Syria Nerve Gas Attack Points to U.S. Need For New Antidote

An aging drug stockpile is due for a revamp.

By **Monte Reel**
April 11, 2017, 5:00 AM EDT
Updated on April 12, 2017, 11:34 AM EDT

A nine year-old sarin gas attack survivor, Hassan Dallal, receives medical treatment at a Syrian hospital on April 5, 2017. *Photographer: Mohammed Karkas/Anadolu Agency via Getty Images*

Back in the early 2000s—after Sept. 11, the anthrax attacks, and the rumors of chemical weapons in Iraq—the U.S. government began stockpiling drugs that could be used as antidotes for deadly nerve agents. To spur pharmaceutical companies to develop new and improved drugs, despite their limited profitability, Congress passed Project BioShield, a multibillion-dollar program that's helped fund more than a decade's worth of research and development.

Last week's mass sarin attack in Syria, as well as February's assassination of North Korea's Kim Jong Nam with VX poison, served as grim reminders that the threat hasn't gone away.

The standard therapy for both of those poisons is the same three-drug cocktail that's been available since the 1990s. Now, just as the reality of chemical weapon use has reemerged, the first new nerve gas treatment developed through Project BioShield is at the final stages of a long testing and approval process.

The "new" antidote is an old drug–midazolam—the same, powerful sedative used in everything from anesthesia to lethal injection. [1] Although it's still awaiting FDA approval for use as a nerve gas antidote, it's far enough along in the development phase that the government could request emergency approval to distribute the drug in the event of a crisis.

Three-drug cocktail

Nerve gases block enzymes in the body that regulate muscle control. This leads to seizures and can stop a person from breathing. The seizures can also cause significant neurological damage. The three drugs currently used in treatment–atropine, diazepam, and 2-pam–do different jobs. Atropine and 2-pam are effective at stripping the nerve agents from the enzymes, restoring their proper function. Diazepam—better known as Valium—is used as an anticonvulsant to stop seizures and protect the brain.

For decades, the U.S. military has supplied soldiers with autoinjectors filled with the three drugs, and the government also includes them in the Strategic National Stockpile's "chempacks"—emergency kits distributed to about 1,960 emergency rooms and fire stations at 1,340 locations around the country. However, for years scientists have suspected that diazepam might not be the best anticonvulsant for the job, and recent tests on rodents and primates reinforced those suspicions.

A U.S. Marine holds the standard-issue Pralidoxime, an anti-nerve gas agent, as well as an Atropine injection in 2002 at Camp Commando in Kuwait. Photographer: Joe Raedle/Getty Images

Midazolam emerged in the 1990s and 2000s as a potential improvement. "In all animal tests, midazolam was twice as potent and more rapidly acting than diazepam," concluded a 2002 report prepared by the U.S. Army Medical Research Institute of Chemical Defense, "thus minimizing the possibility of seizure-induced brain damage." In 2012, the government funded a clinical trial that supported those findings in human patients suffering epileptic seizures. After that, Project BioShield awarded Meridien Medical Technologies, a company owned by Pfizer Inc., a $61 million contract to develop a midazolam autoinjector that would replace diazepam injectors in the standard three-drug treatment.

Meridian already manufactures the spring-loaded autoinjectors used by the military and emergency personnel. Assuming that the FDA approves the use of midazolam for seizure control, the drug not only would replace diazepam as a treatment for nerve gas exposure, but it

would likely emerge as the go-to seizure treatment in ambulances and emergency rooms.

Already used, off-label

Dr. William Meurer, with the University of Michigan's Department of Emergency Medicine, led a recent study that found that ambulances increasingly began using midazolam "off label" for seizure control after the 2012 clinical trial was published.

"Midazolam is now known by the medical community to be superior, even though it's not approved by labeling yet," Meurer said. Before the clinical trial, intravenously administered lorazepam (a cousin of diazepam) was the gold standard for seizure treatment in emergency situations, he said. In 2010, midazolam was used in about 26 percent of pre-hospitalization seizure patients; by the end of 2014, however, it was used in 62 percent of those cases. "It's a grand slam," Meurer said. "It's very unusual for us to find something that's cheaper and better and easier to store."

A hazardous materials team conducts checks inside Kuala Lumpur International Airport in Malaysia on Feb. 26, 2017. Photographer: Mat Zain/NurPhoto via Getty Images

Although Meurer suspects that more ambulances will begin replacing their stores of lorazepam in favor of midazolam, this doesn't necessarily mean that newly approved indications for the drug will be a boon to midazolam manufacturers. Because it's already used in many other

medical situations and is produced by several manufacturers, the financial impact could be buffered.

Meridian's hold on the autoinjector market, however, would only grow stronger. In addition to supplying the government with the anti-nerve agent injectors, the company also holds the contract for the EpiPen epineprhine autoinjector. Meridian has a patent on its autoinjector design through 2025.

Antidotes with other uses

Diazepam's replacement by midazolam is likely to be the first change to the nerve gas exposure treatment, but it might not be the last. Dr. Rick Bright, the director of BARDA (Biomedical Advanced Research and Development Authority, a program within the Department of Health and Human Services), said other drugs are being tested that might be improvements on atropine and 2-pam.

For example, a catalytic antioxidant called AEOL10150, manufactured by Aeolus Pharmaceuticals, is being tested for use against certain chemical weapons, and a drug called LY293558, manufactured by Eli Lilly & Co., has shown promise when administered with atropine to treat the nerve agent soman. Additionally, the anesthesia drug ketamine—sometimes used illegally under the street name "Special K"—recently underwent a nonclinical trial to test its potential to mitigate severe brain injuries in the event of nerve agent poisoning.

"It takes years and years for these drugs to go through the approval process, and because of that, we try to look for drugs out there that are approved for other uses," said Dr. David Jett, the director of CounterAct (Countermeasures Against Chemical Threats), an office within the National Institutes of Health that aims to develop new antidotes.

Even if new antidotes are approved and adopted, it doesn't mean that the threat posed by nerve agents will go away. To work effectively, the drugs should be administered very soon after exposure—within minutes, if possible. If large quantities of nerve gas are unleashed, as appeared to be the case in Syria, no medical response could fully protect exposed populations.

"At high enough doses," Jett explained, "there's not a lot you can do."

1. *Death penalty critics have assailed the drug's use in executions, saying it inadequately sedates the condemned, resulting in unnecessarily--and potentially unconstitutionally--painful deaths. As a result, manufacturers have stopped supplying the drug to several states for use in capital punishment. Starting April 17, Arkansas plans to kill eight death row inmates in 11 days because the state's supply of midazolam will expire at the end of the month. Lawyers representing several of those prisoners have asked the courts to stop the killings, citing in part executions that were botched because of midazolam's ineffectiveness.*