Learning about the Safety of Drugs — A Half-Century of Evolution

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The end of 2011 marks the 50th anniversary of a constellation of events that transformed the way we think about drug safety. A half-century ago, the Food and Drug Administration (FDA) did not have authority to require a manufacturer to meet meaningful efficacy standards or demonstrate that a new product had a reasonable benefit-risk relationship; such determinations were seen as best left to the discretion of physicians.

In 1961, Senator Estes Kefauver (D-TN) introduced legislation that would, among other things, give the FDA authority to compel companies to provide efficacy and safety data before a product should start talking about overall prognosis now, even as we carry out more research on patient preferences and ways of improving such discussions. To make care more patient-centered, we need to start helping our very elderly patients set goals of care that take their overall prognosis into account. We should do so in the ordinary course of clinical practice, letting our patients be our guides.

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could be sold. Kefauver was accused of trying to unnecessarily expand the power of government, threatening the viability of the pharmaceutical industry, and inserting Washington bureaucrats between patients and their doctors, limiting the freedom of both. His legislation seemed doomed.

During this period, Frances Kelsey, a new medical review officer at the FDA, was working on her first assignment: approving a sleeping aid called Kevadon. It was widely used in Europe, and the company seeking a U.S. license expected quick approval by an agency that rarely said no to anything. But Kelsey noted that the manufacturer’s animal safety data were scanty and inconclusive, the clinical evidence was superficial, and there was no assessment of long-term risk. Its studies of the drug’s use in pregnancy were grossly inadequate, despite its promotion for morning sickness. She was also concerned about a recent article in the British Medical Journal associating the drug with persistent neuropathic symptoms. Kelsey told the manufacturer in mid-1961 that in her judgment, there was not enough evidence to warrant approving Kevadon for U.S. use.

Meanwhile, a strange epidemic was unfolding in Europe. Babies were being born in unprecedented numbers with severe limb-reduction defects, their hands or feet emerging directly from their torsos. Once rare, these anomalies were suddenly occurring much more frequently. In the absence of any systematic way to link birth defects with prenatal exposures, causal theories abounded, much as they had a century earlier when cholera swept the continent. Some thought the abnormalities were caused by impure water or nuclear testing or an unknown toxin. Since most cases occurred in West Germany but there were virtually none in East Germany, some questioned whether this was the effect of a surreptitious chemical warfare program originating in the Soviet bloc.¹

The answer was eventually uncovered by two astute clinicians, working independently half a world apart. Widukind Lenz, a pediatrician in Hamburg, came across a striking number of such deformed children whose mothers had been prescribed a new sedative, Contergan, during pregnancy. (The drug had been aggressively marketed by its manufacturer as a safe sleeping pill — and also for the treatment of morning sickness, influenza, depression, premature ejaculation, tuberculosis, premenstrual symptoms, menopause, stress headaches, alcoholism, anxiety, and emotional instability, among other uses.) In a do-it-yourself case-control study reminiscent of John Snow’s 19th-century analysis of the cholera cases clustering around a particular water pump in London, Lenz identified 46 women who had had babies with a limb-reduction deformity and 300 who had borne normal children. A detailed history of each revealed that 41 of the 46 women with deformed babies had taken Contergan, whereas none in the other group had taken the drug in the fourth to ninth weeks of gestation. In November 1961, Lenz contacted Contergan’s manufacturer and asked that the drug be taken off the market; the company refused, saying that the risk was unproven. Two days later, Lenz presented his findings at a pediatric conference in Düsseldorf.²

The same year, in Australia, an obstetrician named William McBride noted a surprising increase in limb-reduction deformities in his maternity hospital. He observed that the mothers of several such babies had taken a drug called Distaval during pregnancy. By November, his findings reached the home office of the British company that sold Distaval — coincidentally, a few days after Lenz made his presentation in Düsseldorf. McBride summarized his findings in a report that appeared in the Lancet on December 16, 1961.³

By the end of that year, as more cases emerged, the details of this pivotal drug-safety catastrophe had come into focus. Contergan was withdrawn from the German market, and Distaval was no longer sold in Australia. However, because the drug was marketed under many different trade names for different indications in various countries, and because international collaborations in pharmacovigilance were not yet in place, the compound continued to be
Radiographs of the Upper Extremities of a Child Born in 1961.

sold elsewhere: as Softenon and Noctosediv in several European countries, as Valgis in Africa, and as Isomin, Glutanon, and 8 other proprietary names in Japan. In all, more than 60 different trade names were used to market the same compound — thalidomide. But by the end of 1961 the drug had been withdrawn in most countries. During its years on the market, it is believed to have caused limb-reduction defects in more than 10,000 children worldwide (see images), as well as a wide spectrum of systemic disorders. An unknown number of fetuses died in utero.

Because of the vigilance of the FDA’s Kelsey, the Kevadon brand of thalidomide was never sold in the United States. Americans were largely spared the birth defects that afflicted so many families in other countries, except for women who obtained the drug while traveling abroad; 20,000 others were enrolled by their doctors in company-sponsored “seeding studies” designed by the drug’s manufacturer to start bringing it to the U.S. market before its expected FDA approval.

Much has changed since the climax of the thalidomide story 50 years ago. The drug became a foundational example for the development of drug-safety policy, legitimizing the idea that governments have the right to require manufacturers to provide adequate data about risk and benefit before they can market a prescription drug. It helped to propel the Kefauver-sponsored legislation from likely failure to the law of the land, setting the stage for new authority for the FDA for decades to come.4 The primitive but effective case-series methods of Lenz and McBride have evolved into much more sophisticated methods for detecting drug risk in populations. Today, large data sets covering tens of millions of patients can be subjected to computer-assisted surveillance in near real-time to assess relationships between medication exposures and clinical outcomes. Although these methods have been practical since the 1980s, the FDA is only now starting to apply them systematically, owing to legislation enacted in 2007 in the wake of the most well-known drug-safety crisis of our own era, that of Vioxx (rofecoxib).

Although thalidomide as a sedative or morning-sickness treatment would never pass any contemporary screen for drug safety, modern pharmacoepidemiology and therapeutics are moving toward managing the fact that useful drugs can cause adverse effects in certain circumstances. Fifty years later, our goals have become more nuanced. We are learning how best to use modern methods of evaluation and surveillance to identify as early as possible drugs that pose unacceptable risk and to constrain or prevent their use. Yet debate continues on whether and how the federal government should restrict the use of medications with unacceptable risks. Since all active compounds have some potential for harm, we are trying to learn how best to regulate, prescribe, and monitor the use of medications in ways that maximize their benefit while reducing the likelihood and severity of adverse effects. The concept of Risk Evaluation and Mitigation Strategies, also mandated in the 2007 legislation, is an attempt to move therapeutics in this direction.5 We still have much to learn about implementing this approach, especially for therapies for new indications that have impressive efficacy as well as substantial risk of toxic effects. One current example is an immunomodulatory agent that has shown great promise for treating both leprosy and multiple myeloma — thalidomide.

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