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## **Thalidomide**

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Eugene Pergament, MD, PhD; Kelly Ormond, MS; Katherine Medlin

Thalidomide is an anti-inflammatory and immunomodulant medication used to treat a variety of medical conditions. In the 1950's and 1960's, thalidomide was used as a sedative and as an anti-emetic for morning sickness during pregnancy. More recently, it is used to treat AIDS-related wasting and aphthous ulcers, acute and chronic graft-versus-host disease, discoid lupus erythematosus, photodermatoses, rheumatoid arthritis, and sarcoidosis (Minor and Piscitelli, 1994). Thalidomide's mechanistic action in all of these disorders relies on its ability to act on phagocytic and endothelial cells but not on T cells. Specifically, it acts on immune cytokine synthesis, especially tumor necrosis factor alpha, TNF-a (Powell, 1996). Thus, thalidomide is able to decrease the anti-inflammatory response of the immune system without suppressing the immune system's function (Klaussner et al., 1996).

Although thalidomide has many beneficial medicinal uses, it is also a well-known teratogen. To date at least 4000 babies worldwide have been born with thalidomide embryopathy (Lenz, 1988). In September 1997, the FDA granted preliminary approval of this drug to treat erythema nosodum leprosum (Celgene, 1997); final approval is pending. This has raised concern over more widespread use of this drug and a potential increase in the number of thalidomide-related birth defects. This RISK/NEWSLETTER will evaluate the use of thalidomide as a cause of birth defects in pregnancy.

## **Historical Perspective**

In 1954, thalidomide was first used in clinical trials for its spasmolytic, local anesthetic, and anticonvulsive actions. While used for a variety of indications, its most pronounced effect was that of sleep induction. First marketed in November 1956 under the names Grippex and Contergan (Lenz, 1988), thalidomide subsequently became available in almost 50 countries throughout Europe, Asia, and Africa. Teratogenicity was not a primary concern because animal studies had shown no evidence of teratogenicity. Several years after its release in 1956, Lenz noted an increase in congenital limb malformations within the West German population, and that many of the mothers whose children had these malformations were exposed to thalidomide during pregnancy (Lenz, 1966; Fraser, 1988). Increased incidence of similar malformations were found in many other countries throughout Europe and Asia. Animal studies using rats and rhesus monkeys exposed to thalidomide were also beginning to demonstrate teratogenicity (Warkany, 1988).

Between 1961 and 1962, the relationship between thalidomide and birth defects was established, and the sale of thalidomide declined dramatically as countries began taking it off the market (Lenz, 1966). The number of babies born with thalidomide embryopathy in a given country was directly related to the total amount of thalidomide sales in that country (Lenz, 1966). In the United States the number of infants born with thalidomide embryopathy was very low because thalidomide was never approved by

the FDA for use; ironically this was because of its potential side effects such as peripheral neuropathy, rather than concerns regarding teratogenicity (Kelsey, 1988).

Several important factors were discovered regarding the relationship between the timing of thalidomide exposure during pregnancy and the severity of birth defects. Thalidomide typically caused birth defects when taken between 34 and 51 days after the first day of a woman's last menstrual period (LMP). The most common birth defects seen in babies exposed during that period were defects of the limbs, eyes and ears (Lenz, 1966). Thalidomide embryopathy became the accepted term for babies who have this association of features in conjunction with thalidomide exposure.

### **Thalidomide Embryopathy**

While estimates of risk range from 10-50%, Weicker (1962) suggested that if a fetus is exposed to thalidomide during the critical period, there is approximately a 20% risk of thalidomide embryopathy (Newman, 1985). Thalidomide embryopathy is characterized by a specific pattern of birth defects which can be divided into four groups: 1. four-limb phocomelia; 2. Upper-limb phocomelia or amelia with other leg defects; 3. Upper-limb phocomelia or amelia with normal legs; 4. Predominantly lower limb defects (femoral hypoplasia or lower limb phocomelia) which are generally associated with bilateral radial club hand and other limb defects. All four categories can be associated with other anomalies involving various organs (Newman, 1985).

### **Limb Reduction Defects (LRDs)**

Limb defects are the most characteristic birth defect associated with fetal thalidomide exposure (Stromland et al., 1994), particularly amelia (absence of limbs) and phocomelia (seal flipperlike limbs). Specific limb defects have been correlated with narrow windows of exposure (Brent and Holmes, 1988), and it is rare for a baby with other thalidomide-associated anomalies not to also have a limb reduction defect. LRDs are usually bilateral, but are not necessarily symmetrical or of similar severity. Upper and lower limbs exhibit preaxial deformities, with the upper extremities commonly exhibiting missing preaxial digits and lower limbs demonstrating preaxial polydactyly (Brent and Holmes, 1988). Hypoplastic or absent shoulder and pelvic girdles are also common (Newman, 1985).

There are many causes of LRDs, and there are some LRDs that would not be attributed to thalidomide exposure. These include amputation-type defects, amniotic band-type malformations, postaxial LRDs, unilateral severe LRDs of the upper limb and severe LRDs of the distal portion of a limb with a normal proximal portion and girdle. Preaxial defects in the limbs are most characteristic of thalidomide embryopathy.

### **Facial Anomalies**

Facial anomalies primarily involve the eyes and ears. Ear malformations are often symmetrical (Newman, 1985) and include anotia, microtia, and sensorineural deafness secondary to inner ear anomalies with or without external ear malformations (Miller, 1991). The critical period of ear development is 34 to 37 days post-LMP.

Ocular abnormalities include horizontal incomitant strabismus and clinical Duane syndrome; these are found in approximately 54% of affected individuals (Stromland et al., 1994). Duane syndrome is often associated with external ear abnormalities or malformations of the upper extremities (Miller, 1991). Finally, severe ocular abnormalities such as uveal colobomas, microphthalmia, and glaucoma have also been associated with thalidomide embryopathy and occur with exposure between 38 and 42 days post-LMP (Miller, 1991). Cranial nerve abnormalities are not uncommon, causing the "jaw winking" phenomenon or crocodile-tear syndrome (Newman, 1986).

### **Systemic abnormalities**

Other abnormalities may be found in various body systems but are rarely diagnostic of thalidomide embryopathy. These include hypoplasia or positional kidney malformations, cardiac anomalies, anal atresia, spinal anomalies, chest abnormalities, and CNS complications. Cardiac malformations, usually conotruncal defects, occur in approximately 30% of infants with thalidomide embryopathy. Neonatal mortality may be as high as 40% (Lenz, 1988).

### **Growth and Mental Function**

Children affected with thalidomide embryopathy have normal prenatal and postnatal growth rates but often demonstrate truncal shortness (Newman, 1986). Mental function is thought to be unaffected by thalidomide exposure in utero. A study by Stromland et al. (1994) demonstrated an increased incidence of autism in individuals with thalidomide embryopathy. In their study of 86 patients diagnosed with thalidomide embryopathy, 4-5% were diagnosed with an autistic disorder. This is a 50-fold increase over the population incidence of 0.08%. Although most insults causing autism are thought to occur in the second trimester, this study may demonstrate the ability of first trimester exposures to result in autism. In order to substantiate this claim, more research must be completed regarding the association between thalidomide exposure and autism.

### **Mechanisms of Teratogenic Action**

One hallmark of teratogenicity is biological plausibility, i.e., explaining the teratogenic effects observed. However, the mechanism by which thalidomide induces a spectrum of birth defects is largely unknown. There are many hypotheses but none have been established. Three mechanistic levels have been explored: biochemical, tissue-organ and cellular mechanisms. While changes in biochemical properties still may hold considerable promise, at the present time none of the biochemical explanations have been substantiated (Heshka, 1988). Tissue and organ specific mechanisms lack experimental support but warrant further inquiry (Heshka, 1994). The cellular mechanisms under investigation include induction of inappropriate cell death, chromosome damage, and cell-cell interactions involved in morphogenesis. Negative and contradictory evidence has been reported for the chromosome damage and cell death hypotheses. Cell-cell interaction is an intriguing hypothesis because of its importance in morphogenesis (Heshka, 1994). Evidence suggests thalidomide may decrease expression of cell-cell adhesion receptors (Neubert et al., 1996). While many hypotheses have been proposed, thalidomide's mechanism of action remains unknown.

### **Guidelines For Thalidomide Use**

Since thalidomide's recent introduction into the United States' market, concern has mounted surrounding the possibility of an increased prevalence of thalidomide-related birth defects. Clinical use of thalidomide must involve informed consent procedures, monitoring for possible side effects, patient education on thalidomide's uses and potential adverse effects, and detailed regulation of its manufacturing, dispensing, and labeling (Powell and Gardner-Medwin, 1994).

The FDA has only approved use of thalidomide for type II leprosy, which affects a high percentage of individuals with leprosy. The manufacturer plans to require physicians and pharmacies to register as providers and to limit thalidomide to a 28-day supply. Women of childbearing age would be required to use two forms of birth control and take a monthly pregnancy test (Celgene, 1997; McLean, 1997).

There is considerable concern that these measures will fail. Accutane is another known teratogen producing severe birth defects. Women who use this drug are required to use two forms of birth control and take regular pregnancy tests. Despite these efforts, in studies with Accutane, 623 pregnancies occurred out of 210,000 women surveyed who used the drug. Thus, while pregnancy prevention measures can be taken, the risk of thalidomide-induced birth defects remains a real concern based on past experience with other known teratogens (Rueters, 1997)

## **Prenatal diagnosis**

Ultrasound is currently the only possible tool for prenatally diagnosing thalidomide embryopathy. One case report of a fetus diagnosed with thalidomide embryopathy by ultrasound has been demonstrated (Gollop et al., 1987). Currently, there are no estimates regarding the sensitivity and specificity of ultrasound in diagnosing fetuses affected by thalidomide exposure, however.

## **Summary**

Thalidomide has many uses in medicine, all of which alleviate the painful symptoms of chronic diseases. Few drugs show its efficacy in treating these diseases. However, its benefits are clouded by the increased potential for birth defects in fetuses of women using thalidomide during pregnancy. It is important for women to weigh both the benefits and risks of using thalidomide. The medical community must increase its awareness of thalidomide's powerful teratogenicity and the importance of effective birth control measures for women taking this drug. In addition, since thalidomide's effects are largely dependant on the timing of exposure (34-51 days post-LMP), it is essential that individuals who must take this drug during pregnancy avoid this critical period. With FDA approval pending, this drug will be more available in the United States than ever before, thus information on the benefits and risks of thalidomide must become common knowledge in the medical community as well as the public.