Dermatology Clinics and Research
DCR, 7(1): 389-390
www.scitcentral.com

ISSN: 2380-5609

Opinion: Open Access

Thalidomide: History, Lessons Learnt, Current Therapeutic Indications and its Unfortunate Inaccessibility in Brazil

Letícia Dupont*, Diego Salomon Mora Castro and Paulo Ricardo Martins Souza

*Santa Casa de Misericórdia de Porto Alegre/UFCSPA, Brazil.

Received November 20, 2020; Revised December 28, 2020; Accepted February 01, 2021

The inadvertent use of thalidomide during pregnancy caused a tragedy in the remote past, between 1956 and 1961. This fact still imposes obstacles on the prescription of the drug, much out of fear and prejudice. Its immunological, anti-inflammatory, and anti-angiogenic properties have been discovered in recent decades, and therefore its judicious use is already allowed in several countries. In Brazil, however, its anachronistic prohibition remains. In this article, the authors contextualize the facts since the first prescriptions, emphasizing the lessons learned since the initial tragedy.

In spite of the tragedy caused by the inadvertent use of thalidomide in pregnant women in the late 1950s, this fact also had an unprecedented and beneficial impact on the prescription of drugs for women of childbearing age, which remains until this day. This article briefly contextualizes the history of thalidomide, reporting its current indications and different forms of prescription in Colombia and the USA, as compared to Brazil.

Thalidomide (N-[2,6-dioxo-3-piperidyl] phthalimide) was synthesized in 1953 in Germany as a sedative-hypnotic drug, and later used for the management of nausea and vomiting during pregnancy. It was exported to over 40 countries, with more than 80 trade names [1].

In 1956, the first case of thalidomide-induced phocomelia was reported, and 5 years later there were approximately 3,000 reported cases of dysmelias–extremely rare congenital limb malformations, such as amelia (absence of any limbs), phocomelia (absence or severe shortening of the proximal structures), and absence/hypoplasia of the thumb or fingers [2]. In 1961, the drug was withdrawn from the German market and progressively from all other markets in the world [3].

It was found that malformations were not limited to the limbs, but also affected the cardiac, renal, digestive, ocular and auditory systems, with the period of sensitivity to the effect of thalidomide on embryonic development between 20 and 36 days after fertilization (34-50 days after the last menstrual cycle) [4].

The tragedy of thalidomide gradually forced governments to issue rules and regulations to ensure safe drug use, creating drug surveillance centers and systems for detecting adverse reactions to marketed drugs. In addition, the clinical trials of new drugs started including demands for strict regulations on products under development to ensure safety and the creation of research ethics committees to monitor clinical trials in humans.

In the past decades, the discovery of its immunoregulatory, anti-inflammatory and anti-angiogenic actions has expanded its possibilities of use. In Colombia, thalidomide was approved by The National Institute for the Monitoring of Medicines and Foods in Colombia (INVIMA) for use in erythema nodosum leprosum, recurrent aphtous stomatitis, Behçet's disease and as an alternative therapy for multiple myeloma [5]. In this country, with a specialist's prescription and an informed consent form on the use of contraceptives, the drug can be used.

In the United States, thalidomide is indicated for the treatment of patients diagnosed with multiple myeloma, and with erythema nodosum leprosum [5]. Both in Colombia and in the United States, it can be prescribed for several other pathologies, including nodular prurigo, refractory uremic pruritus, cutaneous and systemic lupus erythematosus, pyoderma gangrenosum, arthritis, Crohn's disease, ulcerative colitis, amyloidosis, Waldenstrom's macroglobulinemia, various neoplasms and infectious diseases (tuberculosis, HIV/AIDS), and also for refractory cough [6]. The

Corresponding author: Letícia Dupont, Santa Casa de Misericórdia de Porto Alegre/UFCSPA, Rua Professor Annes Dias, 295 - Centro Histórico, Porto Alegre, Brazil, Tel: +5551 999844854; E-mail: dupont.leticia@gmail.com

Citation: Dupont L, Castro DSM & Souza PRM. (2021) Thalidomide: History, Lessons Learnt, Current Therapeutic Indications and its Unfortunate Inaccessibility in Brazil. Dermatol Clin Res, 7(1): 389-390.

indications are many. For instance, it is the first therapeutic choice in individuals with severe recurrent aphtous stomatitis that experience significant impairment of quality of life due to persistent and intractable pain.

Currently, the prescription of drugs for pregnant women is extremely cautious. Nevertheless, the importance of some of these substances for the health of other patients cannot be ignored. Isotretinoin, known to be teratogenic and widely used by women (many of them of childbearing age), has been prescribed cautiously and responsibly for more than two decades. What would be the difference if we exercised the same caution in the prescription of thalidomide? The pain and suffering caused by severe recurrent aphtous stomatitis, for example, could be controlled, with remarkable improvement in quality of life. Expanding the possibilities of thalidomide application can change the lives of these patients, allowing them to eat, talk, and even smile without pain.

Although the harmful effects of thalidomide were extremely serious, 60 years have gone by since that tragedy. Until this day, even male patients remain unable to use the medication. The authors have found no reason other than historical stigma for such a restriction on the use of a drug with so many clinical indications. Thus, we suggest that its prescription be allowed and regulated similarly to systemic retinoids, which are prescribed when indicated, without this anachronistic prohibition that is unique to thalidomide.

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