

Next Generation Nerve Agents: Symptoms, Treatment, and Lessons Learned

In March 2018, a father and his adult daughter collapsed on a park bench in Salisbury, United Kingdom. After ruling out other causes (e.g., opioid overdose), clinicians decided that they were likely suffering from the effects of being exposed to a nerve agent. Eventually, the agent was determined to be a novel nerve agent: Novichok, a fourth generation agent (FGA). In September 2019, ASPR TRACIE interviewed Susan Cibulsky, PhD, a Senior Policy Analyst with ASPR and Mark Sutter, MD, with the Department of Homeland Security's / Countering Weapons of Mass Destruction Office, who have both studied the incident and met with some of the responders and clinicians responsible for treating these patients. Together with other federal and non-governmental partners, they have worked to develop scientific and clinical materials to help responders and providers prepare for, recognize, and treat FGA-exposed patients.

John Hick (JH): *What are key differences between fourth generation agents and other nerve agents in terms of both physical characteristics and clinical presentation?*

Susan Cibulsky (SC): The FGAs are low volatility liquids like VX, but with even lower vapor pressure than VX. The relatively long delay between exposure, from dermal contact, and initiation of symptoms is one big difference between the FGAs and other nerve agents. It can be hours—even days—before symptoms begin. It takes time for the substance to be absorbed through the skin. This is part of the reason that the progression of symptoms may be different than for other nerve agents. In the U.K., the patients did not initially show many signs of nerve agent exposure (consistent with the mnemonics) that we expect. For example, they did not exhibit bronchorrhea or have difficulty breathing.

Mark Sutter (MS): I think you have to interpret their clinical presentation in the world of synthetic opioids, synthetic cannabinoids, and the various novel psychoactive substances that we see. While these patients eventually presented a more cholinergic picture, it was significantly delayed. They had miosis (pinpoint pupils), but without the other overt immediate SLUDGE or DUMBBELS symptoms. If we think about the

Nerve Agent Mnemonics

Patients may demonstrate a combination of:

SLUDGE – Salivation, Lacrimation, Urination, Defecation, Gastrointestinal upset, Emesis

and

DUMBBELS – Defecation, Urination, Miosis/Muscle weakness, Bronchospasm/ Bronchorrhea, Bradycardia, Emesis, Lacrimation, Salivation/Sweating

epidemiology of the “found down” or unresponsive presentations, providers likely assumed these patients resembled someone who had been using one of these novel substances rather than someone exposed to Novichok.

One thing I noted from the discussion with the providers is the need to rely on the basics and keep differential diagnosis open. In the first 24-48 hours after FGA poisoning, optimal outcome is dependent on meticulous

supportive care. Healthcare providers used universal precautions to protect themselves. This highlights a best practice when facing an unknown situation. We don't necessarily have to know the substance, but we must rely on the basics.

JH: *It seems like if there is one physical differentiator, this is an agent that is extremely environmentally persistent. The good news is it's less likely to off-gas, and inhalation isn't a huge risk, but contact is.*

MS: Yes, the environmental persistence and delayed onset of symptoms are both very important for preparedness.

SC: In addition to their low volatility, they are highly water soluble but not readily degraded by water. They can be spread easily, as was seen in the UK. This represents a cross-contamination risk for responders.

JH: *What were the dominant symptoms the patients presented with?*

SC: Both patients had small pupils, slow heart rates, and a decreased level of consciousness on initial presentation.

MS: One patient had bradycardia, and the other patient's heart rate was on the lower side of normal. They were described as staring off into space—in almost an altered, postictal (post-seizure) state. This presentation of bradycardic and

not responding to commands had first responders initially thinking they had overdosed on opioids. In retrospect, the patients did have some cholinergic symptoms at the scene, but I don't know how easy those were to recognize. Responders in this area were previously notified to be on the lookout for fentanyl analogs. The big thing providers noted was lack of pulmonary edema. Both patients had clear lungs, and did not demonstrate any airway or breathing difficulties.

SC: It is so important to leave open differential diagnosis, and keep in mind what the environment outside of the medical scene was like. How did they get to the bench? Who were they? That is one of the things that turned the course of the events—one of the law enforcement officers knew that the male had been a Russian spy and informed the hospital.

JH: *As time went on, did pulmonary issues or hemodynamic consequences increase?*

SC: There were no issues with their airways. They did receive tracheostomies, but much later.

MS: Yes, the tracheostomies were for prolonged intubation—not because of airway failure. On arrival, a key finding was lactic acidosis. Lactates were at 5 and 13 millimoles per liter. Their pH levels were around 7.1 or 7.2, with a bicarb of 14. They

After the 2018 incidents in the U.K. involving an FGA, the White House National Security Council convened a federal interagency working group to identify and develop resources to help the emergency response community prepare for and respond to a similar incident. While FGAs share similar characteristics with other nerve agents, FGAs also pose several unique challenges in terms of toxicity, detection, persistence, and potential for delayed onset of symptoms. Four resources were developed to address these characteristics and challenges and provide tailored guidance to various segments of the emergency response community:

- [Safety Awareness for First On-Scene Responders Bulletin](#)
- [Reference Guide](#)
- [Pre-hospital Medical Management Guidelines](#)
- [Hospital Medical Management Guidelines](#)

These are all located on [CHEMM's Fourth Generation Agents page](#).

were unresponsive, acidotic, had small pupils, and were eventually intubated and provided supportive care. While this could at first be presumed as post-seizure lactic acidosis, the lack of rapid clearance of the lactate made it clear that this was not only from a seizure. The fact that this

persisted kept the differential diagnosis open.

JH: *Did the physicians try atropine to control the bradycardia?*

MS: Yes, and the patients responded well to atropine.

JH: *How long did the hemodynamic issues and other effects last?*

MS: They were intubated in the emergency room, and were started on fluid resuscitation and initially, the providers were still treating them as though they had overdosed on opioids, even though when they look back, there were some things that didn't fit. They got bradycardic overnight—one got to a heartrate of 12—but they did respond to atropine. The nurses noticed that the sheets were wet due to intense sweating, so they changed them overnight, yet neither patient ever became febrile. On the first night, the ICU physician actually considered a cholinergic-type poisoning, but the absence of pulmonary symptoms (i.e., edema) led him away from that diagnosis.

They didn't get extubated for weeks, as sometime in the first 24 hours of the hospital course, they became hemodynamically unstable and needed vasopressors.

JH: *What worked as far as treating their blood pressure issues?*

MS: They went on a vasopressor and fluids, and they also became markedly hypernatremic (i.e., their electrolytes were significantly imbalanced), with a sodium of 157 and potassium of 2.5. Basically, clinicians went into general supportive care mode, then once they realized who the patients were, they started different types of testing and treatment, to include administering atropine and 2-PAM (pralidoxime chloride). The clinicians who cared for the patients believed that 2-PAM helped with hemodynamic stability. It wasn't administered early because the diagnosis hadn't been made; 2-PAM was started somewhere in the 24-40 hour range. In these cases, Salisbury's delayed use of pralidoxime was judged to be clinically effective by the treating physicians and should be considered even if significant time after the exposure has elapsed.

The patients received pralidoxime and also parenteral scopolamine subcutaneously every eight hours (because there were no pulmonary secretions to which to titrate; they did scheduled dosing). Clinicians also used atropine boluses as needed to correct slow heart rates. The clinicians noticed that pralidoxime improved the patients' hemodynamic stability and urine output. But we need to caveat this—the patients were still getting supportive care. There are still a

lot of theories about the medication having effects outside of just regenerating cholinesterases, but animal studies don't show consistent data that they improve hemodynamics with general carbamates or organophosphates. So the reliability of pralidoxime to make a difference is unclear based on literature with cholinesterase inhibitors in animal studies, but the clinicians who cared for these patients felt that it improved their hemodynamics.

JH: *There's relatively little downside to repeat dosing of 2-PAM. It's known to cause some hypertension—is that possibly the effect they were observing?*

MS: We aren't sure. There has been a lot of postulated theory that there are nicotinic receptor effects, including in the kidney, and that may be what contributed to the improved urine output. Did pralidoxime stimulate these receptors? The mechanism is still unknown. Their urine output improved, and that is what the clinicians noted.

JH: *What else have we learned about patient treatment?*

SC: In this case, the treatment was very prolonged, so the hospital went through large amounts of drugs.





MS: While these were prolonged hospitalizations and the cumulative dosage was significant, we weren't seeing these 50 or 100 mg atropine usages in short time frames. Something else to note: the U.S. doesn't currently have parenteral scopolamine, so I don't know how we would make adjustments. When we talk about hospital preparedness, it is important to note these issues; we can't hang our hats on these amounts based on so few actual patient experiences.

JH: *So what are some alternate preparations or formulations that are already available and could be used if needed?*

SC: Ophthalmic atropine can be used sublingually if it's available as the concentration is high.

MS: If you look at the [paper published on contingency countermeasures](#), you have other anticholinergics (e.g., Atropine [1% Ophth 5gtt SL] or Cyclopentolate [1% Ophth 20gtt SL] or Glycopyrrolate [0.4mg IV/

IM/IO]). These are all options, as are inhalers (e.g., Ipratropium inhaler [4-6 puffs] OR Tiotropium inhaler [2 capsules]).

Dosing on these is going to be a challenge because if you are using a sublingual route, and the patient is experiencing significant salivation, you may have to compensate with higher dosing or possibly preparing the patient by placing a cotton ball under their tongue to blot the saliva before administering the medicine. If

we take a step back from FGAs and just talk about nerve agents in general, you really need to factor in how much drug is absorbed sublingually. ASPR's [Biomedical Advanced Research and Development Agency \(BARDA\)](#) is planning a study of the ophthalmic atropine product to determine pharmacokinetics and bioavailability with sublingual administration.

The more complex the drug pharmacology, the more side effects you'll need to anticipate. If we think the patient was exposed to a nerve agent and seizure activity is possible, we try to stay away from drugs that have a wide range of central nervous system effects. The bottom line is we have no data, so we ideally stay away from those types of drugs.

JH: *Benzodiazepines have historically been discussed as both anti-seizure medications and to help manage the psychological effects of earlier generations of nerve agents. Should this still be considered?*

MS: I would use the benzodiazepines first across the board.

SC: Midazolam is now FDA approved for status epilepticus. It's rapidly absorbed after

intramuscular injection, making it easy to use in the field and mass casualty situations.

JH: *Was any decontamination done on the patients once the providers realized what they were dealing with?*

MS: Yes—the first thing to remember is these patients developed significant sweating during the first hospital day. The sheets were changed, and they received traditional patient hygiene while in the ICU. Based on agent detected from skin swabs, on Day 10 of hospitalization, the palms of their hands were treated with Reactive Skin Decontamination Lotion (RSDL). This was repeated on Day 16. Skin-measured levels appeared to drop after each RSDL

application. It's another lesson that we learned—delayed RSDL use still removed the agent.

JH: *For those who do not stock RSDL, would soap and water still be effective?*

SC: Yes, soap and water will work, but healthcare providers need to be careful about the water runoff - they need to try to contain it and avoid contact with it as much as possible.

JH: *Did any providers experience negative health effects from treating these patients?*

SC: No, fortunately their use of universal precautions was effective. ■

Organophosphate and carbamate pesticide exposures are common and can present the emergency department with challenges including provision of safe decontamination and supportive care and specific treatment. The [2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System](#) indicates that Poison Control Centers were consulted in 2017 on three fatal cases and:

- 2,326 case mentions of "Organophosphate Insecticides Alone;"
- 35 "Organophosphate Insecticides in Combination with Carbamate Insecticides;" and
- 493 "Organophosphate Insecticides in Combination with Non-Carbamate Insecticides."