CASE STUDY: Cyanide Poisoning: Winter of Frozen Dreams

Cyanide is extremely toxic, whether it be administered by the ingestion of the flavorless powder potassium cyanide or by the inhalation of the almond scented hydrogen cyanide gas. Winter of Frozen Dreams is a book about the famous Barbra Hoffman murder case in which a beautiful, young University of Wisconsin student was accused and subsequently convicted of murder. Her victims were killed via cyanide poisoning. Other famous uses of cyanide include the suicide of Adolf Hitler (he took cyanide before shooting himself), and the Jonestown tragedy.

Cyanide is an electron transport inhibitor. In particular it binds to the Fe$^{3+}$ heme a$_3$ group on cytochrome oxidase in Complex IV (see Fig. 5.17 and 5.19). The result is a disruption of electron transport to oxygen. By blocking the electron transport, there is an inhibition of the generation of the electrochemical gradient that provides the energy for ATP synthesis. The end result is the cessation of energy production by mitochondria in cells, which leads to cell death, tissue death and death of the organism. The death usually occurs from either shut down of the central nervous system, but there is also some evidence for cardiac failure.

Questions:

1. The heme group is prosthetic group of the cytochrome oxidase enzyme, so why is cyanide an inhibitor if it does not bind directly to the cytochrome oxidase enzyme?

Answer: Prosthetic groups are still a part of the enzyme even though they are not coded for by the gene or composed of amino acids. In the case of cytochrome oxidase the electrons are transferred through the Fe$^{3+}$ on the heme group so the inhibition of the enzyme occurs via the prosthetic group, which in this case is an essential part of the enzyme complex.

2. If the poisoning occurs by blocking of electron transport from oxygen, then why can’t the effects of poisoning just be reversed by the administration of higher levels of oxygen?

Answer: The inhibition occurs because the oxygen cannot be utilized for electron transport not because the oxygen is not present.

3. There are some antidotes available if the poisoning is detected very early. One treatment is to infuse sodium thiosulfate. The proposed mechanism of action is that this compound provides exogenous sulfate, which enhances the metabolism of cyanide to thiocyanate, which is less toxic and can be excreted in the urine. If the reaction from cyanide to thiocyanate requires the activity of an enzyme (in this case the enzyme is called rhodanese), what might be a limitation in using sodium thiosulfate as an antidote?
Answer: The detoxification of cyanide might be limited by the amount of the rhodanese enzyme. If the patient is provided with high levels of sodium thiosulfate but the rhodanese enzyme is at limiting levels or is catalyzing the reaction at its maximum turnover rate then it will be impossible for the body to be able to detoxify all of the cyanide in the system.

Where can I learn more?

CDC Website: http://www.atsdr.cdc.gov/tfacts8.html
http://www.cdc.gov/niosh/ershdb/EmergencyResponseCard_29750037.html
