

# Pharmacology case study

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Tabun gas is a lethal chemical warfare agent. It is a nerve gas, scientifically known as Ethyl N, N-dimethylphosphoramidocyanidate.

Its molecular formula is  $C_5H_{11}N_2O_2P$  and its structural formula is CCN(C)C=NP(=O)(O)O. Molecular weight of Tabun is 162.13. Tabun is a colorless liquid with a fruity odor, readily soluble in water. It is rapidly broken down in an alkaline medium to yield hydrogen cyanide, ethanol and dimethyl amidophosphoric acid. It is less volatile than water and persists in normal environment for 24 to 48 hours.

Tabun is a fast acting, highly toxic organophosphate nerve agent which may enter the body through inhalation, ingestion or absorption through the skin and eyes (Marrs, Maynard & Sidell, 2007). Tabun works by interfering with the normal nerve impulses transmission in the body. It binds with acetylcholinesterase (AChE), the enzyme found at nerve junctions, which regulates the amount of acetylcholine by breaking it down. An excess of acetylcholine would cause hyper stimulation of the nervous system leading to overstimulation of secretory glands and muscles. Tabun binds with the enzyme AChE, and inactivates it.

Therefore, the acetylcholine regulatory mechanism is damaged, which leads to accumulation of acetylcholine at the nerve junctions. Excess of acetylcholine causes constant firing of neurons and, consequently, overstimulation of the nervous system, which manifests as increased secretions from all glands and hypertonicity of smooth muscles like those of intestine, bronchi and respiratory muscles. Constriction of muscles produces such symptoms as: miosis, tightness in the chest and breathlessness. In

cases of severe exposure, there may be an eventual paralysis of muscles and death due to constriction and paralysis of respiratory muscles (Marrs, Maynard & Sidell, 2007). Tabun is broken down slowly by the body, which means that repeated exposure can lead to accumulation in the body. Effects of TABUN on Human Body Nerve agents are so named because they disrupt the transmission of nerve impulses in the body by inhibiting certain enzymes at the nerve junctions, or synapses.

All nerve agents primarily inhibit an enzyme called acetyl-cholinesterase (AChE), required for optimum transmission of impulses between neurons. Tabun inactivates acetyl-cholinesterase and causes acetylcholine to accumulate on the nerve junctions. Accumulation of acetylcholine at the synapses keeps the nervous system constantly stimulated. TABUN may enter the human body through inhalation, ingestion or absorption through the skin and eyes, as it can be used as an aerosol, gas or liquid. Route of entry into the body is vital, as it determines the time period between the absorption of vapors and onset of clinical symptoms. Symptoms develop most rapidly when the vapors are inhaled.

Exposure of a low dose causes increased salivation, running nose, tightness in the chest and constriction of the pupil of the eye (miosis). Due to miosis, there is dimness of surroundings, and night vision is impaired. Due to spasm of ciliary muscles in the eye, short range vision declines and this is associated with a severe headache. Among other symptoms are slurring of speech, fatigue, nausea and hallucinations. If exposed to a higher dose of TABUN, muscular symptoms are more severe.

There may appear bronchoconstriction and secretion of mucous in the lungs and bronchi, leading to breathlessness and coughing. It is accompanied by irritation of the gastrointestinal tract, cramps, vomiting, involuntary urination and defecation. There is increased production of saliva, tears and sweat due to overstimulation of the parasympathetic nervous system, increased or decreased heart rate, arrhythmia, convulsions, loss of consciousness and eventual paralysis of respiratory muscles. Toxic effect on the respiratory center of the central nervous system and constriction and paralysis of respiratory muscles is the primary cause of death in a case of nerve agent poisoning. It is the same as death by asphyxiation (Marrs, Maynard & Sidell, 2007).

**Antidote Drugs**The two antidotes for TABUN poisoning are atropine and pralidoxime chloride. Atropine is an alkaloid which is partially metabolized in the body. It prevents the actions of acetylcholine. Atropine decreases the secretion of saliva, sweat, gastric secretions and secretions of bronchi and nasopharynx. Atropine reduces muscle tone, frequency of contraction, and causes relaxation of smooth muscles of gastrointestinal tract, urinary tract and bronchi. It increases the rate and depth of breathing.

In the eyes, it causes relaxation of ciliary muscles and dilation of pupils (mydriasis). Atropine increases heart rate (tachycardia). If administered parenterally, it initially causes bradycardia because of central vagal stimulation, enhanced AV conduction and reduced refractory period. At therapeutic doses, it has no effect on blood pressure, but at toxic doses, it causes cutaneous vasodilation, which leads to a fall in BP. At therapeutic doses, Atropine does not penetrate the central nervous system; hence, it has

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no significant effect on the CNS. But at higher doses, it causes cortical stimulation leading to disorientation, delirium, restlessness, hallucinations and coma.

Atropine works as an antidote to TABUN blocking the acetylcholine receptor at the nerve junction, so that the acetylcholine that has accumulated at the synapse does not work (Buch, 2010). Pralidoxime chloride is partially metabolized in the liver and excreted in urine. Its action is short lived and this may necessitate repeated administration for effective action. It is given as an intramuscular or slow intravenous injection. It reactivates cholinesterase and is used in combination with atropine to counteract the effects of nerve agents with anticholinesterase action (Geoghegan & Tong, 2012).

TABUN and other nerve agents inactivate acetylcholinesterase at nerve junctions. Pralidoxime reverses their action by activating the AChE and destroying the accumulated acetylcholine so that transmission of neurotransmission can proceed normally. It destroys the bond between TABUN and AChE before it ages and becomes irreversible. Pralidoxime has an anticholinergic effect as it reduces muscle spasms and tachycardia (Geoghegan & Tong, 2012). Effect of Antidote Drugs In the absence of exposure to nerve agents, administration of atropine would have a variety of effects on different organs.

In therapeutic doses, it will cause initial bradycardia followed by tachycardia. There will be an increase in the rate of breathing and decrease in secretion of mucus in bronchi. Atropine will cause pupils of the eye to

dilate and this may cause photophobia as the pupils are unable to constrict in response to the amount of light entering the eyes. There is a rise in intraocular pressure causing glaucoma. It also reduces lacrimal secretion leading to irritation and dryness of eyes (Seth & Seth, 2009).

Atropine reduces salivary secretion causing dryness in the mouth (xerostomia). It also reduces sweat production, blocking the loss of heat from the body and causing a rise in body temperature. It reduces motility of intestines and gastric acid secretion, relaxes the intestinal wall and effects closure of sphincters causing constipation. Atropine relaxes the tone of urinary bladder and causes retention of urine (Seth & Seth, 2009). Therefore, in cases of belladonna poisoning, the patient presents with dryness of eyes and mouth, mydriasis, photophobia, initial bradycardia, tachycardia, hyperthermia, hot and dry skin, constipation, urinary retention and restlessness (Seth & Seth, 2009).

If Pralidoxime is taken by an individual not exposed to nerve agents, he/she may complain of blurred or double vision, loss of accommodation in eyes, headache, drowsiness, nausea, increased BP, tachycardia, hyperventilation and weakness in muscles (Geoghegan & Tong, 2012).

Angelica's Contact with GasAngelica suspected that she might have come in contact with the nerve gas. Hence, she injected herself with two antidotes: atropine and pralidoxime.. But the pralidoxime syringe failed and only atropine entered her blood.

An analysis of the signs and symptoms presented by Angelica shows that she took atropine without being exposed to a nerve agent. If she had been

exposed to TABUN, it would have entered her body through inhalation from air and her pupils would have constricted immediately along with an increase in salivary secretion and sweating (Marrs, Maynard & Sidell, 2007). Instead she found that her pupils had dilated and her mouth had gone dry, so much so that she could hardly speak. Her heart rate had also increased. All these symptoms appeared before injecting atropine. These are signs of stimulation of sympathetic nervous system in emergency situations.

In times of stress, adrenaline and nor-adrenaline levels in the body are increased to help the body cope with emergencies. It is known as the general adaptation syndrome and causing dryness of mouth, increased heart rate and blood pressure and dilation of pupils (Rhoades & Bell, 2009). After seeing these symptoms, Angelica injected herself with atropine. The effect of atropine was enhanced by the hot, desert environment in the Middle East and the stress her body was already undergoing. Injection of atropine would have increased her heart rate and blood pressure further, caused her body temperature to rise and caused exhaustion and extreme drowsiness.

The stress syndrome in the body also causes exhaustion and muscle relaxation as it fades. The combination of panic attack and unchallenged atropine injection in a tropical climate caused Angelica to faint (Rhoades & Bell, 2009).