The Fine Line Between Poison and Remedy

After the 1941 attack on Pearl Harbor, scores of wounded were taken to a triage area to treat their injuries. They were given a normal dose of a short-acting barbiturate general anesthetic known as sodium pentothal. While healthy patients would have tolerated the dose, it had tragic consequences on those in shock from blood loss.

“The standard dose killed so many people that when the results of the experience at Pearl Harbor were reported in the journal Anesthesiology in 1943, the author called intravenous anesthesia an ideal form of euthanasia,” says Michael Avram, anesthesiology.

Fortunately, a case report and editorial accompanying this report concluded it was not the drug that was at fault, but the way it was administered.

That fatal lesson is at the center of the Mary Beth Donnelley Clinical Pharmacology Core Facility, of which Avram is director. The core facility studies the effects of the body on drugs (pharmacokinetics) and the effects of drugs on the body (pharmacodynamics). Researchers do this by studying drug absorption into the blood stream, distribution throughout the body, and elimination by various means, including metabolism and renal excretion.

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The core is also interested in the relationship between drug concentration and effect and the time for the drug to reach the sites of action or receptors.

In addition, they look at how disease can interfere with this process. For example, if a drug enters the bloodstream and is later filtered by the kidneys, then what happens if the person has poorly functioning kidneys? Drug concentrations are likely to stay elevated for longer than predicted, so the dose needs to be adjusted accordingly.

“The physician Paracelsus is one of our heroes,” says Tom Krejcie, associate director of the core. “In the early 1500s, Paracelsus said ‘All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.’”

“When we lecture to medical students, we tell them that if they don’t remember anything else, remember that,” Avram adds.

The Clinical Pharmacology Core had its origins in the Department of Anesthesiology 30 years ago when Avram and Krejcie learned the discipline by working with Arthur J. Atkinson Jr., who had established the Clinical Pharmacology Laboratory at Northwestern in 1970. Avram says that anesthesiology was a natural home for clinical pharmacology because anesthetics are so powerful and potentially toxic that it’s important to understand how the body handles them in order to administer them safely and effectively. Ten years ago, the focus of the facility changed after Avram received a phone call from Steven Rosen who at the time was expanding resources for the Lurie Comprehensive Cancer Center.

“Dr. Rosen wondered if we’d be interested in collaborating with oncologists,” Avram recalls. “I had waited for that phone call for 20 years. I was delighted.”

In order to study state-of-the-art therapeutics for oncology, the facility required a whole new state-of-the-art laboratory, which is now located on the 13th floor of the Ward Building in Chicago. With a generous donation from the Donnelley family, Northwestern was able to purchase a triple quadrupole mass spectrometer. The equipment enables researchers to detect small quantities (less than a nanogram) of drugs in biological matrices, such as plasma, cerebral spinal fluid, and breast milk.

In 2008 Judith Paice, medicine: hematology/oncology, approached Avram and his colleagues at the core with a serious concern. Paice, who directs the Cancer Pain Program at Northwestern Memorial Hospital, had a strong suspicion that the topical morphine gel they were administering to hospice patients was not working. For patients who were unable to swallow medicine, a topical solution was ideal as it was supposed to be absorbed through the skin. After the Donnelley Clinical Pharmacology Core completed a randomized, placebo-controlled crossover comparison of the topical gel with subcutaneous injection in volunteers, Paice’s suspicions were confirmed.

“Using the mass spectrometer, we measured plasma morphine concentrations in the volunteers at multiple times after the gel was applied to their skin,” Avram says. “It showed that the topical gel didn’t work because none of the morphine was being absorbed. This study completely changed the practice of providing pain relief in hospice.”

In addition to testing drug effectiveness, the core is an integral part of drug development. The core provides support for preclinical and clinical studies of cancer chemotherapeutic agents, analgesics, and other small molecules. Members of the core work closely with Northwestern’s entrepreneur-in-residence, Andrew Mazar, to make connections with drug development researchers at the University.

Krejcie says some drugs never reach their potential in clinical trials because they are tested at the wrong dose and concentration. The core facility can develop mathematical models using data from classical pharmacokinetic studies that can guide investigators in the design of efficient concentration-controlled pre-clinical or clinical trials.

“You can’t give healthy people and wounded people the same dose,” Krejcie says. “Likewise, you shouldn’t give me the same dose as Shaquille O’Neal. You could test different doses on volunteers and hopefully not kill anybody or you can approach it the smart way and come up with a mathematical model to see what happens in healthy people. Then make adjustments in the model to compensate for physiological changes. We don’t want to throw promising drugs into the trash because we didn’t take the time with modeling.”

“Oh worse than that,” Avram adds, “we don’t want to advance drugs that don’t belong in clinical trials.”

For more information about the Mary Beth Donnelley Clinical Pharmacology Core, visit http://www.feinberg.northwestern.edu/research/cores/units/clin-pharm.