Mysteries about drug metabolism in the obese weigh on doctors

The surgery was a success, but a question loomed after the procedure: given that the patient was obese, what was the right antibiotic dose? "The thought was, well, she's twice as big as a normal person, so we'll give her twice the dose," says Aaron Cook, a clinical pharmacy specialist at the University of Kentucky in Lexington. "For that drug, levofloxacin, there's just no information to go on, no dosage recommendation for obese patients."

The patient fared well, but such conundrums are becoming increasingly common as obesity rates rise around the globe. Just a month ago, researchers released new figures estimating that the US will see an additional 65 million obese individuals by 2030 (*Lancet* **378**, 815–825, 2011). Already in the country approximately one in three adults and one in six children are obese—a condition that can precipitate heart disease, diabetes, respiratory failure and other illnesses that often require medication. But experts say that merely doubling the dose isn't the solution because the physiological changes that accompany obesity, such as increases in the volume of blood pumped by the heart and fat mass, can in turn lead to changes drug absorption and metabolism.

Chandrahas Sahajwalla, who conducts pharmacological research at a US Food and Drug Administration (FDA) office in Silver Spring, Maryland, has tried calling attention to the paucity of information in this area. A comprehensive review by Sahajwalla and his colleagues published in July found that, to date, only a handful of approved drugs carry meaningful label information regarding obesity, such as specific dose adjustment (*Clin. Pharmacol. Ther.* **90**, 77–89, 2011).

"Unless a specific drug is studied in obese patients during drug development, it's very difficult to extrapolate not only pharmacokinetics but also efficacy and safety information from normal-weight individuals to obese patients," Sahajwalla says. "The main hurdle is lack of sufficient number of patients with varying degree of obesity in clinical trials."

It's not that they're excluded. The FDA, for instance, encourages pharmaceutical companies to enroll obese subjects to collect data for dosing recommendations, says Sahajwalla. He's hopeful that as the scientific community continues to shed light on the need for actively including this population in trials, drugmakers will respond.

There are various efforts already underway to learn more. Earlier this year, for instance, Italian scientists proposed a systematic approach to dosing recommendations for anesthesia medications (*Best Pract. Res. Clin. Anaesthesiol.* **25**, 27–36, 2011). And another group of Italian clinicians is currently conducting a three-year study looking at the changes in drug metabolism and pharmacokinetics in patients with morbid obesity after bariatric surgery.

In Cook's case, the lack of information prompted him and his colleagues to conduct their own study. They administered a single 750-milligram intravenous dose of levofloxacin to obese individuals who were hospitalized as well as those who were otherwise healthy. Their findings, published this summer, revealed that although peak concentrations of the antibiotic in both groups were comparable to that in normal-weight individuals, the elimination of the drug from the body was accelerated in the nonhospitalized obese arm (*Antimicrob. Agents Chemother.* **55**, 3240–3243, 2011). The findings are medically relevant, Cook notes, because faster clearance of the antibiotic might make those patients more vulnerable to infection. "It's concerning," he says, "because our data suggested that drug exposure would be almost half what it would be in a normal-weight individual, which might lead to more failures in obese patients."

The study may have answered Cook's original question, but it also highlights how much remains unknown: "The more that we learn about how drugs behave in obese individuals," he says, "the more we find that one size doesn't necessarily fit all."

Alisa Opar

Ten years on from anthrax scare, analysis lags behind sequencing

A decade ago this month, a microbiologist at Northern Arizona University, in Flagstaff, took a special delivery from the US government. Federal investigators wanted the scientist, Paul Keim, to identify the anthrax that appeared in letters mailed to news organizations and US lawmakers. Overnight, he used PCR to determine that the anthrax sent was the Ames strain, commonly used in research—but that was just the beginning of a scientific investigation that would catapult the still wet-behind-the-ears science of microbial forensics to the forefront of the criminal inquiry.

Ten years on, Keim's PCR-based technique seems downright quaint in comparison with modern, speedy DNA sequencing. "In a lot of ways we've matured," says Bruce Budowle of the University of North Texas Health Science Center in Fort Worth. But there are challenges ahead, adds Budowle, who retired in 2009 from the US Federal Bureau of Investigation (FBI), where he was involved in the anthrax studies as a senior scientist in the laboratory division: "In a lot of ways, we've got a long way to go... We haven't grown in the interpretation of the results and what they might mean."

Overall, the country has improved in many aspects of preparedness. The US government spent $60 billion on biodefense over the last decade, including the 2004 founding of Project BioShield. The $5.6 billion initiative, managed by the government's Biomedical Advanced Research and Development Authority (BARDA) since 2006, is charged with stockpiling medicines and funding research on new therapies that could be used in instances of bioterrorism. And the spending continues: last month, BARDA awarded a five-year $68 million contract to the New Jersey company Elusys Therapeutics to develop a prophylactic treatment against anthrax.

At the same time, investments continue in the area of microbial forensics, which encompasses chemical analysis, carbon dating and microscopy in addition to DNA sequencing. Shortly after the 2001 anthrax scare, the FBI and Department of Homeland Security created the National Bioforensic Analysis Center, housed at the US Army Medical Research Institute for Infectious Diseases (USAMRIID) in Fort Detrick, Maryland. (Ironically, USAMRIID employed Bruce Ivins, who committed suicide in 2008 around the time he was fingered by the FBI as the culprit behind the anthrax letters.) Researchers there have converted medical tests—intended to identify pathogens in blood samples—to work for other kinds of evidence such as soil samples, carpet fibers and clothing.

Although next-generation DNA sequencing has radically accelerated the decoding of pathogen genomes since 2001, analysis techniques have not kept pace. "The biggest challenge

New fee structure proposed by FDA might lead to more talk

Ever since 1992, when US lawmakers passed the Prescription Drug User Fee Act (PDUFA) to accelerate review of new drugs by the US Food and Drug Administration, industry money has had an increasingly important role in fueling the regulatory agency. In the program's first year, drug companies paid less than $9 million total to the FDA through the initiative. But in the past two decades the amount has ballooned; this year, the agency anticipates receiving at least $619 million in user fees, composing roughly 65% of its budget for overseeing human drugs.

Despite the torrent of funds, the FDA has still failed to meet its goal of completing the review of 90% of new drug applications within ten months. Industry isn't exactly pleased with this report card, and they have spent the past year in negotiations with the agency to plan how the fees can be used to make drug review more efficient.

On 1 September, the FDA released a draft of its performance goals and procedures for the fifth iteration of PDUFA, which is slated for reapproval in 2012. The proposed plan takes a 'more is more' approach: user fees will increase 6% between 2013 and 2017, and, in exchange, industry is promised better communication throughout the entire drug review process.

"It's just a much more standardized set of communication and timelines," says Michael Hay, a senior biotechnology analyst at Sagient Research Systems, a San Diego-based market research firm focusing on the investment and healthcare industries. "The end result is that, hopefully, a higher rate of [new drug] applications will be approved on the first review."

Communication breakdown

When the FDA says "communication," it really means "meetings." The proposal calls for a new 60-day pre-filing period for new drug and biologic applications during which drug companies can meet with the FDA to map out the review process. "Drug sponsors can make the FDA aware of the goals and strategy for the development of the drug, and the agency can give any comments and express any concerns with the study protocol," says James Czaban, chief FDA lawyer at Wiley Rein in Washington, DC. Sponsors preparing drug approval applications then have time to address those issues, which they otherwise may not have learned of until later in the process.

The new PDUFA proposal calls for two new mandatory meetings during the drug review process: a mid-cycle review, to discuss the need for a risk evaluation and mitigation strategy, and a late-cycle review, to lay out issues the advisory committee might raise. The user fees will even fund a new ten-employee office within the FDA to organize the meetings themselves and to smooth out correspondence between sponsors and the agency. Notably, the FDA plans to hold at least four public meetings each year to receive input from patients, doctors and researchers on side effects of drugs both pending approval and already on the market. "It will be very interesting to see how this works in practice, as it seems actually like a lot of work," says Hay.

However, the measure of success is still how many applications the FDA reviews within ten months, and extra hand-holding doesn't ensure that efficiency. "More meetings are better, but meetings don't replace action," says Peter Pitts, president and cofounder of the Center for Medicine in the Public Interest, a New York–based think tank, and former associate commissioner for external relations at the FDA. Without user fees, the drug agency will shut down, so drug sponsors can't really threaten to withhold those fees if there is no improvement. "If the FDA slides on its review times, there have to be consequences to those actions," says Pitts. "Industry has been kind of wussy in terms of holding the FDA's feet to the fire."

Hannah Waters

is databases and statistical power," says Jacques Ravel, a microbiologist at the University of Maryland School of Medicine in Baltimore. Ravel helped sequence the 2001 anthrax strain while at The Institute for Genomic Research in Rockville, Maryland. If the next biological strike involves, say, bubonic plague, sequencing the attack strain will be no good unless investigators have a vast array of plague bacteria for comparison.

Virtual reality

The FBI is starting with a "virtual collection," says Jason Bannan, senior biological programs advisor for the Bureau's laboratory in Quantico, Virginia. That is, an FBI working group is figuring out what strains are available in collections across the country, so it can quickly access them when needed. Once this work is complete, the Bureau will proceed to calling in samples for a physical strain library.

Over the past decade, government leaders have also focused on how to better integrate the biodefense efforts of disparate agency cultures at, for example, the FBI and the US Centers for Disease Control and Prevention. In 2009, the White House issued a microbial forensics strategy, noting that current capabilities only "scratch the surface" of what's needed. Key recommendations included better technology and interagency coordination. To address these issues, last year the government established the Interagency Microbial Forensics Advisory Board to coordinate research and development among different departments.

The various agencies "are generally singing off the same page now," says Thomas Inglesby, director of the Center for Biosecurity at the University of Pittsburgh Medical Center in Pennsylvania.

But some experts worry that the collaboration has not yet trickled down to local health authorities, too. At an Institute of Medicine workshop on pathogen surveillance held in mid-September in Washington, DC, Joe Gibson, director of epidemiology for the Marion County Public Health Department in Indianapolis, Indiana, noted that patient privacy laws and a general reluctance of schools and health departments to share epidemiological data hinder his department's access to surveillance data and suggested that building trust and clarifying how data will be used would help foster cooperation.

Even as scientists hammer out the details of bioterrorism countermeasures, they are already using advances in the microbial forensics field to deduce the origins of naturally occurring threats to public health. Biologists have used these techniques to ferret out the sources of severe acute respiratory syndrome (SARS), recent *E. coli* infections in Germany and the cholera outbreak in Haiti following the 2010 earthquake.

"On the whole, there's a better appreciation of what microbial forensics can and can't deliver," Inglesby says. The science can only provide a clue, not a conclusion. Good old-fashioned detective work, he adds, is still necessary to catch the bad guy.

Amber Dance