

SUMMARY
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NERVE AGENTS

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***Please note: Data and analysis discussed in these presentations were current when presented. Data collection and analysis are ongoing in many cases, therefore updates may be forthcoming elsewhere on this website, through publications such as [CDC's Morbidity and Mortality Weekly Report](#) or other venues. Presentations themselves will not be updated. Please bear this in mind when citing data from these presentations*

OVERVIEW:

- “Nerve agents” are aptly named, since they affect the nervous system
- Structural name for these agents is organic phosphorous compounds (OPCs)
- Term “nerve agents” commonly used to refer to a specific **military** class of OPCs (soman, sarin, tabun, VX)

BACKGROUND:

Nerve agents are basically chemical agents that work on the nervous system. These chemical agents are part of a bigger class of compounds. They were discovered in the first part of our century while we were investigating or looking for ways to control insecticides. During the search for *new* organophosphates, the nerve agents were found to be more lethal and have military use; so they were developed as military agents.

Common organophosphates would be a parathion or malathion, and are commonly seen in situations of suicide attempt or accidental poisoning. Military agents such as nerve agents work a little bit differently than organophosphates. They share the same basic mechanism. However, they emphasize (or they work more on) certain target organs that are different than what the organophosphates work on. Unfortunately, they can both kill humans, whether in war or terrorism or just by suicide or simple accident.

Carbonates and carbamates are mentioned because they are cousins of organophosphates. They are different chemical compounds. They do act in the same way by inhibiting the same enzyme in your body. They're different, though, because they are reversible. In general, the organophosphates and the nerve agents may become irreversible with time, because of their action on a binding enzyme.

The carbonates, however, are usually used in the treatment of myasthenia gravis as well as in anticholinergic drug poisoning. They were used by the military to protect from nerve agents during the Gulf War.

HISTORY:

Nerve agents were developed by the Germans in the 1930s

- In 1934, Gerhard Schrader discovered tabun and called it GA (G is for German and A is for the first element)
- Soon after that he discovered sarin, which is GB
- He then discovered GD, which was soman, and
- GF, which is cyclosarin
- It wasn't until later on in the 1960s that British scientist (R. Gosh) discovered the VX gas
- Iraq reportedly used tabun and sarin and maybe cyclosarin in the Iraq/Iran war between 1984 and 1988
- It was used against soldiers, as well as civilians, and caused a lot of damage

Another use of the nerve agents occurred in Japan in two instances:

- The first time was in Matsumoto in 1994
- The second (in a larger scale) took place in 1995 in the Tokyo subway system

The Aum Shinrikyo Cult tried to terrorize the public, as well as the government, by using these agents. In the first attack in Matsumoto they were able to kill seven people and injure more than 600. In the second attack, where ten members of the cult released the sarin gas in five different trains, it killed twelve people and injured more than 5,000 victims.

The U.S. has stockpiles of VX as well as sarin. There are over 30,000 tons of these agents and the U.S. is working hard to deactivate these agents and to comply with an international treaty to limit chemical agent development.

It is not very easy to deactivate these agents and a lot of controversy is ongoing addressing the best way to actually deactivate them.

MILITARY DESIGNATIONS FOR NERVE AGENTS:

- GA is tabun
- GB is sarin
- GD is soman
- GF is cyclosarin
- VX is VX; it doesn't have another name
- Cyclosarin or GF is rarely used—although it's theorized that Iraq might have developed it

PHYSICAL PROPERTIES:

- They're liquids
- Most of them are odorless
- Some (such as) tabun and sarin might have a vague odor, but is not reliable
- VX is oily in texture

The two most important properties for these agents:

- Volatility, or basically how much of that evaporates at room temperature. How much of the liquid is a gas that you can inhale and get sick from?
- Persistence, which means, if this agent was placed on your skin, how much is left on your skin? Did it evaporate, did it disintegrate, or what happened to it?

In general, think about VX as an oil that is highly persistent and poorly volatile, it doesn't evaporate all that well. And think about the other agents, the G agents, as highly volatile, but have poor persistence.

The clinical significance of this differentiation is based on the route of exposure. If persistent agents such as VX are on the patient's skin, it will get absorbed and cause an effect by dermal absorption rather than by evaporating. This is because they have poor volatility and will not cause a lot of symptoms by inhalation.

If you place agents like sarin, soman, or tabun on the skin (or around the patient) they will evaporate and the patient will most likely inhale them. If they go on the skin, and evaporate off the skin, then dermal absorption is less important. The G agents evaporate very rapidly and have more inhalational effects than VX.

And VX (being oily and persistent) doesn't evaporate much. The absorption, however, is very good via mucous membranes or gastrointestinal route (e.g., if somebody ingested VX or the G agents, they would be absorbed quickly). Thus, the commonly feared routes are the dermal and inhalational routes.

TOXICITY

These agents are one of the most toxic agents to human beings. They say one drop of VX or one to ten CCs of the G agents may be fatal. A common example is the Lincoln Memorial Columns on the penny. It is said that as much VX as the size of the column of the Lincoln Memorial will be enough to kill a human being.



These agents in general act pretty rapidly, especially the ones that evaporate like G agents. They go through the lungs and poison the patient. If VX is present in a small quantity, it might take some time to cause a clinical effect. Keep in mind that if you put a lot of VX on your skin you will get effects pretty rapidly. If you put a small amount of VX, you may see a so called delayed effect of VX up to 18 hours after the exposure. In general, when we talk about G agents that evaporate and get inhaled, we're talking about minutes. This is what was seen in the sarin Tokyo attack where patients had symptoms shortly after the gas was released.

MECHANISM OF ACTION:

What do these agents do? They inhibit acetylcholine (ACh) esterase. This is a very important enzyme in the body. The enzyme breaks down ACh at synapses and neuromuscular junctions in the body.

When you block this enzyme, the neurotransmitter ACh is no longer destroyed. This leads to an excess of ACh in your body. Excessive ACh in your body that is not being broken down is responsible for the clinical effects seen in nerve agents poisoning.

ACh basically mediates muscle contraction. If you have a lot of ACh you will have a lot of muscle contractions to the point of paralysis. ACh exists in your brain, so if you have a lot of ACh you will also have a change in your mental status and seizures.

ACh makes:

- bowels contract
- bladders contract
- salivary gland release saliva
- sweat glands release sweat

If you have a lot of ACh you will have:

- Diarrhea

- The bladder contracting and leaking urine
- Excessive sweating
- A lot of saliva or salivation

Another tricky effect of ACh is its effect on the preganglionic synapses. These are basically synapses at sites that do not have a direct effect, but they (instead) affect other neurons. This is why we say that excessive ACh can stimulate the adrenergic, adrenaline system, and can also stimulate the parasympathetic system.

Therefore, clinical symptoms of nerve agent exposure are symptoms of ACh excess, because the enzyme breaking down ACh is not functional. The enzyme inhibition that the nerve agents cause may become irreversible with time. We call this process “aging.”

The term aging is important for nerve agents, especially soman, which causes aging pretty rapidly. Basically, when you inhibit the ACh esterase (if you wait several hours), this inhibition might become irreversible (as opposed to carbonates, which have reversible bindings). They bind to the enzyme, and after a couple hours they move away and the enzyme can function intact and break down ACh again.

This aging phenomenon is a problem because once aging occurs, the enzyme cannot be used again. The body has to synthesize new enzymes and it takes several weeks. Aging varies from agent to agent. Typically, sarin gas ages within several hours. The notorious one is soman, which ages within minutes.

CLINICAL PRESENTATION:

SLUDGE MIOSIS

- Salivation
- Lacrimation
- Urination
- Diaphoresis
- GI distress (diarrhea, vomiting)
- Emesis

TRIPLE Bs (BBB)

- Bradycardia
- Bronchorrhea
- Bronchospasm

SLUDGE and the TRIPLE Bs:

The SLUDGE is salivation, lacrimation, urination, diaphoresis, GI distress, diarrhea and E is for emesis (vomiting). Triple Bs are bradycardia, bronchorrhea, bronchospasm, and then there’s the “M” for miosis. These are all called muscarinic effects.

Another effect of excess of ACh is the nicotinic effect. Since ACh works at the neuromuscular junction, you will have fasciculations; even paralysis and weakness.

Nicotinic: MTWThF

- Mydriasis (pupil dilation)
- Tachycardia
- Weakness
- Hyperthermia
- Fasciculation

Children who were exposed to nerve gasses in Tokyo or Matsumoto (or in the Iraq/Iran war), seemed to be prone to more toxicity because they breathe faster, they inhale more, their body weight is smaller, and there may be some metabolism differences in their body.

- Compared with adults, children exposed to nerve agents are thought to be less likely to have miosis and more likely to have increased secretions,
- Children are also thought to have more seizures, hypotonia, and weakness than adults,
- No studies have been done on nerve agents and children, even though historical incidents have affected children.

DIFFERENTIAL DIAGNOSIS FOR NERVE AGENT POISONING:

What else should you think about when seeing the symptom complex insinuates a nerve agent exposure?

- Gastroenteritis
- Ingestion of muscarinic mushrooms (*Amanita muscaria*, *Clytocybe*, *Inocybe*)
- Pesticide poisoning
- Carbamate overdose
- Metal ingestion

Think about:

- Carbonate overdose, (if someone took too much of their myasthenia gravis medication), or
- Pesticide poisoning

DIAGNOSTIC WORKUP:

No lab workup is useful for acute nerve agent poisoning. RBC and plasma cholinesterase (butylcholinesterase) levels may be checked, but these results are usually not immediately available.

PREHOSPITAL CARE AND DECONTAMINATION:

- First responders: Respirators, goggles, protective clothing
- Self-contained breathing apparatus (SCBA) is recommended in response to any nerve agent vapor or liquid
- Butyl rubber gloves (most agents are lipophilic)
- 20 percent of healthcare workers in Tokyo had mild symptoms after taking care of patients – these symptoms included nausea, eye pain, and headache
- Inhalation exposure: Remove from the exposure
- Dermal: wash with soap and water or mild (0.5%) sodium hypochlorite (bleach) solution if availability of water is limited
- Ingestion: no charcoal as these patients are at risk for vomiting and aspiration

Remember, these are gasses and liquids that can be absorbed through the skin. They're very easily absorbed through mucous membranes, GI route, eyes, respirators, and lungs. Protect our prehospital providers by providing goggles and having them wear respirators.

In Tokyo, 20 percent of the health care workers taking care of patients exposed to gas still got sick and reported some kind of symptoms. They were not very severe, but they had nausea, eye pain, and headaches. We think this is because of the pockets of gas in the clothes of the victims that were released when they were getting undressed.

DECONTAMINATION TECHNIQUES:

If somebody is exposed to a gas, all you need to do is remove them from exposure. If they have dermal exposure, we recommend soap and water. Again, 5% sodium hydrochlorite or bleach is thought to deactivate the nerve agent and is recommended. If somebody ingests a nerve agent, we usually do not recommend binding it with charcoal because these patients are going to be vomiting and we don't want them to vomit charcoal and aspirate, causing pneumonia.

ANTIDOTES FOR NERVE AGENTS:

- Nerve agents cause an excessive amount of ACh in our body
- **Atropine** is a muscarinic receptor antagonist or blocker. It occupies muscarinic receptors and hinders the ACh's ability to exert its effect at all these target organs
- Unfortunately, atropine only treats the muscarinic symptoms and does not do the same for the nicotinic receptors. Remember, nicotinic receptors are the ones that cause paralysis, weakness, and sometimes cardiac symptoms, so atropine is not enough
- When we give atropine; it goes inside the brain and also helps out in some of the muscarinic effects on the brain, which is good
- We can give atropine IV, IM, or by an endotracheal tube
- The dose is: 2 mg every 5–10 minutes
- The end point is resolution of bronchorrhea or improvement in the secretions in the respiratory tract
- For children, give 0.5–1.0 mg IM/IV every 5–20 minutes. For children < 6 months old, the dose is 0.05 mg/kg, with the minimum dose being 0.1 mg
- Glycopyrrolate may also be used, but it does not penetrate the CNS and will not improve muscarinic central nervous system symptoms
- **Oximes** complete what the atropines fail to do, which is basically to dissociate the nerve agent from the ACh esterase, thereby freeing our ACh esterase
- Oximes reverse the binding of the nerve agent to the enzyme, especially if given prior to aging – also it acts as a scavenger and inactivates circulating nerve agents
- With oximes, the ACh esterase can break down the excessive ACh and resolve the problem from its root
- The good thing about oximes is that they actually work everywhere in your body; they can work against the ACh esterase, which is close to the muscle and will work on nicotinic symptoms
- The common oxime that we use is pralidoxime or 2-PAM. Slow IV bolus. Dose is 25–50 mg/kg in children or 2 gm in adults, targeting a serum level of > 4 mg/L. If given IM using the auto-injector, the level is achieved in 8 minutes
- May repeat the dose in 1 hour. The effect is lost after 3 hours of exposure to sarin, because of aging
- Keep in mind that the longer you wait the more likely the enzyme nerve agent bond has aged and pralidoxime will not work, because the enzyme inhibition has become irreversible

Side effects of oximes (like pralidoxime) include elevated blood pressure but in general it's a safe drug. There's ongoing research right now to develop better agents, specifically agents that will help us out with nerve agents like soman:

- **Benzodiazepines** are used to treat seizures. Diazepam (Valium) is given IM or IV (5 mg) and is thought to work better than other benzodiazepines
 - ~That doesn't mean that you should not use other benzodiazepines if Valium is not available.

- ~If you have Valium, 5 mg (either IV or IM) it can be repeated every five to fifteen minutes.
- **Pyridostygmine** is another medication that is used
 - ~It's a carbamate that will reversibly inhibit the ACh esterases
 - ~The soldiers in the Gulf War took it orally. Therefore, they were inhibiting a certain amount of enzymes, enough to survive if they were exposed to a nerve agent. This is because the blocked enzyme would be released later and a healthy, functional stock of the enzyme would be liberated to break down the excess ACh.



The Mark I kit is famous, because our soldiers in Iraq carried. It contains 600 mg of the pralidoxime as well as 2 mg of atropine. Soldiers have specific training on how to use it and if somebody is exposed to a nerve agent then he/she has an antidote.

PSYCHOLOGICAL IMPACT:

Every single terrorist event will cause a lot of psychological damage. One study looked at the Tokyo sarin gas attack and found 60 percent of the victims had post traumatic stress disorder six months after the event. They feared riding the subway; they had nightmares and depression. It is not clear whether these effects are due to exposure to nerve agents or because of the whole terrorist event.

There are experimental therapies being evaluated for the treatment of nerve agents. Some examples include (Paroxinases that degrade the nerve agents).

ADDITIONAL RESOURCES:

- <http://www.bt.cdc.gov/agent>
- The Nationwide Telephone Number for Poison Control Centers: 1.800.222.1222 (Toxicologist is "on call" 24/7)
- Medical Management of Chemical Casualties Handbook (<http://www.fas.org/nuke/guide/usa/doctrine/army/mmch/NervAgnt.htm>)

Questions and Answers:

Question:

There is concern regarding some of the upcoming events that we're facing – the conventions for one, and the Olympics for another. Do you have any comments on large events, especially with many people sitting in one arena or area? What we should be thinking about as healthcare providers?

Ziad Kazzi:

Some of the things that we should think about [includes] atropine. How much atropine do we have? Do we have atropine in our hospital? Do we have pralidoxime? Be familiar with the dosages, with the side effects. The more familiar we are with the topic the better

we will be at handling such an unfortunate event. By the second event in Japan, the Japanese were ready to treat these victims because of the first event that happened in Matsumoto. It was still a disaster in a lot of ways. You can prepare as much as you want for disaster, but once it happens you will be overwhelmed (as will the hospital resources), but at least (in this case) they had enough atropine. They had pretty good response to the second event and I think that probably prevented more deaths from the attack.

Question:

You said that for prehospital care, the responders needed to wear rubber gloves; are vinyl gloves not effective?

Ziad Kazzi:

If you have vinyl gloves, you have to wear what you have, but rubber is better because these agents are lipophilic (lipid soluble) and they might be able to penetrate if it's a VX agent, for example. But you have to wear what you have and protect yourself. And, again, think about it this way, too. What happened in the Tokyo attack and in Matsumoto; these agents that were used like sarin, the exposure was by inhalation; [they] were gases. This is very important to think about. Also if you don't have a respirator, you should try your best. I'm not saying that you should not respond to the victim, but if such an event occurs, these are things we need to think about.

Question:

Any specific recommendations on stockpiling of drugs, the atropine, or what have you?

Ziad Kazzi:

There's ongoing work right now by the federal government on providing these stockpiles or making them ready. I know the hospitals will have a supply of atropine and pralidoxime. Remember also that you are giving larger doses of atropine here than you would usually use in a code situation or like a cardiac arrest situation for a medical reason.

There is some research that is ongoing right now about reconstituting atropine. I know atropine is an ampule and stocking these ampules in large amounts is not very practical. The more practical way would be to stock powder atropine and you can reconstitute in any ER in case of the need to use it, which would allow you to stock more and keep it for a longer shelf life. This is a great question, though, and the only thing I could tell you now is we are aware of this shortcoming and we're working on it. (For more information: <http://www.bt.cdc.gov/stockpile/index.asp>)

Question:

Is being exposed to these nerve agents going to create any type of permanent brain damage or psychological disorders?

Ziad Kazzi:

This is another very good question. Nerve agents are organophosphates. Organophosphates have been linked with chronic syndromes; people that get exposed to pesticides like malathion or parathion sometimes develop the intermediate syndrome or the chronic neuropathy from the pesticides. We do not have that experience with nerve

agents. However, we don't have enough experience with it to be able to draw a definite conclusion.

Regarding the psychological impact that was seen in Tokyo (if you read the study); you cannot really tell if this was due specifically to the nerve agent. It could be that the sarin can cause some problem in your brain leading to nightmares and the fear of riding subways. But, you cannot really refute the possibility that this could be that they were exposed to a horrifying experience and if you were actually exposed to a different agent, (e.g., if you were exposed to a blistering agent) you might have the same problem. I think that the answer to your question is not final yet.

When we respond to a terrorist attack, atropine, pralidoxime, all these medical measures that we take are wonderful, but we should also think about a psychological response, psychological support for these victims. I think we should keep this in mind and not overlook it.

Question:

We're establishing DCON procedures here at our facility. We will have a complete decontamination unit where we do a complete wash down of the patients as we receive them *before* they are admitted into the emergency room area. The staff that will be treating these patients – are they [the staff] going to require level D personal protective equipment? How are we going to establish this?

Ziad Kazzi:

If they [the patients] are already decontaminated, you should be okay, especially if it's a gas exposure. However, the other agencies in the CDC are actually taking the lead on this, such as NIOSH, as well as the EPA. They will be setting up recommendations for decontamination and end points for decontamination. I would rather not speak for them, but from what we just talked about, gas exposure is not supposed to cause a big problem as far as contamination as long as you avoid the first exposure when the people take off their clothes. That is the first level, or basically, the first interaction with the patient [by the responder]. When it's a liquid, it's a different situation. If it's a VX, it will be a different. Where the decontamination needs to be completed and what the end point is, I would rather leave to the EPA.

Question:

Of the patients who died (in Tokyo), did they have direct exposure as opposed to those who were injured. Or were they were secondary exposures (where you have vast numbers); seven died and 600 were exposed in one instance, and 12 died and 5,000 were injured in the other.

Ziad Kazzi:

Is your question: Is there a difference between the exposures?

Question:

No, of the people who died – were they directly exposed as opposed to those who were injured. You said, "12 died and 5,000 were injured." Of the 5,000 that were injured, were they secondary exposures?

Ziad Kazzi:

No, of the 5,000 that were injured, it was all primary exposure. They were all in the subway system.

Question:

The seven that died, were they directly in the area as opposed to the 5,000 that were all the way down in the back of the subway on another train?

Ziad Kazzi:

Toxicity from these nerve agent gasses is dependent on exposure *time* as well as exposure. The concentration of the agent around you, how long do you stay around it, and how close you are to it. So, the theory is that those patients that died were closer to the people that released the gas and the bags – and the people that were further away had less exposure. Yes, this is the thinking behind that.

Question:

What was the proximity of the hospital to the second sarin attack? I'm curious as to 5,000 casualties, how many patients were showing up at the nearest hospitals?

Ziad Kazzi:

I don't have the exact answer. I know that one of the subways (there were five subway systems); one of the subway *stations* was across the street or very close to the St. Luke hospital in Tokyo. They saw a large number of the victims; not all the victims. I have seen a video of that event and it was total chaos. It was chaotic. It's really beyond what we imagine we can be prepared for, but I don't know, off hand, how close the other hospitals were to those patients. I can get back to you if you want, I can give you my e-mail or Judi will actually forward your question to me.

Question:

This question is in regard to the victims of soman, who were not likely to have received pralidoxime in time. What's the length of time that we would expect to have to ventilate them? I imagine its dose dependent, but sort of a ball park.

Ziad Kazzi:

I can give you a range. You can expect several weeks. I've seen in my reading up to 120 days.

Question:

The life span of a red blood cell?

Ziad Kazzi:

As you said, it's depending on the exposure and the agent.

Question:

Do you have any data on the long-term physical impact on the 5,000 that were injured in the sarin gas attacks and is that being studied?

Ziad Kazzi

I actually don't have any data on that. I do have that study that you have referenced in your article that talks about some of their symptoms. I do have some data about progressive improvement in their weakness takes some time, but they will hopefully get back to normal if they survive the initial event.

Thank you very much for your participation. If we did not get to your question, will you please e-mail your question to coca@cdc.gov and we will make sure that Dr. Kazzi receives that immediately. That's coca@cdc.gov.

I also wanted to mention that our COCA Website went live this morning. If you will take your computers to www.bt.cdc.gov/coca. I think you'll find a lot of information that you may have been looking for. Lastly, I wanted to mention that our next COCA call will be in August. It's tentatively planned for August 17th and the topic will be viral hemorrhagic fevers (<http://www.bt.cdc.gov/agent/vhf/index.asp>) and we hope that you all will be able to participate.

Dr. Ziad Kazzi, I can't thank you enough for taking time out of your day to help us with this COCA call.

Ziad Kazzi:

Thank you so much for listening and thank you for the opportunity of doing this. Please send any questions to us and we will answer them.

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