ORGANOPHOSPHORUS AGENTS

INCLUDES ORGANOPHOSPHATES, CARBAMATES AND CHEMICAL NERVE AGENTS

DELIBERATE SELF-POISONING RESPONSIBLE FOR ~100, 000 DEATHS WORLDWIDE ANNUALLY, GENERALLY CAUSING DEATH BY RESPIRATORY FAILURE

RISK ASSESSMENT:

- Deliberate self-poisoning by ingestion of organophosphates almost always produces life-threatening toxicity → carbamates produce similar serious toxicity, but usually shorter duration and less likely to be life threatening
- Dermal or inhalation can cause toxicity but is rarely life-threatening
- Nosocomial exposure/poisoning does not occur

TOXIC MECHANISM:

- INHIBITION OF ACETYLCHOLINESTERASE ENZYMES → ↑ACh both at muscarinic and nicotinic receptors
    - Clinical features are due to widespread effects of ↑d ACh at CNS, autonomic and skeletal muscle neuromuscular synapses
- Irreversible loss of an alkyl side chain and permanaent binding of the organophosphate (AGEING) prevents reactivation of AChE by PRALIDOXIME → time taken for ageing depends on the agent. AGEING DOES NOT OCCUR WITH CARBAMATES

TOXICOKINETICS:

- **Well absorbed after ingestion**
- Large volume of distribution and some accumulate in lipid stores
- Carbamates are distributed LESS TO CNS

CLINICAL FEATURES → SEE CHOLINERGIC SYNDROME:

- Timing of symptoms depends on agent, dose and route of exposure
- ACUTE, INTERMEDIATE AND DELAYED INTOXICATION SYNDROMES
- ACUTE INTOXICATION:
    - MUSCARINIC EFFECTS (“DUMBBELS”):
        - Diarrhoea
        - Urination
        - Miosis
        - Bronchorrhoea
        - Bronchospasm
        - Emesis
        - Lacrimation
        - Salivation
            - Plus bradycardia/hypotension
    - NICOTINIC EFFECTS:
        - Fasciculation, tremor, weakness, respiratory muscle paralysis
        - Tachycardia, hypertension

    - CNS:
        - Agiation, coma, seizures
    - RESPIRATORY:
        - Chemical pneumonitis if hydrocarbon solvent is aspirated
- INTERMEDIATE:
    - Delayed paralysis can occur with some agents → ?due to prolonged motor end-plate stimulation, delayed redistribution from lipid stores and inadequate pralidoxime
- DELAYED:
    - Organophosphate-induced delayed neuropathy → 1-5 weeks later→ ascending sensorimotor polyneuropathy
    - Chronic neuropsychiatric disorder

INVESTIGATIONS:

- All tox patients get ECG, BSL and paracetamol level
- RED CELL AND PLASMA (BUTYRYL-) CHOLINESTERASE ACTIVITIES:
    - Diagnosis is CLINICAL, but these are useful for definitive diagnosis → features develop when levels are <25% normal
    - Plasma is sensitive biomarker for EXPOSURE but bears no relation to severity of poisoning
    - Red cell cholinesterase activity correlates better with severity

MANAGEMENT:

- DO NOT DELAY RESUSCITATION FOR EXTERNAL DECONTAMINATION → STAFF USE UNIVERSAL PRECAUTIONS
    - Remove clothes of patient and wash skin with soap and water
- If there is miosis, excessive sweating, poor air entry, wheeze, cough, bradycardia or hypotension → use escalating doses of ATROPINE
- Agitation control with benzos
- ANTIDOTES:
    - ATROPINE:
        - Competitive antagonist of acetylcholine at muscarinic receptors and reverses the excessive parasympathetic stimulation that results from inhibition of acetylcholinesterase. No nicotinic activity. Poor oral bioavailability. Excessive administration manifests with anticholinergic toxidrome → delirium, tachycardia, mydriasis and urinary retention.
        - Escalating doses indicated to control significant features of CHOLINERGIC EXCESS
        - 1.2mg (50microg/kg in kids) and DOUBLE THE DOSE EVERY FIVE MINUTES → until resolution of bradycardia and drying of secretions
        - Doses as large as 100mg have been given
        - NO EFFECT ON neuromuscular junction and muscle weakness
    - PRALIDOXIME:
        - Reverse neuromuscular blockade by reactivating inhibited AChE (only if administered before ageing occurs) → re-establishes enzymatic function leading to rapid reversal of nicotinic and muscarinic effects of OP poisoning. Action with

atropine is SYNERGISTIC at muscarinic receptors. Improvement in muscle strength is usually observed within 10-40 minutes

- Initiated in addition to atropine in all patients with objective evidence of organophosphate intoxication→ start as soon as adequate “atropinisation” has occurred
- NOT NECESSARY WITH CARBAMATES→ but if there is doubt, administer pralidoxime
- GIVE 2G IV then infusion of 0.5g/hour for 24 hours minimum → higher infusion rates are rarely needed