Research in the News: Thalidomide Gets A Second Chance (Grades 9-12)

Thalidomide Gets A Second Chance

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Lebanon, Charles de Gaulle, Califorina Baseball Starkweather Homicide, Children of Thalidomide"
From "We Didn't Start the Fire," by Billy Joel

The "children of thalidomide" in Billy Joel's song "We Didn't Start the Fire" were 10,000 babies born with shortened arms and legs, or with no limbs at all. Their mothers had taken a new prescription drug called thalidomide early in their pregnancies to help them sleep, and to keep them from feeling nauseated. Tragically, no one realized that thalidomide could cause terrible birth defects.

But the United States was largely spared this disaster because Frances Kelsey, an alert reviewer at the Food and Drug Administration (FDA), was not convinced that the manufacturer of thalidomide had proven that the drug was safe. Despite pressure, Kelsey refused to clear the drug for sale in the U.S. Her caution paid off. Of the 10,000 babies injured worldwide, only seventeen were born in this country.

Now, some thirty years later, thalidomide is back in the news. Doctors are investigating its potential as a treatment for a variety of diseases, including arthritis and some symptoms of AIDS. This time around, however, doctors will know not to prescribe the drug for women who are, or might become, pregnant.

The Thalidomide Story

A drug company in Germany developed thalidomide in the 1950s as a sleeping pill. Sales boomed because the drug was cheap, seemed to be safe even when taken in large quantities, and apparently caused no harm to experimental animals. The company wanted to sell thalidomide in the United States. So, in 1960, the company applied to the FDA for approval, because FDA reviews the safety of all drugs before they can be sold in the United States.

Given thalidomide's popularity in Europe, FDA officials thought that approval for the drug would be simple and straightforward. They gave the folder on thalidomide to Kelsey -- their newest medical reviewer -- expecting approval to be routine.

From the start, Kelsey refused to be hurried into approving the sale of thalidomide. She felt strongly that, even though the drug was in use all over Europe, too little information was known about its side effects. Kelsey found it peculiar that the drug affected experimental animals differently from humans. While thalidomide had no reported harmful effects on the animals, it also did not have the beneficial effect of making them sleepy.

Refusing to take "no" for an answer and eager to sell their product, the drug manufacturers pressured Kelsey, but she stood her ground. She would not give thalidomide her stamp of approval until she had better proof of its safety.

Then, in February 1961, Kelsey read in the British Medical Journal that thalidomide could have harmful effects. A British physician reported that long-term use of thalidomide caused tingling, numbness,and burning pain in the fingers and toes, and he speculated that damaged nerves were the cause.

For Kelsey, this report raised a red flag. She suspected that a drug that damaged nerves could have wide-ranging effects on a developing fetus. In graduate school, Kelsey had been intrigued by teratogens, drugs that harm the fetus, and she suspected that thalidomide was one of them.

In November 1961, a German doctor reported that thalidomide caused birth defects, and the drug was taken off the German market. Soon after, the drug manufacturers formally withdrew their application for approval in the United States.

On July 15, 1962, a reporter celebrated Kelsey on the front page of the Washington Post as the "heroine...[whose] skepticism and stubbornness...prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children."

Just a few American women gave birth to "thalidomide babies." Most of these had taken the drug while participating in investigational studies or had obtained it while living abroad.

Frances Kelsey receives the Gold Medal for Distinguished Civilian Service from President Kennedy in 1962. Courtesy of the National Library of Medicine.

As the gatekeeper who had prevented thalidomide's widespread distribution, Kelsey received the highest award for federal civilian service from President Kennedy. A New York Times front-page article on August 5, 1962 praised Kelsey for leading "a two-year battle with the makers of thalidomide."

Thalidomide: New Uses

Thalidomide was not completely shelved after the 1960s tragedy. In 1965, an Israeli doctor used it to treat a patient who had leprosy. He had given the man a drug to fight the bacteria that cause the disease. The drug induced an extremely uncomfortable inflammatory reaction. To ease the patient's discomfort and help him sleep, the doctor then gave him thalidomide. The patient slept well and, in addition, thalidomide brought the inflammation under control. This second effect was "dumb luck or pure serendipity," says Lawrence Fox, who is now studying some of thalidomide's other effects.

This chance observation led doctors to consider whether thalidomide would help in diseases that involve inflammations, in which tissues get red, hot, and swollen. For example, thalidomide seems to help patients who suffer from arthritis, an inflammation of the joints. Fox discovered that thalidomide heals mouth and throat sores in people infected with HIV, the virus that causes AIDS. These sores make eating extremely painful, and, when patients cannot eat, they become thin, frail, and even more vulnerable to infection.

Fox cautions that thalidomide must only be "administered by a physician who is vigilant for the possible serious side effects." Thalidomide irreversibly damages nerves in the fingers and toes. Such damage can be extremely painful and can lead to problems with muscle control, such as difficulty walking. One patient described feeling as though his foot were sealed in a metal shoe. In addition, because the drug is unquestionably teratogenic, doctors carefully monitor women of child-bearing age who are involved in research studies and caution them not to become pregnant during the study period.

Lucky Breaks

The story of a doctor accidentally finding that a drug has unexpected benefits is fairly common, says John Decker, an emeritus scientist at NIH who formerly directed its research hospital. Decker cites the example of a doctor in Paris who injected his patient with gold in the early 1900s to treat tuberculosis. The patient also had arthritis. Unexpectedly, the gold injections reduced the swelling and redness in the patient's joints. Gold injections later became a standard treatment for arthritis. Doctors still use gold, although in a more refined form, to treat arthritis.

Billy Joel inadvertently made an accurate prediction when he sang of thalidomide in "We Didn't Start the Fire." Today, doctors are using thalidomide to extinguish the flames of discomfort in patients who have inflammation -- a word that means "setting on fire."

How Thalidomide Works in the Body

When a person takes thalidomide, the drug travels throughout the bloodstream, reaching all areas of the body. No one knows exactly how it works. But scientists have observed both its effects and side effects, and from these they have proposed at least three possible mechanisms of action for the drug.

In the 1950s when doctors prescribed thalidomide as a sleeping pill for pregnant women, they noticed that it induced a more healthy sleep than did most other sleeping pills. Thalidomide's mechanism of action was different -- it turned on the part of the brain that tells the body to sleep rather than shutting down the part of the brain that tells the body to stay awake. One of its targets in the body is, therefore, the brain.

A second target is blood vessels. Thalidomide seemed to block the normal development of fetal limbs by preventing angiogenesis, new blood vessel growth. Without blood and the nutrients and growth factors it carries, fetal development was stunted. Thalidomide's capacity to obstruct angiogenesis prompted doctors to test the drug as a treatment for cancer patients, because like a fetal limb, a tumor needs new blood vessels to grow. Drugs that inhibit the formation of blood vessels stymy tumor growth as well.

Third, doctors realized in the 1960s that thalidomide reduces inflammation. When the body fights foreign material, injured cells release proteins that increase blood flow. TNF-alpha is one of the proteins that is released. Scientists think that thalidomide may block production of TNF-alpha.

How the FDA Reviews Drugs

The FDA regulates all foods and drugs sold in the United States. It is a public health agency that is part of the United States Department of Health and Human Services.

After the thalidomide disaster, legislators recognized that the drug approval process had to be more tightly controlled. Congress bolstered the FDA's regulatory powers by passing the Kefauver-Harris Drug Amendments Act in October 1962. As a result of this ruling, scientists had to prove that a drug was safe and effective before it could be sold to the American public.

Now, on average, the approval process for a drug takes eight years. FDA physicians, scientists, and other staff review test results from laboratory and animal experiments submitted by drug companies, and this information helps them decide whether the drug is safe enough to test in humans. Animal experimentation is useful, but it cannot always indicate what will happen in humans. For example, thalidomide is not a particularly potent teratogen in most animals, yet it is very dangerous for humans. The only animals that respond to the drug the way humans do -- with missing or shortened limbs -- are primates and a few breeds of rabbits.

When FDA officials conclude that a drug can be sold to the public, they determine what its label should include regarding directions for use, side effects, and warnings. Detailed information about the drug approval process is posted at the FDA website.

Additional Resources:

1. Evolution of the U.S. Drug Law http://www.fda.gov/fdac/special/newdrug/benlaw.html