THE NORTHERN HOSPITAL

ORGANOPHOSPHOROUS POISONING

Ceiling of the Sistine Chapel, Vatican City. Fresco on plaster, Michelangelo Buonarroti 1508-12.

By the end of 1540, when Michelangelo had completed the upper two thirds of the fresco, he hired the carpenter Ludovico to lower the scaffolding. Pope Paul heard the news, arrived at the locked Sistine door unannounced. He had given up the use of his personal chapel so that Michelangelo might have his privacy. Urbino, who answered the banging on the door, could not refuse to admit the pontiff.

Michelangelo came down from the new, low scaffold, greeted by Pope Paul and his master of ceremonies, Biagio da Cesena, with cordial words. The Pope stood facing the Last Judgement, walked stiffly toward the wall without removing his eyes. When he reached the altar he sank to his knees and prayed.

Not so Biagio Da Cesena, who stood glaring up at the fresco. Paul rose to his feet, made the sign of the cross over Michelangelo and then the last judgement. There were tears of pride and humility on his cheeks.
"My son you have created a glory for my reign."
"It is disgraceful…!" spat out Biagio Da Cesena.
Pope Paul was astounded.
"And totally immoral! I cannot tell the saints from the sinners. There are only hundreds of nudes showing their private parts. It is shameful."
"You think the human body shameful?" asked Michelangelo.
"In a bagno bath, no. But in the Popes Chapel! Scandaloso!"
"Only if you wish to create a scandal Biagio," replied Paul firmly. "On judgement day we shall all attend naked before the Lord. My son how do I express my overwhelming gratitude?"
Michelangelo turned to the Master of Ceremonies with a conciliatory gesture, for he wanted to make no enemies for his fresco. Biagio da Cesena broke in roughly.

“One day this sacrilegious wall will be annihilated, even as you destroyed the beautiful Peruginos beneath it.”
“Not while I live,” cried Pope Paul furious. “I will excommunicate anyone who dares touch this masterpiece!”

They left the chapel. Michelangelo stood rubbing a sorely painful area under his left breast. He asked Urbino to mix some intonaca and lay it on the blank spot on the extreme lower right-hand corner of the wall. This done he painted a caricature of Biagio da Cesena, representing him as the judge of the shades of Hades, with the ears of an ass, and a monstrous snake coiled around the lower part of the torso: a lethal likeness, the pointed nose, lips drawn back over buck teeth. It was a poor revenge, he knew, but what other was open to an artist?

Word leaked out somehow. Biagio da Cesena demanded a second meeting before the Fresco.
“You see, Holy Father,” cried the Master of Ceremonies, “the report was true. Buonarroti has painted me into the fresco. With some kind of repulsive serpent for my genitalia”.
“It’s a covering,” replied Michelangelo. “I knew you would not want to be portrayed wholly naked.”
“A remarkable likeness,” observed the Pope, his eyes twinkling. “Michelangelo, I thought you said you could not do portraiture?”
“I was inspired, Holiness.”
Biagio da Cesena hopped up and down on either foot as though it were he instead of his picture standing over the fires of hell.
“Holiness make him take me out of there!”
“Out of hell?” the Pope turned surprised eyes on the man. “Had he placed you in purgatory, I should have done everything in my power to release you. But you know from hell there is no redemption.”

Irving Stone, The Agony and the Ecstasy, 1961.

If poor Biagio had had the foresight not to be quite so antagonistic to Michelangelo he may have found himself in the potentially reversible situation of purgatory. Not even the Pope himself however could save could save Biagio from the fires of Hell. This was an irreversible situation.

If we have the foresight to act quickly with pralidoxime we will be able to reverse the bond of the patient’s acetylcholinesterase and the organophosphate. Should we hesitate however, we will face the irreversible situation of the “ageing” of this complex from which there will be no redemption.

ORGANOPHOSPHOROUS POISONING

Introduction

Organophosphorous insecticides include the organophosphates and the carbamates.

Organophosphate insecticides are responsible for large numbers of deaths worldwide each year.

Aggressive and timely supportive care together with the use of the specific antidotes, **atropine and pralidoxime** can be life saving.

Organophosphates should not be confused with organochlorine pesticides or glyphosate (an organophos**phonate** as opposed to an organophos**phate**) both of which are different poisons and both of which do *not* have specific antidotes.

Classification of Anti-cholinesterases

Types and examples of organophosphorous anticholinesterases:

Reversible binding to cholinesterases:

1. Short acting:
    - Edrophonium
2. Long acting:

    Do not readily cross BBB:

    - Neostigmine
    - Pyridostigmine
    - **Carbamate Insecticides:**
        - ♥ Aldicarb, carbendazole, carbedazim, carbazine, propoxur.

    Readily cross BBB:

    - Physostigmine
    - Tacrine

Irreversible binding to cholinesterases:

1. **Insecticides:**
    - The thioates: Malathion, Parathion, Fenthion
    - Coumaphos
    - Diazinon
    - Dichlorvos

- Dimethoate
- Clorpyrifos.
- Trichlorfon

2. Nerve gases:

- Sarin (GB)
- Soman (GD)
- Tabun (GA)
- VX

Pharmacokinetics

Absorption

- Organophosphates are **well** absorbed orally.
- They can be absorbed dermally.
- They can be inhaled.

Distribution

- These agents generally have large volumes of distribution with many accumulating within lipid stores, especially the thioates.
- Carbamates less readily cross the blood brain barrier, hence have less CNS toxicity.

Metabolism and elimination

- The thioates (malathion, parathion and fenthion) act as indirect agents, ie they must be metabolized to their active forms.
- Organophosphate compounds are mostly metabolized through *hydrolysis by serum paraoxomases*.

  Others undergo *hepatic microsomal (cytochrome p450)* metabolism with excretion if inactive metabolites in the urine.
- Most carbamates are metabolized in the liver by oxidation, hydrolysis or by conjugation and then excreted in the urine.

Pathophysiology

Summary of cholinergic physiological effects of organophosphates:

<table>
<tr><th>Muscarinic effects</th><th>Nicotinic effects</th><th>Cholinergic CNS effects</th></tr>
<tr><td>Salivation</td><td>Muscle fasciculation and cramping (initially)</td><td>Agitation</td></tr>
<tr><td>Lacrimation</td><td>Muscle weakness and paralysis (later)</td><td>Confusion</td></tr>
<tr><td>Urination</td><td rowspan="8">Tachycardia and hypertension (due to stimulation of nicotinic receptors in sympathetic ganglion) may be seen on occasions. This will usually be overshadowed by muscarinic induced bradycardia however.</td><td>Seizures</td></tr>
<tr><td>Diarrhea</td><td>Coma</td></tr>
<tr><td>Abdominal cramps</td><td rowspan="7">Respiratory depression</td></tr>
<tr><td>Nausea and vomiting</td></tr>
<tr><td>Miosis</td></tr>
<tr><td>Bronchospasm</td></tr>
<tr><td>Bradycardia</td></tr>
</table>

Cholinesterases rapidly hydrolyze acetylcholine to inactivate it.

The two principal cholinesterases are

- Erythrocyte (RBC) or true cholinesterase (acetylcholinesterase)
- Serum cholinesterase (pseudocholinesterase),

Organophosphates act as irreversible cholinesterase inhibitors. Here the organophosphate-cholinesterase bond with time will irreversibly lose an alkyl side chain which will result in the permanent binding of the complex (and prevent reactivation of the acetylcholinesterase by the antidote pralidoxime.) This process is known as **“ageing”.**

The time taken for ageing to occur will depend on the individual agent, in general terms this can range from **2-36** hours, (*personal communication, Dr Shaun Greene*).

Carbamates on the other hand act as reversible cholinesterase inhibitors. Ageing does *not* occur with the carbamates. The carbamate-cholinesterase bond reverses spontaneously in 4 to 8 hours.

The reversible carbamates are therefore less toxic than the irreversible organophosphates. The carbamates also have poorer CNS penetration.

The inhibition of cholinesterase activity leads to the excess accumulation of acetylcholine at synapses.

This will produce hyperactivity at both:

- **Muscarinic** receptors (postganglionic parasympathetic nerve endings)

And

- **Nicotinic** receptors (autonomic ganglia and skeletal junctions).

Risk Assessment

- Organophosphates and carbamates may both produce life threatening toxicity when ingested.
    - ♥ Carbamates in general have shorter durations of toxicity and are less life threatening than the organophosphates.
- The onset of clinical poisoning can be significantly delayed with some agents, (up to 12 hours).
- Dermal or inhalational exposure can cause toxicity but is rarely life threatening.
- Significant secondary poisoning of staff has never been documented. [1]

Clinical Features

Following ingestion symptoms may occur **within minutes** or be delayed up to **12 hours** depending on the exact agent involved, the amount involved and the route of exposure.

Note that the constellation and progression of symptoms is variable, largely depending on the dose the actual agent that has been ingested, and either muscarinic or nicotinic features can predominate.

In general terms the following clinical syndromes can be seen:

1. **Acute:** Minutes to 12 hours.

2. **Intermediate:** 2-4 days

3. **Delayed syndrome:** 1-5 weeks.

4. **Chronic syndrome:** Long term effects

Acute syndrome:

This is characterized by a typical **cholinergic syndrome**:

This may be seen in particular with: **dimethoate, chlorpyrifos.**

Features include:

1. Peripheral muscarinic effects:

    - Miosis, (pinpoint pupils)
    - Diarrhea, (nausea, vomiting and abdominal cramps may also be associated).
    - Urination
    - Lacrimation
    - Salivation
    - **Bronchospasm**
    - **Bradycardia, conduction delays and hypotension.**

2. Nicotinic effects:

    - Tachycardia and hypertension, (may occur initially, but then muscarinic effects will usually predominate).
    - Muscular: fasciculation, followed by weakness then paralysis.
    - Respiratory paralysis, **this will be the usual cause of death.**

3. CNS:

    - Confusion/ agitation
    - Coma/ seizures/ death.

Intermediate syndrome:

- This may be seen with certain specific agents, (**fenthion, malathion, diazinon**)
- Delayed (2-4 days) paralysis may be seen.
- The exact pathophysiology of this condition is not understood. Prolonged motor end plate stimulation and inadequate pralidoxime dosing may be factors.

Delayed syndrome:

This may be seen following exposure to: **fenthion, parathion and chlorpyrifos.**

- Organophosphate induced delayed neuropathy (OPIDN) is rare.
    - ♥ It is an ascending sensorimotor polyneuropathy possibly secondary to ageing of axonal neuropathy target esterase (NTE).
- It occurs 1-5 weeks post acute exposure to certain agents.

Chronic syndrome:

- This is essentially a neuropsychiatric disorder.
- It may appear following acute toxicity from chronic low level exposure.

Investigations

Blood tests:

1. FBE
2. U&Es/ glucose
3. **Acetylcholinesterase activity:**

    The definitive diagnosis of organophosphorous poisoning is made by demonstrating **decreased cholinesterase activity in the blood.**

    Levels are also useful in monitoring therapy. [1]

    Red blood cell or serum cholinesterase levels can be done.

    Red blood cell cholinesterase activity:

    - RBC cholinesterase levels correlate better with severity
    - Levels take longer to recover (120 days)

- They will return to normal following successful oxime therapy
- They can be used to monitor progress when oximes are withdrawn.

Serum cholinesterase activity:

- These fall more rapidly than RBC cholinesterase levels
- They recover more quickly (4-6 weeks)
- Low plasma levels may be seen in workers with repeated occupational exposure.

In general terms:

- Latent poisoning is 50% less than 100% normal activity.
- Mild poisoning is 20% - 50% of normal activity
- Moderate poisoning is 10% - 20% of normal activity
- Severe poisoning is less than 10% of normal activity.

Note that access to these assays is limited and that blood samples must be processed promptly due to ongoing in vitro reactions.

CXR

- For those with respiratory symptoms.

ECG

- To document and assess any cardiac arrhythmias.

Management

1. Immediate attention to any ABC issues.

    - If a paralysing agent is required for intubation, then **suxamethonium may** be used, despite concerns that its action will be prolonged.

      Patients who require intubation will require ventilation for a prolonged period of time in any case to ensure that acetylcholinesterase activity has been restored.

2. Decontamination:

- Note that resuscitation must not be delayed by any external decontamination attempts, which may proceed simultaneously.

- Staff should apply simple universal precautions, with protective gowns and gloves/mask to prevent accidental dermal absorption.

  More sophisticated **personal protective equipment** than this is **not** necessary. There are excessive concerns about the risk of nosocomial poisoning. This has not been described following exposure to the organophosphate poisoned patient.

  Most irritant effects experienced by staff are in fact due to chemical **solvents** used with the organophosphate preparation, rather than the organophosphate itself.

- Remove clothing and wash skin with soap (organophosphorous compounds are soluble in this) and water. Bag the clothing.

3. Charcoal:

   - Charcoal is not effective and not indicated.

4. **Specific antidotes:**

   It should be noted that the organophosphates are quite a heterogenous group of chemicals and that the clinical course and response to treatment is probably very variable between the different agents.

   There are two specific antidotes, atropine and pralidoxime.

   Atropine will reverse the **muscarinic and central effects** but not the nicotinic (NMJ or autonomic ganglia) effects.

   Pralidoxime will reverse the **cholinergic nicotinic** effects, that are unaffected by the use of atropine. It will also reverse the muscarinic effects.

   Atropine:

   This is the life saving antidote for organophosphorous poisoning.

   Atropine in escalating doses is required to control the **muscarinic** cholinergic symptoms of organophosphorous poisoning.

   Adults should initially receive 1.2 mg IV every 5 minutes until adequate atropinization is established.

   Doses can be doubled every 5 minutes over the first few doses to gain quick control over toxicity. (Children 50 micrograms per kilogram).

A continuous infusion of atropine may also be used.

Note that atropine does not reverse muscle weakness.

In severe poisoning very large doses (**up to 100 mg**) may be required. *Anticipate this need and secure stocks early.*

Adequate atropinization will be indicated by:

- Resolution of bradycardia (rate of 80 and systolic pressure of at least 80).
- Drying of secretions
- Resolution of wheeze.

Note that resolution of miosis is **not** now considered an reliable "end point".

The development of **anticholinergic** features, such as delirium, tachycardia, urinary retention and **mydriasis** represents **over atropinization.**

Adequate supplies of atropine should be secured early in anticipation of toxicity, even before it happens.

Pralidoxime:

There is some controversy regarding the use of this agent, however it currently remains the standard of care.

This is used to primarily reverse the muscle paralysis.

It is used for the reactivation of organophosphate-bound cholinesterase by cleavage of phosphorylated active sites and release of free acetyl cholinesterase. It must be given early however before the irreversible "ageing" process has occurred.

Pralidoxime is not necessary in carbamate toxicity unless symptoms are severe or there is doubt about the exact nature of the organophosphorous compound the patient has taken.

The initial dose is 2 grams pralidoxime in 100 mls of normal saline IV over 15 minutes.

Then

Commence a pralidoxime infusion at 500 mg per hour.

The infusion may be ceased after 24 hours provided the patient is clinically well and remains under close observation. If symptoms recur then the infusion should be recommenced for a further 24 hours.

See also separate documents on:

- **Pralidoxime (in Drugs folder).**
- **Atropine (in Drugs folder).**

Disposition:

The onset of organophosphate poisoning can be quite delayed.

Any patient with actual or suspected organophosphate poisoning should therefore be admitted for observation for **at least 12 hours.**

All patients with confirmed poisoning will require longer term follow up by a toxicologist to detect possible intermediate or delayed sequelae.

References

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2. Little M, Murray L. Consensus statement: risk of nosocomial organophosphate poisoning in Emergency Departments. Emergency Medicine Australasia 2004: 16: 456-458.

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4. Eddleston M, Eyer P, Worek F et al. Pralidoxime in acute organophosphorus insecticide poisoning a randomised controlled trial. PLoS Med. 2009 June; 6(6):e1000104. Published online 2009 June 30.

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