ANTICHOLINESTERASES

INDIRECT ACTING CHOLINOMIMETICS

CHOLINESTERASE INHIBITORS

Dr.Attiya Munir

SOURCES:
BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY 15TH EDITION
GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 13TH EDITION.

MOTTO AND VISION

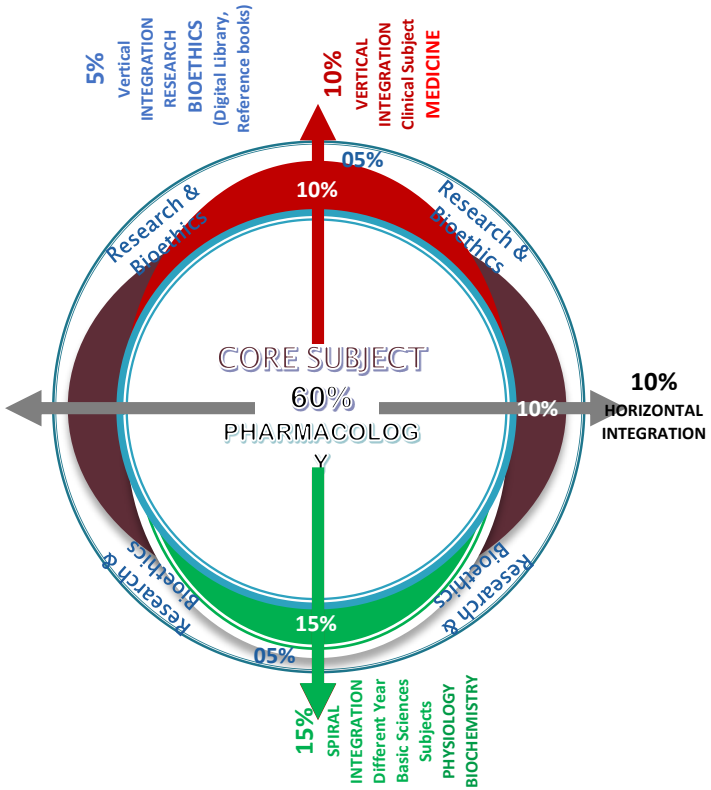
- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

LEARNING OBJECTIVES

- At the end of this session, students will be able to:

- ✓ Classify indirectly acting cholinomimetics.
- ✓ Discuss mechanism of action.
- ✓ Describe the organ system effects produced by these drugs.
- ✓ Enumerate uses and adverse effects of cholinomimetics.

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	

CLASSIFICATION ON THE BASIS OF STRUCTURE

REVERSIBLE

ALCOHOLS

Edrophonium(Quaternary)

CARBAMATES

Tertiary Amines

Physostigmine

Quaternary Amines

Neostigmine

Pyridostigmine

CONTINUED….

OTHERS

Tacrine

Donepezil

Rivastigmine

Galantamine

IRREVERSIBLE

ORGANOPHOSPHATES

Therapeutic use

Echothiophate

Insecticides

Malathion

Parathion

Nerve gases

Tabuin

Sarin

Soman

CONTINUED….

CARBAMATES

Carbaryl

Propoxur

CLASSIFICATION ON BASIS OF DURATION OF ACTION

SHORT ACTING (5-10MINS)

- Edrophornium

INTERMEDIATE ACTING (3-6HRS)

- Neostigmine
- Physostigmine
- Pyridostigmine

LONGER ACTING (6-8HRS)

- Donepezil
- Tacrine

VERY LONG ACTING (IRREVERSIBLE)

- Insecticides
- War Gases
- Ecothiopate

PHARMACOKINECTICS

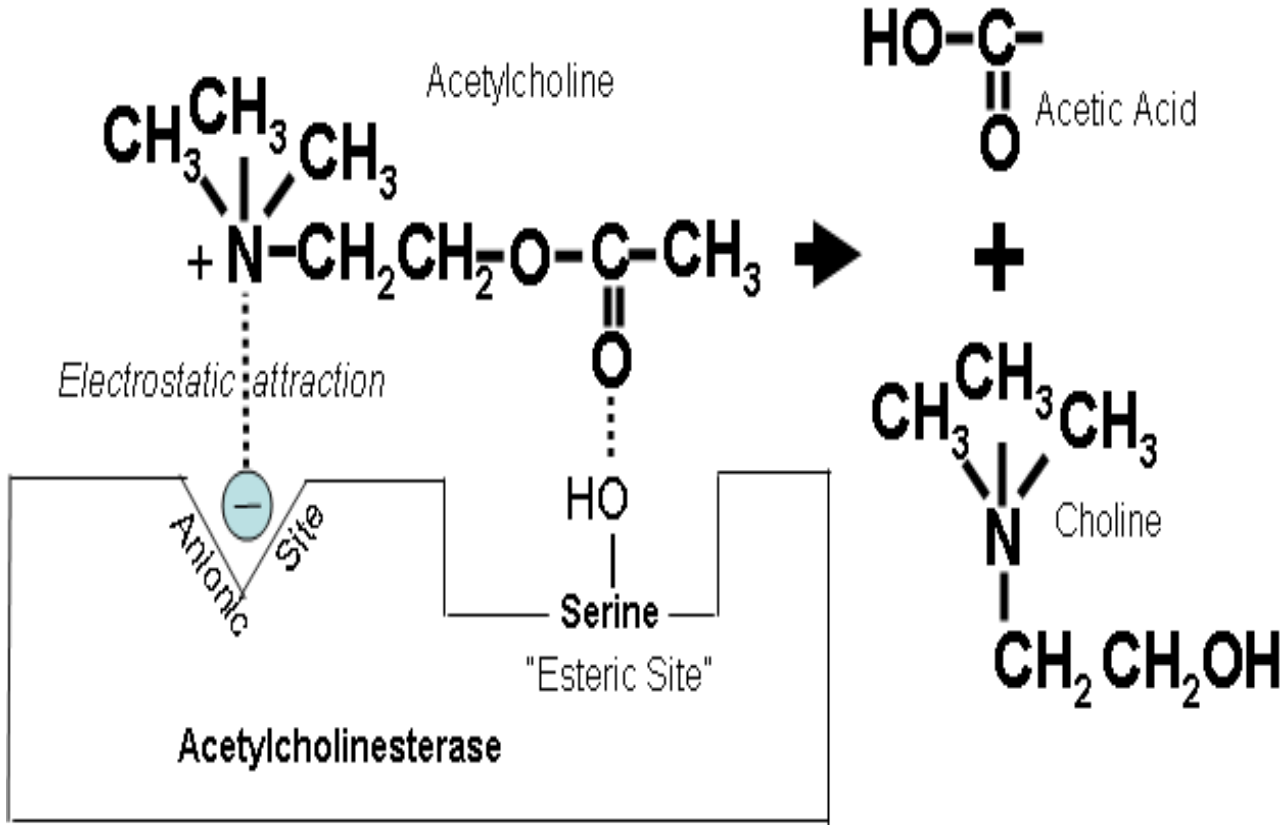
Indirect-acting, alcohol	
Edrophonium	Highly polar; used IV Duration: 5–10 min
Indirect-acting, carbamate	
Neostigmine	Moderately polar but orally active Duration: 2–4 h
Pyridostigmine	Moderately polar but orally active Duration: 4–8 h
Physostigmine	Lipid soluble; can be used topically in the eye Duration: 2–4 h

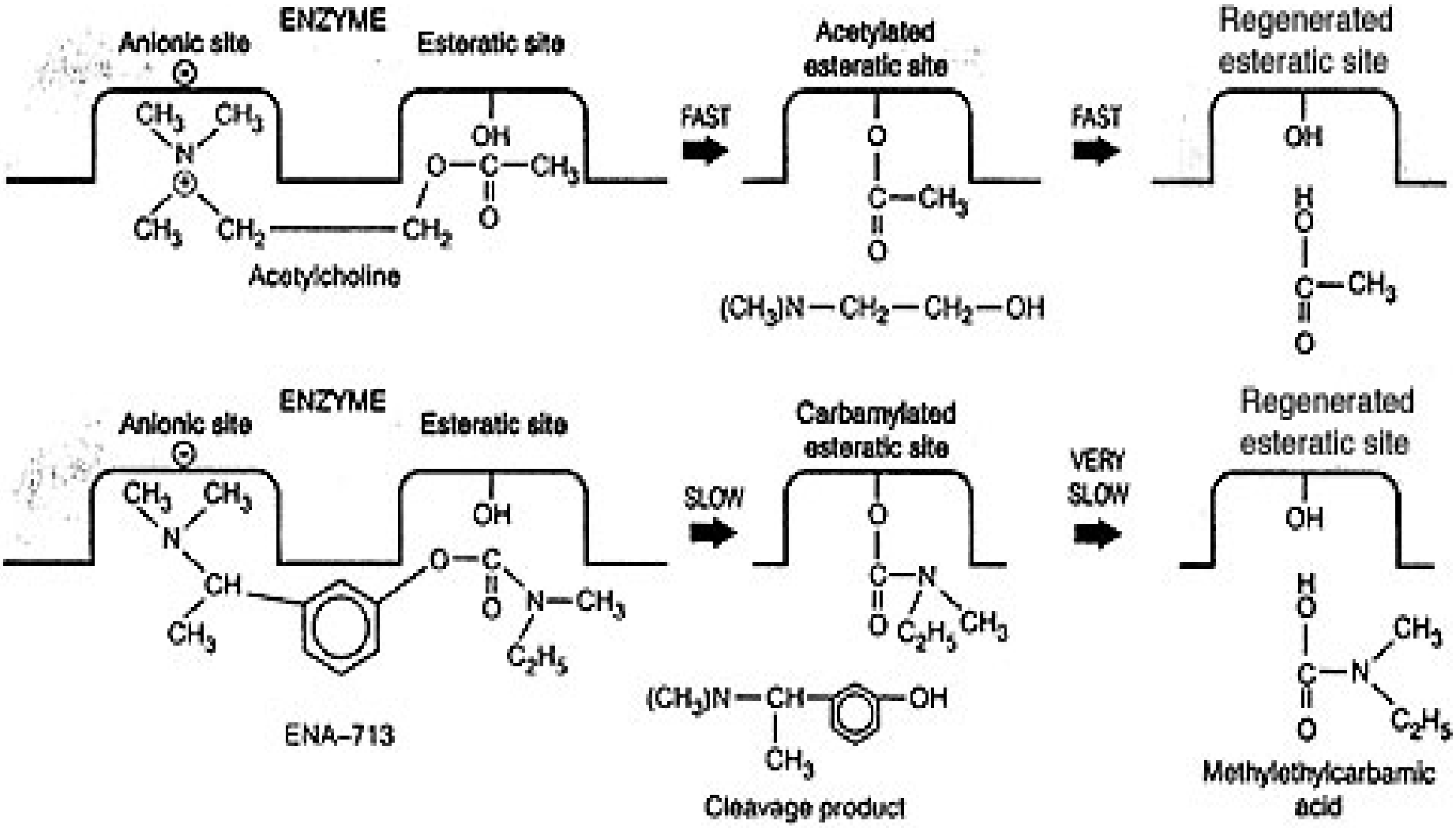
Indirect-acting, organophosphate	
Parathion	Highly lipid-soluble
Malathion	Highly lipid-soluble but metabolized to inactive products in mammals and birds
Sarin, tabun, others	Like parathion but more rapid action

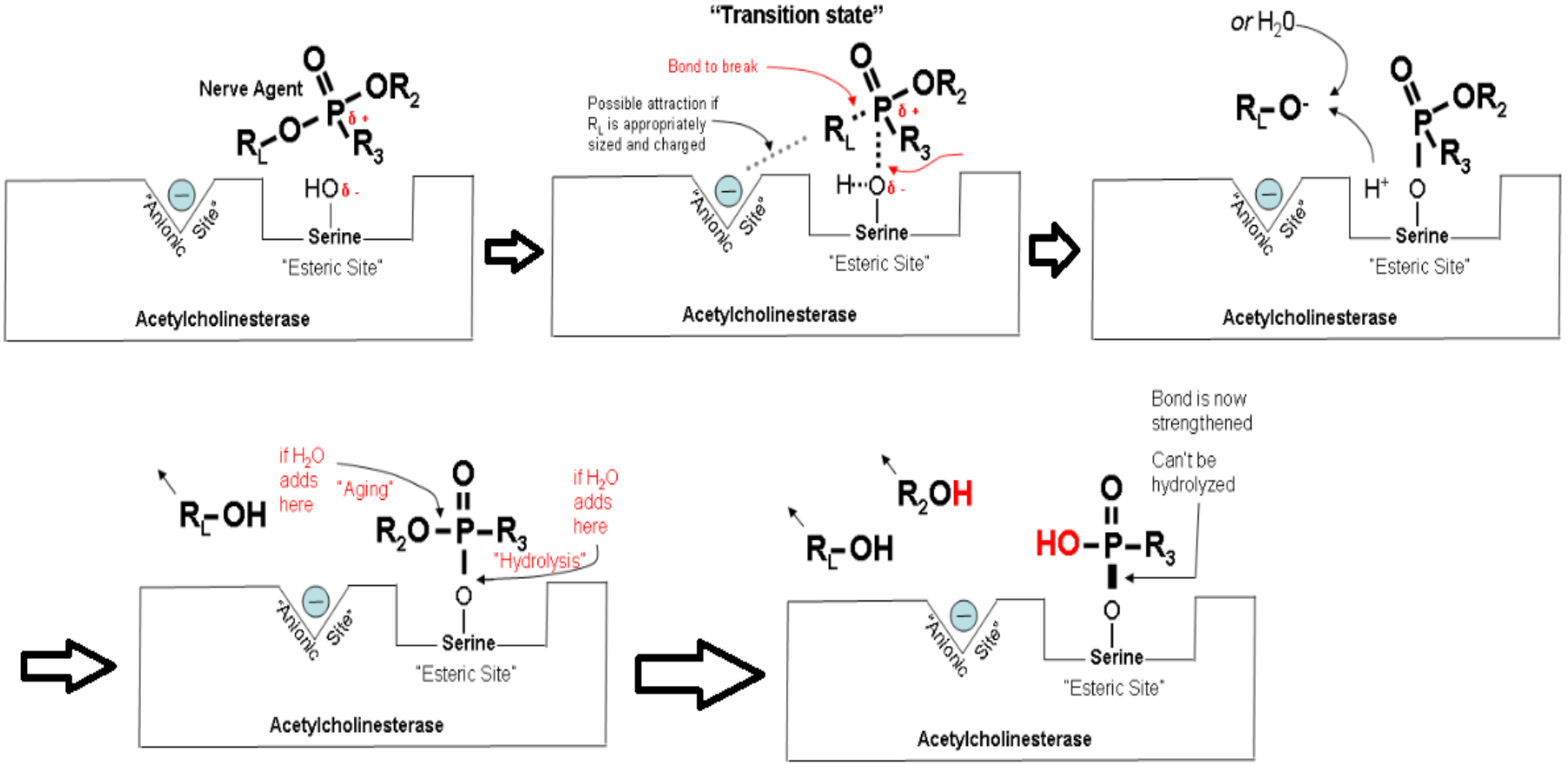
MECHANISM OF ACTION

- **Acetylcholinesterase** is the primary target of anticholinestrases.
- They react with the enzyme essentially in the same way as acetylcholine.
- Cholinesterase has two sites that bind acetylcholine

anionic site(N2) **esteratic site**(-CO)


Acetylcholine
Electrostatic attraction
Anionic Site
Serine
"Esteric Site"
Acetylcholinesterase
Acetic Acid
Choline


ENZYME
Anionic site
Esteratic site
Acetylcholine
FAST
Acetylated esteratic site
(CH3)N—CH2—CH2—OH
FAST
Regenerated esteratic site
ENZYME
Anionic site
Esteratic site
ENA-713
SLOW
Carbamylated esteratic site
(CH3)N—CH—OH
CH3
Cleavage product
VERY SLOW
Regenerated esteratic site
Methylethylcarbamic acid


Nerve Agent
"Anionic Site"
Serine
"Esteric Site"
Acetylcholinesterase
"Transition state"
Bond to break
Possible attraction if R_L is appropriately sized and charged
or H_2O
if H_2O adds here
"Aging"
"Hydrolysis"
Bond is now strengthened
Can't be hydrolyzed

Organ system effects

- G.I.T
- URINARY BLADDER
- EXOCRINE GLANDS
- LUNGS
- C.V.S
- SKELETAL MUSCLES

Therapeutic Uses of Inhibitors of Acetylcholinesterase

1. Glaucoma (wide angle)
2. Atony of the bladder or GIT (after surgery).
3. Intoxication by antimuscarinic agents, tricyclic antidepressants (TCA's) or phenothiazines (use physostigmine)
4. Recovery of neuromuscular function after competitive blockade of Nm receptor of skeletal muscle fibers
5. Myasthenia gravis

How to differentiate between
Myasthenic crisis & Cholinergic crisis

Myathenic crisis

- Skeletal muscle weakness due to untreated or inadequately treated myasthenia Gravis.
- **Neostigmine** : Improved muscle strength
- **Treatment: Give or ↑ the dose of** neostigmine

Cholinergic crisis

Skeletal muscle **weakness due to over treated myasthenia gravis i.e.** depolarization block.

- **Neostigmine:** No effect or increase muscle weakness
- **Treatment**: Decrease the dose of neostigmine

TREATMENT

- Indirectly acting cholinesterase inhibitors
  - ✓ Neostigmine
  - ✓ Pyridostigmine
- Corticosteriods
- Plasmapheresis
- Thymectomy

ADVERSE EFFECTS

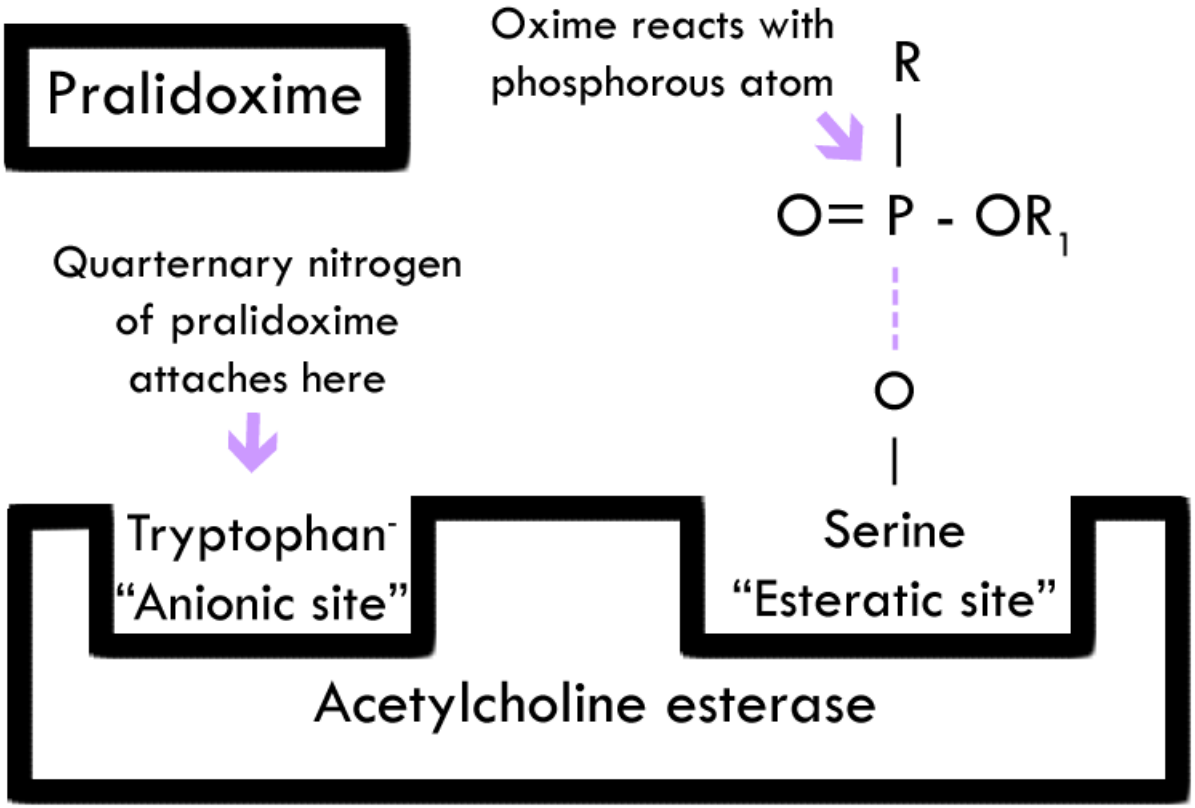
ORGANOPHOSPHOROUS POISONING

- **Features**

- ✓ Diarrhea
- ✓ Urination
- ✓ Muscle weakness/miosis
- ✓ Bradycardia
- ✓ Bronchoconstriction
- ✓ Emesis
- ✓ Lacrimation
- ✓ Salivation/sweating
- ✓ Convulsions , coma

TREATMENT

- Maintenance of vitals
- Decontamination
- Atropine
- Diazepam
- Cholinestrase enzyme regenerators
  - Pralidoxime
  - Diacetylmonoxime



- Chronic exposure
- Intermediate syndrome
- Prophlaxsis of chemical warfare

RESEARCH

- Žnidaršic, N., Štrbenc, M., Grgurevic, N. and Snoj, T., 2023. Potential revival of cholinesterase inhibitors as drugs in veterinary medicine.

ARTIFICIAL INTELLIGENCE

- Nour H, Abdou A, Belaidi S, Jamal J, Elmakssoudi A, Dakir M, Chtita S. Discovery of promising cholinesterase inhibitors for Alzheimer's disease treatment through DFT, docking, and molecular dynamics studies of eugenol derivatives. Journal of the Chinese Chemical Society. 2022 Sep;69(9):1534-51.

EOLA

1. Which of the following condition limits the use of muscarinic agonists:

a) Bronchospasm
b) ↑ Intraocular pressure
c) Loss of memory
d) Muscles weakness
e) Xerostomia

2. Which of the following cholinergic is used in treatment of Alzheimer's disease;

a) Acetylcholine
b) Bethanechol
c) Edrophonium
d) Galantamine
e) Physostigmine

3. A middle age farmer while spraying pesticide suffered diarrhea, urination, miosis, lacrimation,bronchoconstriction, bradycardia, salivation, sweating, muscle weakness & seizures. Which of the following chemical antagonist is used in this medical emergency?

a) Atropine
b) Carbachol
c) Donepezil
d) Paralidoxime
e) Rivastigmine