BEATING THE SEIZURE COUNTDOWN

Marshaling the efforts of 4,314 paramedics, 79 receiving hospitals and 33 EMS agencies across the country, an NIH study coordinated by the U-M charts a new standard for treating seizures that won't stop.

It's a scene familiar to paramedics across the country: a man lies in the grass at a local park, his body wracked by seizures. They note that he is in status — shorthand for status epilepticus — meaning that unlike most seizures, which are fleeting, these convulsions have been going on for more than five minutes and are creating a feedback loop that will require medical intervention to short circuit.

BY IAN DEMSKY

The clock is ticking. The longer the seizure is allowed to continue, the less effective the medics' go-to drugs will be, and the harder the seizure will be to break. As the minutes wear on, his overtaxed neurons will start to die, lowering his chances of survival and putting him at risk for permanent brain damage if he does survive.

The best way to speed medication into his system is through an IV line, but he's thrashing so violently, the paramedics know it will be difficult and time consuming to place a needle safely into one of his veins. They have a few backup options: administer the medicine rectally, or squirt it into his mouth or nose, where it can be absorbed through mucous membranes — though they know those routes aren't nearly as effective and risk the medication being expelled.

Soon, first responders may be able to count on a safe, easy-to-administer alternative, thanks to a National Institutes of Health-sponsored study co-led by Robert Silbergleit (M.D. 1992), associate professor of emergency medicine in the Medical School. The findings "should lead to a systematic change in the way patients in status epilepticus are treated en route to the hospital," proclaimed an editorial that accompanied the study in the February 16 issue of the *New England Journal of Medicine*.

Journal Watch, a publication that highlights key research from more than 250 medical journals, referred to the Rapid Anticonvulsant Medications Prior to Arrival Trial (RAMPART) paper as a "landmark article." The research also holds important implications for military and civilian chemical defense preparedness.

A TALE OF THREE DRUGS

For the last three decades, paramedics' primary tool for halting seizures has been benzodiazepines, a class of sedating drugs that includes household names like Valium and Xanax. Although similar to each other, each medication has a unique molecular structure and distinctive properties. Prior to RAMPART, a lack of definitive data had fueled a sibling rivalry of sorts between medications and delivery methods, with no clear answer for front-line medics as to what was best for status patients.

Diazepam, popularly known as Valium, became the flagship benzodiazepine in the 1960s, touching off a wave of development for similar drugs. "It was discovered to be a great anticonvulsant and was the mainstay of treatment for many years," says Silbergleit. Lorazepam, marketed under the name Ativan, came along in the late 1970s as an anti-anxiety medication and gradually was recognized for its power to stop seizures.

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Comparison studies came later: In 1998, a hospital-based study found lorazepam to be the more effective first-line treatment. Then, in 2001, RAMPART's other principal investigator, Daniel H. Lowenstein, M.D., director of the University of California, San Francisco's Epilepsy Center, was the first author of a study that showed both drugs were superior to a placebo when used by first responders in the field — with lorazepam again appearing to be the superior choice. "Today, lorazepam is the standard of care in hospitals," Silbergleit says.

But the same is not true of emergency medical services, he adds. Most EMS providers still rely on diazepam, because refrigerated storage is recommended for lorazepam, which loses its potency while stored in ambulances, especially in warmer months. "And with either one, it can be very hard or impossible to get an IV started in someone who's having a violent convulsion," says Silbergleit.

Enter midazolam.

"Eventually people started recognizing that there's another benzodiazepine that is known to be extremely well absorbed transmucosally and intramuscularly," Silbergleit explains. "Midazolam, which has also been around for decades, gets absorbed and distributed to the brain quite rapidly. Its fat solubility helps it cross the blood-brain barrier."

Silbergleit co-authored a 2010 meta-analysis of a handful of small studies in children and young adults that showed non-

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Robert Silbergleit with the RAMPART study kits

IV midazolam, formerly sold under the trade name Versed, was as safe and effective as diazepam by any delivery route.

Meanwhile, a small fraction of EMS systems were already starting to use midazolam to stop seizures. "The majority of the EMS community wasn't willing to do it at all because it was completely speculative," Silbergleit says. "Nobody really knew if it was as effective, if it was safe, what the right doses would be."

Silbergleit and his colleagues knew that answering those questions would require comparing medications in real-world practice. "Clinical trials in the pre-hospital setting are challenging regardless," notes Silbergleit. "And when you're talking about status epilepticus, you're talking about one of the most time-critical things paramedics do — it's right up there with cardiac arrest. So you have to design the trial so that it fits in seamlessly with the care they need to provide."

Moreover, the researchers wanted to know how long each drug took to administer, which drug worked faster, and by how much. Asking medics to record times after the end of a run would be too imprecise a measure. So, the trial organizers worked with faculty and students at the U-M College of Engineering to design a study kit that relied upon a built-in clock and voice recorder to capture the action.

Researchers later listened to the recordings and compiled a dataset from the verbalizations medics made as they administered the drugs and noted the cessation of seizures. The bright yellow kits also kept data on storage length and ambient temperature to prevent degraded medicine from being given to patients. "Because these technologies have become cheap, easy and ubiquitous, it was possible to make an inexpensive device that could do everything we needed it to do," says Silbergleit.

The kits also allowed patients to be assigned randomly to one of the two arms of the study. When the EMS crew determined a status patient met the trial requirements, they opened the study kit and gave the patient two drugs in quick succession, one of which was a placebo. Patients first received a shot in the thigh with an autoinjector — a pre-filled canister tipped with a spring-loaded needle, similar to an EpiPen — and then medics started an IV line to administer the second agent.

"Using the autoinjector was important to the study because it allowed the intramuscular dose to be given very rapidly and only cause a small delay, about 20 seconds, before moving on to place the intravenous line. Since half the patients would be getting a placebo in the IM injection, we wanted to keep that delay as short as possible," says Silbergleit.

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'INCREDIBLY SERENDIPITOUS'

The autoinjectors used in the study were provided by the U.S. Department of Defense, which was already looking to test midazolam as a replacement for diazepam in the autoinjectors included in nerve gas antidote kits. "It turned out to be incredibly serendipitous," says Silbergleit. "Our goals to advance emergency treatment in the field meshed with the chemical threat community's desire to test the midazolam autoinjector."

David Jett, Ph.D., director of the Countermeasures Against Chemical Threats program at the National Institute of Neurological Disorders, part of the NIH, says the research is a great example of collaborative work between federal agencies and university-based researchers.

The study, in conjunction with previous data from human and animal tests, is being used to seek FDA approval to use the devices to deliver midazolam, Jett says. "Data from RAMPART will be a critical part of that overall process," he says. "We needed to test the efficacy in humans, but obviously we're not going to test nerve agents on people. So, the RAMPART findings will serve as a surrogate.

William Barsan

"Whether a seizure is initiated by a disease process or a chemical agent," Jett says, "the faster you can stop it, the better — and the evidence indicates midazolam will stop a seizure faster than what's currently available."

During a chemical exposure affecting a large number of people, the benefits of autoinjectors would be profound, Jett notes. "The autoinjectors can deliver medication in seconds, whereas starting an IV can take minutes, so each first responder would have the capacity to attend to many more victims," he says.

The RAMPART study didn't set out to prove that intramuscular injections of midazolam were better than lorazepam given intravenously, only that it was a "non-inferior" treatment. "We designed the study to see if we could give midazolam through the IM-route and have it work just as well as IV lorazepam, the standard of care," says Silbergleit. "In fact, we found that it worked better, which wasn't part of our hypothesis."

Analysis showed that upon arrival at the emergency room, 73 percent of patients who received midazolam had stopped having seizures, compared to 63 percent of patients who got the lorazepam. Moreover, fewer patients who received midazolam required hospitalization — 58 percent versus 66 percent.

Silbergleit and his colleagues weren't entirely sure to what they should attribute midazolam's unexpected success. "It's interesting to speculate that a difference of just a few minutes with earlier administration in the intramuscular group may have been enough to drive the slight superiority of the intramuscular route with respect to outcome," they wrote in the *NEJM*. "However, it is also possible that the difference in outcome between the two treatment groups reflects differences in the efficacy of the agents used, rather than the route of administration."

Either way, says Silbergleit, "The takeaway is that intramuscular midazolam should be the preferred way to treat status epilepticus in the field."

While medics could start giving midazolam injections to seizure patients using a syringe, they won't be able to carry autoinjectors until the devices receive FDA approval. Eventually making them available for home use would require further study. "The fact that autoinjectors can be safely used by paramedics doesn't tell us that they can be safely used by family members," Silbergleit says. "It's certainly a possibility. If the breathing depression caused by seizures is worse than side effects for breath-

ing caused by the drug, then it could be that family members could safely use it."

A PUBLIC GOOD

RAMPART was the first trial completed by the Neurological Emergency Treatment Trials (NETT) network, which was launched with a $7.7 million grant in 2006 — and which recently had its funding renewed for another five years and $11.5 million.

The NETT's unique hub-and-spoke model spans the U.S. and makes it possible to overcome one of the biggest roadblocks to finding new and better treatments for neurological emergencies: access to large numbers of patients and the ability to treat them quickly, says emergency physician William Barsan, M.D., principal investigator of the NETT's U-M-based clinical coordinating center. For RAMPART, the NETT enlisted the help of 4,314 paramedics, 79 receiving hospitals and 33 EMS agencies, to treat 1,023 episodes of patients with status epilepticus. Subjects ranged in age from a few months old to 103 years.

"With RAMPART, we knew that whether the results were positive or negative, we would change clinical practice," says Barsan, professor of emergency medicine at the U-M and former chair of the department. "What makes the NETT unique is we're not focused on a particular disease, but rather on the acute phase of treatment for any neurologic disorder that comes through the emergency department such as stroke, head trauma, epilepsy and cardiac arrest."

RAMPART is also a great example, Barsan says, of the type of research that has direct, immediate benefits for the public that private companies aren't interested in pursuing. "This is what we mean when we talk about 'comparative effectiveness research,'" adds Silbergleit. "When we have multiple existing ways of doing things, it's a public good to compare them to figure out which works best. We've had a research system that's primarily been driven by new technology or the latest molecule, rather than trying to determine which of the available resources work best."

Although it may take some time for midazolam protocols to be widely adopted by EMS agencies across the U.S., the reception so far has been extremely positive, says Silbergleit. In April, the Neurocritical Care Society published new guidelines on the treatment of status epilepticus that incorporated RAMPART's finding that midazolam was at least as effective as lorazepam and listed it as the "drug of choice for IM administration." [M]

BY THE NUMBERS

ALMOST 1 IN 10
Risk of suffering a seizure in one's lifetime

1 TO 2 %
Proportion of emergency department visits for seizures

70%
Proportion of first-time seizures for which no cause is apparent

120,000 TO 200,000
Number of people each year who experience status epilepticus

UP TO 55,000
Number of deaths each year to which status epilepticus contributes

1 IN 5
Mortality rate for status epilepticus that continues for more than half an hour

$4 BILLION
Estimated annual inpatient cost for status epilepticus patients