

Thalidomide

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Abstract

A drug sold during 1950s and 1960s was withdrawn from the market due to its teratogenic effect. Thanks to ever open mind of researchers that it was tried on multiple myeloma and was approved for its use in multiple myeloma as well as other diseases. The drug Thalidomide is reviewed for its new use.

Introduction

Thalidomide was first introduced in 1957 primarily as a tranquillizer, a medication prescribed particularly for imparting drowsiness and sleep. Then, it was given to pregnant women to provide them with relief from morning sickness. Soon after being prescribed to pregnant women, thalidomide was linked to death or severe disabilities in newborns. Some children who had been exposed to thalidomide while in the womb (in utero) failed to develop limbs or had very short limbs. Others were born blind or deaf or with other physical problems (Fig. 1).^{1,2}

Chemical Formula (Fig. 2)

Thalidomide is a sedative, hypnotic, and multiple myeloma medication. The drug is a potent teratogen in rats, rabbits, non-human primates and humans.¹ Thalidomide was developed by German pharmaceutical company Grünenthal. It was sold from 1957 to 1961 in almost 50 countries under at least 40 names, including Distaval, Talimol, Nibrol, Sedimide, Quietoplex, Contergan, Neurosedyn, and Softenon. Thalidomide was chiefly sold and prescribed during the late 1950s and early 1960s to pregnant women,

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Fig. 1

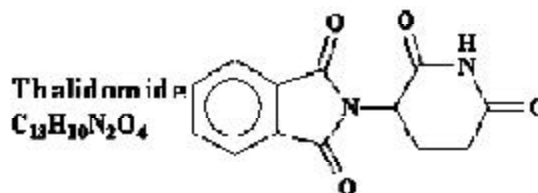


Fig. 2

as an antiemetic to combat morning sickness and as an aid to help them sleep. Before its release inadequate tests were performed to assess the drug's safety, with catastrophic results for the children of women who had taken thalidomide during their pregnancies.^{1,2}

History

A German pharmaceutical company, Chemie Grünenthal at Stolberg, synthesized thalidomide in West Germany in 1953 while searching for an inexpensive method of manufacturing antibiotics from peptides. By heating phthaloylisoglutamine, the company's chief researcher produced phthalimidoglutaramide, which they soon

labelled 'thalidomide'. Chemie Grünenthal patented the molecule and began searching for disease thalidomide could cure.

The Grünenthal scientists could not find any antibiotic activity, or any other encouraging effects, in mice and rats. However, the new chemical seemed to be harmless; high doses did not kill rodents, rabbits, cats or dogs, nor show any other side effects. The research team began to describe thalidomide as "nontoxic" and Grünenthal began to consider the lucrative prospects of their new find. Although no sedative or tranquillizing effects were observed in animals, Grünenthal management considered "a nonlethal sedative would have enormous market potential".

With no teratogenicity tests (tests on pregnant animals), no clinical trial plans, and no scientific rationale, Grünenthal began distributing free samples of thalidomide to doctors in Switzerland and West Germany in 1955. It was first recommended for the prevention of seizures in patients with epilepsy; although no anticonvulsant effect was found, patients reported experiencing a deep sleep. Other patients said they felt calming and soothing effects. Some reported side effects, but they were not believed to be serious.⁴ One author later said that "Thalidomide was introduced by the method of Russian Roulette. Practically nothing was known about the drug at the time of its marketing".⁵

The sedative effects had not been seen in animals, so the Grünenthal scientists came up with a "jiggle cage" to measure the movements of mice to see if treated mice "jiggled" the cage less than non-treated mice. Grünenthal also pointed out that their "powerful hypnotic drug was completely safe".⁴

An employee of Chemie Grünenthal brought home samples of the new drug for

his pregnant wife and ten months before thalidomide was put on the market in Germany, on Christmas Day in 1956, their child was born without ears. Years later, the father learned that his daughter was the first living victim of the epidemic of thalidomide-induced infant malformations and deaths.⁴

The company began selling the drug over the counter in Germany in October 1957, under the brand name Contergan. The company claimed that "Even a determined suicide could not take enough Contergan to cause death" and "accidental overdoses by children would be unheard of with this drug". Not one of those statements turned out to be true. Soon the drug was being sold in 46 countries under "at least 37 names",⁴ without any additional independent testing, and was the drug of choice for pregnant women with morning sickness.⁶

Food and Drug Administration (FDA) approval was not expected to be controversial, and the case was given to the agency's newest reviewer, Frances Oldham Kelsey, who had joined the FDA only one month before.

At the time, the prevailing US law was the 1938 Federal Food, Drug, and Cosmetic Act, which required proof of safety be sent to the FDA before a medication could be approved for sale in the United States. The law did *not* require demonstration of efficacy for approval. It also allowed "investigational" or "experimental" use of a drug while approval for its sale was being sought, meaning that a medication could be widely distributed before it was approved.⁷ The law gave the FDA 60 days to review a drug application. If the FDA reviewer told a drug company that its application for a particular medication was incomplete, it was considered withdrawn and the company would have to submit more data when it resubmitted the application. With each resubmission, the 60 days started all

over again.¹

On November 18, 1961, the German paper *Welt am Sonntag* published a letter by German paediatrician Widukind Lenz.⁷ Lenz described more than 150 infants with malformations, including phocomelia, and associated them with thalidomide given to their mothers.⁴ A stunning statistic was that 50 per cent of the mothers with deformed children had taken thalidomide during the first trimester of pregnancy.¹ The limits of danger were amazingly narrow: women who took even one tablet of thalidomide between the 20th and 36th day after conception were at risk for delivering malformed infants – beyond that time, the drug caused no deformities at all.⁴ Lenz notified Chemie Grünenthal about the dangers of its flagship product; ten days later, German authorities removed thalidomide from the market against Grünenthal's wishes. Grünenthal withdrew thalidomide soon afterward from the market and notified Richardson-Merrell of its decision.

In December, *The Lancet*, one of the oldest peer-reviewed medical journals in the world, published a letter by William McBride, an Australian physician, who noted large numbers of birth defects in the children of women who had taken thalidomide.⁸ Other countries quickly pulled the drug from their stores and pharmacies. However, Grünenthal continued to dispute the claims that thalidomide was responsible for the defects, saying that their action was “merely a response to the sensationalism”.⁴

Richardson-Merrill withdrew its Kevadon application in March 1962, but the sheer number and variety of brand names meant the drug remained available in some countries – thalidomide could be found in Brazil, Italy, and Japan as long as nine months after the German withdrawal.⁹

Unfortunately, Grünenthal's decision was

too late for thousands of families. An estimated 8,000 to 12,000 infants were born with deformities caused by thalidomide, and of those only about 5,000 survived beyond childhood.⁴ The medication never received approval for sale in the United States, but 2.5 million tablets had been given to more than 1,200 American doctors during Richardson-Merrell's “investigation” and nearly 20,000 patients received thalidomide tablets, including several hundred pregnant women. In the end, 17 American children were born with thalidomide-related deformities.⁴ An estimated 40,000 people developed drug-induced peripheral neuropathy. Exact numbers will never be known because the companies and doctors kept incomplete and inaccurate records. Fortunately, no thalidomide victims have passed defects to their children, because thalidomide is not a mutagen.¹⁰

Thalidomide Today

FDA Approval

On May 26, 2006, the U.S. Food and Drug Administration granted accelerated approval for thalidomide (Thalomid, Celgene Corporation) in combination with dexamethasone for the treatment of newly diagnosed multiple myeloma (MM) patients.³ The FDA approval came seven years after the first reports of efficacy in the medical literature (Desikan R, Munshi N, Zeldis J, *et al.* Activity of thalidomide (THAL) in multiple myeloma (MM) confirmed in 180 patients with advanced disease. *Blood* 1999; 94 : Suppl 1 : 603a-603a. abstract), and Celgene took advantage of “off-label” marketing opportunities to promote the drug in advance of its FDA approval for the myeloma indication. Thalomid, as the drug is commercially known, sold over \$300 million per year, while only approved for leprosy.⁴

Teratogenic Mechanism

Thalidomide is racemic – it contains both left- and right-handed isomers in equal amounts. One enantiomer is effective against morning sickness. The other is teratogenic and causes birth defects. The enantiomers can interconvert *in vivo* – that is, if a human is given pure (R)-thalidomide or (S)-thalidomide, both isomers can be found in the serum – therefore, administering only one enantiomer will not prevent the teratogenic effect in humans. The mechanism is being debated, with current literature that suggests that it intercalates into the DNA in G-C rich regions (Fig. 3).²

Adverse Drug Reactions²

1. Tendency to induce birth defects

A 1962 photo of baby born with an extra appendage connected to the foot caused by the pregnant mother taking the drug Thalidomide (Fig. 4).

2. Also causes peripheral neuropathy
3. Fatigue
4. Constipation
5. Increased risk of deep vein thrombosis especially when combined with dexamethasone
6. Pulmonary oedema
7. Atelectasis
8. Aspiration pneumonia

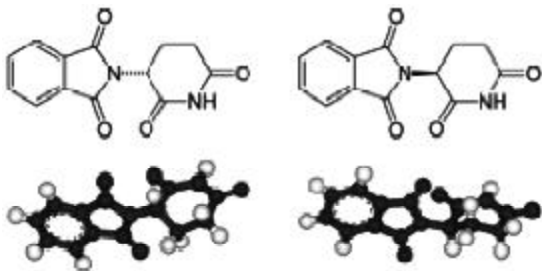


Fig. 3 :The two enantiomers of thalidomide:
Left:(S)-thalidomide
Right: (R)-thalidomide

9. Refractory hypotension.

10. Because thalidomide can cause drowsiness, other medicines that also cause drowsiness may increase this effect of thalidomide. Some medicines that cause drowsiness are:

- Alcohol-containing medicines
- Barbiturates such as phenobarbital
- Certain antidepressants or tranquillizers
- Muscle relaxants
- Certain antihistamines used in cold medicines

Thalidomide Analogues

The exploration of antiangiogenic and immunomodulatory activities of thalidomide has led to the study and creation of thalidomide analogues or immunomodulatory thalidomide derivatives (IMiDs).

They exhibit variety of pharmacological properties which includes:-

- Stimulation of T cells and NK cells.
- Inhibition of angiogenesis and tumour cell proliferation.



Fig. 4

- Modulation of haematopoietic stem cell differentiation.

Lenalidomide constitutes a lead compound in the new class of IMiDs. This orally administered agent has been tested in multiple myeloma, myelodysplastic syndrome and an expanding array of other clinical settings. Pre clinical data suggests that it is more potent, less toxic and has less teratogenic effects than thalidomide.¹¹

Another analogue, Actimid (CC-4047), is in the clinical trial phase⁵

Uses of thalidomide^{2,11}

1. Thalidomide in combination with dexamethasone is used in the treatment of multiple myeloma. (FDA Approved).
2. Also is FDA Approved for the treatment of erythema nodosum leprosum (ENL).
3. Myelodysplastic syndrome
4. Colon cancer : In a colon cancer study, 400 mg per day of thalidomide was given in combination with an anti- cancer drug irinotecan.
5. In a trial using thalidomide to treat prostate cancer, both low doses (as low as 200 mg per day) and high doses (as high as 1200 mg per day) were tried. The patients taking high doses fared somewhat better.
6. It is capable of eliminating skin eruptions, such as sores, or ulcers in the mouths of patients with AIDS.

References

1. Bren, Linda. "Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History", FDA Consumer, US Food and Drug Administration, 2001-02-28. Retrieved on 2006-09-21.
2. <http://www.answers.com/topic/thalidomide?cat=health>
3. Burkholz, Herbert. "Giving Thalidomide a Second Chance", FDA Consumer, US Food and Drug Administration, 1997-09-01. Retrieved on 2006-09-21.
4. Silverman, MD, William (2002-04-22). "The Schizophrenic Career of a "Monster Drug"". *Pediatrics* 110 (2): 404-406. Retrieved on 2006-09-21.
5. Sjostrom, Henning; Nilsson, Robert (1972). *Thalidomide and the power of the drug companies*. Hammondsworth: Penguin. ISBN 0-14-052298-0.
6. Karen Geraghty (July 2006). Profile of a Role Model. AMA (Virtual Mentor). American Medical Association. Retrieved on 2006-09-21.
7. Rouhi, Maureen. Thalidomide. *Chemical and Engineering News*. American Chemical Society. Retrieved on 2006-09-21.
8. Thalidomide and congenital abnormalities. *The Lancet*. James Lind Library (December 1961). Retrieved on 2006-09-21.
9. Lenz, Widukind. The History of Thalidomide. 1992 UNITH Congress address. Thalidomide Victims Association of Canada. Retrieved on 2006-09-21.
10. Smithells, Dick (Nov 1998). "Does Thalidomide Cause Second Generation Birth Defects?". *Drug Safety* 19 (5): 339-341. Retrieved on 2006-09-21.
10. Reuters, Thalidomide helps elderly cancer patients: study
11. Goodman, Gilman's. "The Pharmacological Basis of Therapeutics", 11th edition.

BOTOX UNDER REVIEW

The US Food and Drug Administration is reviewing the safety of botulinum toxins and reports of adverse reaction, including respiratory failure and death. Most serious cases were in children treated for cerebral palsy. Such treatment has been approved in about 60 countries including the UK, but not the USA.

The Lancet, 2008.