

Straight Tox

Organophosphates: From the Farmer's Field to the Battlefield

By Dwain Fuller, D-FTCB, TC-NRCC

In the quiet of my office, I was startled by the abrupt ping of an email alert. Within seconds, it pinged again. The two emails were identical, both from a reporter from a foreign news service out of Washington, D.C. Before I could finish reading the email, my phone rang. It was the same reporter, breathlessly expressing her desire for me to participate in an on-air interview about a breaking story; the apparent poisoning deaths of 23 school children in India. She wanted me to talk specifically about "whether it could happen here." At the time however, the source and identity of the poison had not been determined. I was finally able to convince her that it would be "quite speculative of me to opine on whether it could happen here, when we did not yet know what had happened." Evidently my logic prevailed and she decided that perhaps she should wait for further information.

We now know that the poison was monocrotophos, an organophosphate insecticide, marketed under various names, including Azodrin, Bilobran, Crisodrin, Monocil 40, Monocron, Nuvacron, Pillardrin, and Plantdrin. Monocrotophos use was discontinued in the United States in 1988 and was a "Restricted Use Pesticide" before its withdrawal.

I have not previously written about organophosphates even though they are abundant in our daily lives. So I am taking this opportunity to provide a refresher for the veteran

toxicologist who may not have encountered an organophosphate case in a while and a primer for those newer to the field who may not have encountered one at all.

"Organophosphate" is a general term for esters of phosphoric acid, but the term also includes esters of phosphorous acid and phosphinic acid, as well. Organophosphates range in their use from agricultural pesticides such as malathion to "nerve agents", such as sarin, used in chemical warfare. While the relative toxicity across this spectrum differs greatly, the mode of action is essentially the same.

History

In 1932, the German chemist, Willy Lange and his graduate student, Gerde von Krueger, first described the effects of organophosphates on the cholinergic nervous system. Later German chemist, Gerhard Schrader began experimenting with organophosphates as insecticides. In January 1936 Schrader had an opportunity to observe the effects of organophosphates on humans first hand, when a drop of the organophosphate known as Tabun was spilled on a laboratory counter. Within minutes, Schrader's laboratory assistant began to experience miosis, shortness of breath, and dizziness. He didn't fully recover for three weeks.

It wasn't long until the Nazi government recognized the potential of organophosphates as chemical warfare agents and put Schrader in charge of their development. The most effective organophosphates as poisons are those which contain: a terminal oxygen connected to phosphorus by a double bond, two lipophilic groups bonded to the phosphorus, and a leaving group, such as a halide, bonded to the phosphorus. Schrader's laboratory discovered what is now known as the G (German) series of weapons, which include Sarin, Tabun, and Soman. The Nazis produced large quantities of these agents, but did not use them in World War II. This may have been because the Nazis believed that the Allies also had knowledge of these compounds, assuming that they were not being discussed in scientific journals because information about them was being suppressed. This, however, was not the case, even though tabun and sarin had been disclosed in scientific journals as early as 1902, and both of these compounds had been patented in 1937 and 1938, it wasn't until the allies advanced that stocks of these nerve agents were discovered. The United States and the British split the seized stocks, while the Red Army apparently captured a factory producing these agents and subsequently dismantled it and moved it in its entirety back to Russia. That notwithstanding, Hitler was warned by his advisors that if he used these agents, the Allies would likely retaliate and be able to produce these compounds in much larger quantities than the Nazis.

While today many countries possess nerve agents, since World War II, there have been few documented incidents of their use. In 1988, in the closing days of the Iran – Iraq war, the Kurdish village of Halabja was attacked with chemical weapons that likely included nerve agents, killing 3200 – 5000 people. And in 1995, a terrorist attack by the Aum Shinrikyo religious group, resulted in the release of Sarin into the subway system in Tokyo.

No nerve agents were known to be used during the Gulf War; however a number of U.S. and U.K. personnel were exposed to them as the Khamisiyah chemical depot was destroyed.

The use of organophosphates in the U.S. as insecticides has decreased by 75% between 1980 and 2007, the date of the latest EPA estimate. However an estimated 33 million pounds of organophosphates were still being used in 2007, accounting for 35% of all pesticide use.

Toxic Mechanism

As a quick review, acetylcholine (ACh) is a neurotransmitter that acts upon acetylcholine receptors in the synaptic cleft to facilitate nerve transmission. The enzyme, acetylcholinesterase (AChE), is responsible for terminating nerve transmission by hydrolyzing ACh in the synaptic cleft.

The action of an organophosphate is to phosphorylate AChE. This phosphorylation deactivates AChE, leading to an accumulation of the ACh. This deactivation, or inhibition, results in an increased and prolonged stimulation of the ACh receptors. The type and location of the ACh receptors affected determines the effect on the body: In cardiac tissue ACh neurotransmission has an inhibitory effect, which lowers heart rate. However, ACh also behaves as an excitatory neurotransmitter at neuromuscular junctions in skeletal muscle. Accumulation of ACh at motor nerves causes overstimulation of nicotinic receptors and results in muscle weakness, fatigue, muscle cramps, fasciculation, and paralysis. Accumulation of ACh at the autonomic ganglia causes overstimulation of nicotinic receptors in the sympathetic nervous system resulting in tachycardia, hypertension, and hypoglycemia. Accumulation of ACh in the central nervous system causes overstimulation of nicotinic receptors and results in anxiety, headache, convulsions, ataxia, bradypnea, depressed circulation, tremor, general weakness, and potentially coma. The action of ACh on the muscarinic receptors causes visual disturbances, tightness in the chest, wheezing, increased bronchial secretions, increased salivation, increased lacrimation, increased sweating, increased peristalsis, and increased urination.

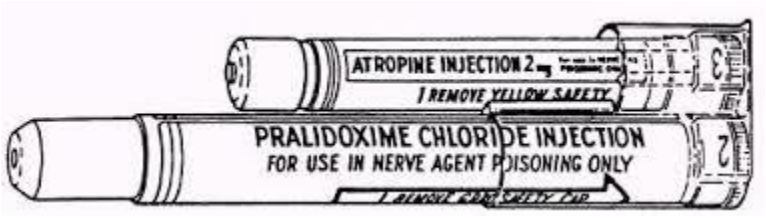
Diagnosis

As an aid in remembering the effects of organophosphates on the muscarinic system, medical students are often taught one or more mnemonics, such as: **SLUDGEM** (**S**alivation, **L**acrimation, **U**rination, **D**efecation, **G**astrointestinal motility, **E**mesis, **M**iosis) or **MUDDLES** (**M**iosis, **U**rination, **D**iarrhea, **D**iaphoresis, **L**acrimation, **E**xcitation, **S**alivation). Personally, I find **DUMBELS** easiest to remember, standing for **D**iarrhea, **U**rination, **M**iosis, **B**radycardia (and/or **B**ronchorrea), **E**mesis, **L**acrimation, and **S**weating (and/or **S**alivation).

Clinical testing to confirm a diagnosis of organophosphate poisoning often consists of measuring the activity of butylcholinesterase and acetylcholinesterase in the blood.

Treatment

The treatment for organophosphate poisoning is typically to administer atropine, an anticholinergic, which acts as an antagonist at the muscarinic ACh receptors. Often atropine is accompanied by an oxime, the purpose of which is to dephosphorylate the phosphorylated AChE, thereby reactivating it. However, the efficacy and safety of the use of oximes is disputed.



On the battlefield of today, troops facing the danger of poisoning by nerve agents are issued appropriate clothing to serve as a barrier to dermal exposure, respirators to prevent inhalation, and autoinjector devices designed to administer atropine and/or an oxime directly into the muscle of the thigh in case of exposure to organophosphate agents.

As is the case with many discoveries, organophosphate compound have the potential for good and evil. As insecticides they help combat mosquito-borne pathogens and protect harvests that feed the hungry. However, as chemical warfare agents, they can be the instruments of devastation as well.

References and Further Reading

Indian Police Arrest School Principal in Food Poisoning Case. http://www.reuters.com/article/2013/07/24/us-india-children-idUSBRE96N0HJ20130724, Accessed 7/24/13

Monochrotophos. http://en.wikipedia.org/wiki/Monocrotophos, Accessed 7/24/13

Acetylcholine. http://en.wikipedia.org/wiki/Acetylcholine, Accessed 8/12/13

Acetylcholinesterase. http://en.wikipedia.org/wiki/Acetylcholinesterase, Accessed 8/12/13

Atropine. http://en.wikipedia.org/wiki/Atropine, Accessed 7/23/13

Organophosphate. http://en.wikipedia.org/wiki/Organophosphate, Accessed 7/24/13

Organophosphate Poisoning. http://en.wikipedia.org/wiki/Organophosphate_poisoning, Accessed 7/23/13

Balai-Mood M, Shariat M. Treatment of Organophosphate Poisoning. Experience of Nerve Agents and Acute Pesticide Poisoning on the Effects of Oximes. J Physiology (Paris), 1998; 92, 375-378

Bardin PG, Van Eeden SF, Joubert JR. Intensive Care Management of Acute Organophosphate Poisoning. South African Medical Journal, 1987, 72; 593-597

Lee P, Tai DYH. Clinical Features of Patients with Acute Organophosphate Poisoning Requiring Intensive Care. Intensive Care Medicine, 2001, 27; 694-699

Rosenstock L, Kiefer M, Daniell WE, McConnell R, Claypoole K. Chronic Central Nervous System Effects of Acute Organophosphate Pesticide Intoxication. Lancet, 1991, 338; 223-227

Nerve Agent. http://en.wikipedia.org/wiki/Nerve_agent, Accessed 8/12/13

Halabja Poison Gas Attack. http://en.wikipedia.org/wiki/Halabja_poison_gas_attack, Accessed 8/12/13

2006-2007 Pesticide Market Estimates. http://www.epa.gov/opp00001/pestsales/07pestsales/table_of_contents2007.htm#pdfreport, Accessed 8/14/13