has become widely incorporated in front-line myeloma treatment, either in combination with high-dose dexamethasone-based regimens, in preparation for autologous transplantation, or with low-dose melphalan and prednisone, in elderly or frail patients (Delforge et al., 2010). Despite better awareness of neurotoxicity, peripheral neuropathy is still reported in up to 50% of patients. However, important progress has been made, and severe grades have dropped below 10%.

Calculation of a total neuropathy score helps to ascertain proper dosing so as to prevent permanent nerve damage (Molloy et al., 2001). Although the sensory nerve action potential (SNAP) can be used for monitoring peripheral neuropathy, it cannot be used for early detection.

**REGULATORY PROCESS AND PHARMACOVIGILANCE**

Pharmacovigilance is the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities. The prerequisite for this to be effective is that approved drugs have proven efficacy and safety before marketing. As described previously, this was not the case for thalidomide. Because of Dr Kelsey it was not approved for use in

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It is unfortunately true, as the thalidomide incident so well illustrates that the drug industry does not now always adhere to high standards, either in planning or in investigation, selecting the investigators, or providing the investigators with full information about the hazards, the proposed regulations would change this. And they would have made it impossible for Richardson–Merrell to distribute millions of tablets to physicians who made no pretense of being investigators.

TOWARDS MODERN CLINICAL TRIALS

Philip J. Hilts has presented the story behind the birth of clinical trials as follows. The law passed in 1962 laid out a rational system for drug testing. The previous law had said that companies could sell drugs at will unless the FDA objected, on the basis of data submitted by the sponsor, within 60 days of being notified that a drug was to be marketed. The power rested with the companies, and the burden with the FDA. The tests of safety for any drug were vague, and the standards generally quite low. The new law reversed that. The new law put into writing that companies wanting to sell new drugs should show that they can be used safely and that they worked for the stated purposes. “Experiments” like the thalidomide distribution in America were prohibited; doctors and companies would now be required to keep records of what they gave to patients in experiments; and the patients must give their consent. The key result was that the FDA would be more closely involved in oversight.

The few words in Section 505 set the basic standards for evidence. The law said that safety and effectiveness should be shown by “adequate” investigations, meaning large and numerous enough studies. The studies had to be “well controlled,” meaning testimonials and unverified results would no longer suffice. “Controlled” meant the studies should include comparisons of patients who took the treatment with those who did not. It took some time for the full effect of this line in the law to be felt. Opinion was out; science was in; and companies and the FDA together would have to literally create a set of standards for what makes a good clinical experiment. It took more than a decade for the industry and the FDA to establish in discussion and in practice just what practical rules would fulfill the language; it was the birth of the modern clinical trial (Hilts, 2006).

Could the thalidomide disaster have been prevented? Probably not quite, as thalidomide birth defects are not detected even by today’s tests. But the scale would probably have been reduced to a few cases in the pharmacovigilance system we have today with spontaneous reporting, records for prescribing, dispensing, and birth defects. Physicians also typically use only drugs that are classified as safe for birth defects in pregnant women.

PRECAUTIONS

Thalidomide is prescribed and dispensed according to a specific Thalidomide Pregnancy Prevention Program (EMA, 2011; FDA, 2011). This program must be fulfilled for male and female patients and their partners as well as for the responsible prescriber and dispensing pharmacist. It includes educational material and a requirement focusing on all putative risks for malformation, including handling of the medication, methods for contraception, and pregnancy testing. In the USA this program is named STEPS (System for Thalidomide Education and Prescribing Safety) and was initiated by the manufacturer of thalidomide (Zeldis et al., 1999).

Because of the teratogenic potential of thalidomide, the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) consulted representatives of thalidomide victims and myeloma patient groups from across the EU to develop measures that can effectively minimize the risk of fetal exposure to thalidomide (EMA, 2008). After discussions, the CHMP has approved a risk management plan that includes a number of actions intended to prevent pregnancies in women being treated with thalidomide and exposure of unborn children to the medicine. One of the consequences from the discussion with the victims’ organizations was that the same name should be used in all European countries and
that it should start with Thalidomide to avoid some of the mistakes from the 1960s described above.

The risk minimization plan developed during the thalidomide approval process can be used also for other drugs and various purposes and risk in future approval of drugs, and can be considered a new strategy for pharmacovigilance.

NEW TERATOGENIC THALIDOMIDE DERIVATES: IMMUNOMODULATORY DRUGS

New thalidomide derivatives belonging to a new group of immunomodulatory drugs (IMiDs) have been developed (Ito et al., 2011). Among them, lenalidomide and pomalidomide have potent pharmacological effects. Lenalidomide is effective for the treatment of myeloma, myelodisplastic syndrome (MDS), chronic lymphocytic leukemia, non-Hodgkin’s leukemia, and solid tumors, and has been approved for the treatment of multiple myeloma and 5q-MDS in the USA and the EU. This risk management plan is mandatory also for lenalidomide.

REFERENCES
