TOX IMPACT STATEMENT

The Tragedy of Birth Defects: Thalidomide

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The Problem

Thalidomide was developed in the late 1950s as a non-addictive, non-barbiturate sedative and was touted as being completely safe. The drug was aggressively marketed and distributed in 46 countries for the treatment of nausea in pregnant women and became one the most prescribed drugs at the time. However, within years of its widespread use in Europe, Australia, and Japan, physicians began to observe an increase in rare birth defects among children of mothers who took the drug during pregnancy. Before its complete removal from the market in 1962, more than 10,000 children were born with deformities such as phocomelia, a congenital deformity in which the limbs are extremely shortened and the feet and hands arise close to the trunk. This remains the worst man-made medical disaster in history. In addition to easily recognizable limb anomalies, other effects attributed to thalidomide use include congenital heart disease, malformations of the inner and outer ear, and ocular abnormalities.

The thalidomide tragedy was averted in the United States because of the hold on its approval by US Food and Drug Administration (US FDA) reviewer Frances Kelsey. Despite pressure from the manufacturer to expedite approval of a drug which had already been in widespread use throughout the rest of the world, Dr. Kelsey was concerned about peripheral neuropathy observed in patients and the potential effects of the drug during pregnancy. In recognition of her vigilance, President John F. Kennedy presented Dr. Kelsey with the medal for Distinguished Federal Civilian Service in 1962. Dr. Kelsey also was awarded honorary membership to the Society of Toxicology in celebration of the Society's 50th anniversary in 2011.

Role of Toxicology

Give thalidomide's unprecedented, broad spectrum of effects on embryonic development, understanding its mechanism of action became a major focus for researchers in the biomedical field, including toxicologists. Although the mechanism of thalidomide-induced embryopathy is not fully understood, research has demonstrated that most of the damage to the forming embryo occurs during a short window of sensitivity between days 20 and 36 after fertilization. Reports indicate that a dose as little as 50 mg of thalidomide during the window of susceptibility is sufficient to cause birth defects in up to 50% of pregnancies. Not surprisingly, this corresponds

to the most active period of embryo development in humans. Taking the drug before and after this time-sensitive window is thought to not cause major damage to the embryo.

Over the last 50 years, more than 30 mechanistic hypotheses and models have been proposed for thalidomide's teratogenicity. More recent research has focused on hypotheses involving disruption of angiogenesis, generation of oxidative stress and damage, DNA intercalation, disruption of tubulin, and binding to cereblon, a key regulator of protein ubiquitination and degradation angiogenesis. It is quite possible that several of the proposed mechanisms work in parallel or synergistically to induce the hallmark thalidomide-associated limb anomalies. Understanding thalidomide's mechanisms of toxicity is critical for several reasons—first and foremost, to ensure that a similar event can be avoided in the future.

In recent years, thalidomide has been repurposed for the treatment of other diseases, including leprosy, multiple myeloma, AIDS, and more, because of its potent anti-inflammatory and antiangiogenic activities. Tragically, and despite strict guidelines in its use, the widespread use of thalidomide to treat endemic leprosy in Brazil during the 1990s led to a new thalidomide episode, probably as a result of patients sharing drugs. Understanding thalidomide's mechanism of action also could help researchers design the next generation of derivative drugs which lack the devastating side effects.

Public Health Impact

The disaster surrounding thalidomide prompted many countries to introduce stricter rules for the safety evaluation and licensing of drugs, such as the US Kefauver Harris Amendment to the Federal Food, Drug, and Cosmetic Act in 1962, Directive 65/65/EEC1 of the European Economic Community in 1965, and the United Kingdom's Medicines Act 1968.

The thalidomide episode encouraged adoption of systemic testing of pharmaceutical products for developmental toxicity prior to marketing. The US FDA laid the foundation for the development of the segment 1 (fertility and general reproductive toxicity), II (teratogenicity), and III (peri- and postnatal toxicity) testing protocols in 1966. Prior to the development of segment I, II, and III testing protocols, toxicology testing was hypothesis driven compared to the systemic bioassay testing strategy that is in place today.

The legacy of thalidomide extends further than the creation of detailed testing protocols. The thalidomide disaster provided the first evidence for species differences in drug reaction and response. For example, mice are less sensitive to thalidomide than other species, such as non-human primates and rabbits. As a consequence, developmental toxicity testing for pharmaceuticals now requires assays in at least two species. As a result of these more stringent

drug screening regulations, there has not been a repeat of the developmental toxicity disaster experienced with this drug.

References and Resources

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