CLINICAL SPECTRUM OF ORGANOPHOSPHORUS POISINING IN PEDIATRIC AGE GROUP

Thesis

Submitted in Partial Fulfillment for Master Degree (M.Sc.) Degree In Pediatrics

By

Alaa Saleh El-Sebaey

(M.B.B.CH)

Supervised by

Prof. Dr. Ahmed Saad El-Din El- Beleidy
Professor of Pediatrics, Cairo University

Prof. Dr. Abd El- Rahman El- Naggar
Professor of Pharmacology & The Director of
National Center for Clinical and Environmental Toxicology
Cairo University

Prof Dr. Mohamed Hesham Sayed
Professor of Pediatrics, Cairo University

Department of Pediatrics, Faculty of Medicine
Cairo University
2008

Abstract

We conducted a retrospective study of infants and children with organophosphate and carbamate poisoning who were hospitalized at our center. The study was designed to determine the clinical manifestations and complications of organophosphate and carbamate toxicity in infants and children, the usefulness of plasma cholinesterase activity assays for diagnosis, the efficacy of supportive therapy, the effect of oxime and atropine therapy in children, and helps to identify at an early stage those patients who would ultimately require ventilatory support.

Key Words :

Cholinesterase – Organophosphates – Trimedoxime .

Contents

	Page
1- Aim of the work	**1**
2- Introduction	**3**
- Toxicokinitics	5
- Toxicodynamics	6
- Mechanism of toxicity	7
- Treatment	8
- Decontamination	10
- Diagnostic testing	12
3- Review of literature	**14**
- Organophosphate and carbamate poisoning in young children (a clinical and laboratory study).	14
- Comparative study of organophosphate and carbamate poisoning in adults and children.	18
- Complications in organophosphate and carbamate poisoning.	19
- Gas chromatography-mass spectrometry analysis.	33
- Use of cholinesterase activity testing in pesticide poisoning.	33
- Management of acute organophosphorus pesticide poisoning.	37
- The pharmacokinetics of continuous infusion pralidoxime.	47
- The role of oximes in treatment of organophosphate poisoning.	50
- Effect of the pre-hospital systematic treatment.	61
- The effects of fresh frozen plasma on cholinesterase levels.	62
- Gene therapy to prevent organophosphate intoxication.	62
- Hemoperfusion for organophosphate poisoning.	63
4- Methods	**65**
5- Results	**69**
6- Discussion	**82**
7- Conclusion	**93**
8- References	**97**
9- Arabic summary	**108**

List of Tables

Tables	Page
Table (1) Methods of Gastrointestinal Decontamination	11
Table (2) Age distribution in 47 cases of pesticide poisoning	70
Table (3) Sex distribution in 47 cases of pesticide poisoning	70
Table (4) Route of intoxication in 47 cases of pesticide poisoning	71
Table (5) Clinical signs and symptoms of the patients	73
Table (6) Mode of treatment in 47 cases of pesticide poisoning	74
Table (7) Levels of the cholinesterase activity U/L with number of patients through 36 hours	75
Table (8) Pattern of liver enzymes in 47 cases of pesticide poisoning	76
Table (9) Pattern of Natremia in 47 cases of pesticide poisoning	77
Table (10) Pattern of Kalemia in 47 cases of pesticide poisoning	78
Table (11) Clinical features of 47 patients with insecticides	80
Table (12) Complications in patients with insecticide poisoning	81
Table (13) Muscarinic signs of 47 patients of insecticides poisoning	87

List of Figures

Figures	Page
Figure (1) Sex distribution in 47 cases of pesticide poisoning	71
Figure (2) Route of intoxication in 47 cases of pesticide poisoning	72
Figure (3) Mode of treatment in 47 cases of pesticide poisoning	74
Figure (4) Levels of the cholinesterase activity U/L with number of patients through 36 hours	76
Figure (5) Pattern of liver enzymes in 47 cases of pesticide poisoning	77
Figure (6) Pattern of Natremia in 47 cases of pesticide poisoning	78
Figure (7) Pattern of Kalemia in 47 cases of pesticide poisoning	79
Figure (8) Complications in patients with insecticide poisoning	81

List of Abbreviations

AACT	American Academy of Clinical Toxicology
AChE	Acetylcholinestrase
ARDS	Adult respiratory distress syndrome
BuChE	Butylcholinesterase
ChE	Cholinesterase
CNS	Central nervous system
COPIND	Chronic organophosphate induced neuropsychiatric disorders
CPAP	Continuous positive airways pressure
DFP	Diisopropylphosphorofluoridate
EAPCCT	European Association of Poisons Centres and Clinical Toxicologists
E-AChE	Erythrocyte acetylcholinesterase
GCMS	Gas chromatography-mass spectrometry
GIT	Gastrointestinal tract
IMS	Intermediate syndrome
IMV	Intermittent mandatory ventilation
I.V.	Intravenous
ICU	Intensive care unit
OP	Organophosphates
OPP	Organophosphate poisoning
OPIDN	Organophosphate-induced delayed neuropathy
P.I	Protection index
P=O	Phosphates
P=S	Phosphothioates
PAM	Pralidoxime

PChE	Pseudocholinesterase
PON1	Serum paraoxonase
PQTS	Prolonged QT syndrome
RICU	Respiratory intensive care unit
RNS	Repetitive nerve stimulation
MgSO4	Magnesium sulfate
MV	Mechanical ventilation
NECTR	National Center for Clinical and Environmental Toxicology
NMT	Neuromuscular transmission
NTE	Neuropathy target esterase
RBCs	Red Blood Cells
RCTs	Randomized clinical trials
RF	Respiratory failure
SAOPP	Severe acute organophosphorus pesticide poisoning
S-ChE	Serum cholinesterase
SGOT	Serum glutamic oxalocetic transminase
SGPT	Serum glutamic pyruvic transminase
SLUDGE	(salivation, lacrimation, urination, diarrhea, gastrointestinal distress, and emesis)
SPECT	Emission computerization tomography
Toxogonin	Obidoxime chloride
TMB-4	Trimedoxime
U/L	Unit per liter

Aim of the work

Aim of the work

We conducted a retrospective study of infants and children with organophosphate and carbamate poisoning who were hospitalized at our center. The study was designed to determine:

(1) the clinical manifestations of organophosphate and carbamate toxicity in infants and children.

(2) the complications of organophosphate and carbamate poisoning.

(3) the usefulness of plasma cholinesterase activity assays for diagnosis.

(4) the efficacy of supportive therapy.

(5) the effect of oxime and atropine therapy in children.

(6) and helps to identify at an early stage those patients who would ultimately require ventilatory support.

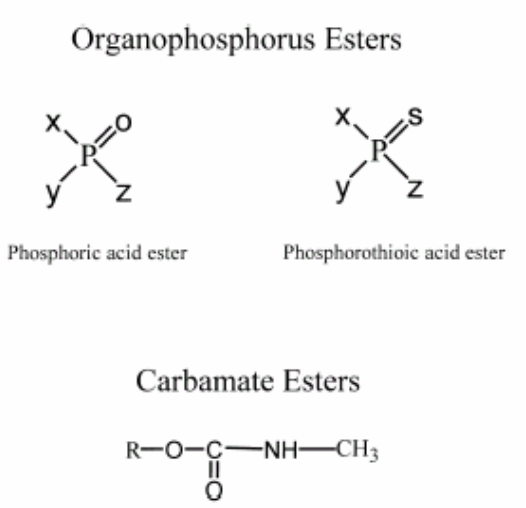
The time of disappearance of symptoms, the recovery time of cholinesterase (ChE), atropinization time, atropine dosage, pralidoxime chloride dosage, hospitalization days and other targets were observed.

Introduction

Introduction

The organophosphates and carbamates are used in large quantities around the world as agricultural insecticides. Toxic exposure to these toxic chemicals is a serious global public health problem, with more than 3 million poisonings and 200,000 deaths reported per year (**Jeyaraatnam, 1990**). Poisonings are most common among agricultural workers, manufacturing workers, and small children (**O'Malley, 1997**). Suicidal self-poisonings with these easily accessible agents is a major problem in developing countries (**Senanayake and Karalliedde, 1986**).

The organophosphates and carbamates are usually esters of phosphoric acid, phosphothioic acid, or carbamic acid. There is considerable structural diversity in the side chains among the commonly used organophosphates and carbamates. The side chains determine the toxicokinetics and toxicodynamics of pesticide poisoning (**Moretto, 1998**). There are more than 200 organophosphates and 25 carbamates, formulated into thousands of products (Scheme. 1).



Kwong (2002) reported in his review that the toxicokinetics and toxicodynamics of organophosphate poisoning vary not only with the

route and extent of exposure, but also the chemical structure of the agent. The mechanism of toxicity is the inhibition of acetylcholinesterase, resulting in an accumulation of the neurotransmitter acetylcholine and the continued stimulation of acetylcholine receptors. The standard treatment consists of reactivation of the inhibited acetylcholinesterase with an oxime antidote and reversal of the biochemical effects of acetylcholine with atropine. Patients who receive treatment promptly usually recover from acute toxicity but may suffer from neurologic sequelae (**Kwong, 2002**).

TOXICOKINETICS

These pesticides can be absorbed rapidly via all routes—respiratory, gastrointestinal, ocular, and dermal. The onset of symptoms is quickest after inhalation (**Vale, 1998**). Dermal absorption is slower but can result in severe toxicity if exposure is prolonged and can be enhanced if the agent is lipophilic and helped by the solvent and emulsifier used in the formulation (**Phillips, 2001**). Oral ingestion is often accidental by children but is usually associated with suicide attempts by adults.

The pesticides distribute and accumulate rapidly in fat, liver, and kidney. The phosphothioates (P=S) are more lipophilic than the phosphates (P=O) and are stored extensively in fat. The phosphothioates are biotransformed to their active phosphate (P=O) analogs by oxidative desulfuration mediated by cytochrome P450. Therefore, the appearance of toxic symptoms after exposure to phosphothioate pesticides is delayed. Most patients become symptomatic within 12 hours of exposure if the causative agents are not the fat-soluble organophosphates (e.g., fenthion) or those requiring metabolic activation (e.g., parathion) (**Vale, 1998**) and

Aaron & Howland, 1998). Elimination is slow because of extensive fat storage; for the more lipophilic phosphothioates, it can take many days.

TOXICODYNAMICS

The organophosphates and carbamates are powerful inhibitors of carboxylic ester hydrolases, including acetylcholinesterase (found in nervous tissues and erythrocytes) and butyrylcholinesterase (plasma or pseudocholinesterase). As a result of this enzyme inhibition, the substrate acetylcholine accumulates. The continued stimulation and eventual paralysis of the acetylcholine receptors account for the clinical signs and symptoms of organophosphate poisoning, including muscarinic, nicotinic, and central nervous system effects (**O'Malley, 1997** and **Aaron & Howland, 1998**).

The most common manifestations of muscarinic effects of the parasympathetic nervous system (salivation, lacrimation, urination, diarrhea, gastrointestinal distress, and emesis) can be remembered by the acronym SLUDGE. Sweating is due to inhibition at the sympathetic postganglionic sites. Other frequently seen muscarinic effects include bradycardia, bronchorrhea, and miosis. Nicotinic effects at the somatic nerve endings include muscle fasciculation, weakness, and paralysis and, at the autonomic synapses, hypertension, tachycardia, and dilated pupil (**O'Malley, 1997** and **Aaron & Howland, 1998**).

Central nervous system manifestations include restlessness, headache, drowsiness, confusion, slurred speech, emotional lability, psychosis, ataxia, tremor, delirium, and seizure. Many young patients, however, have different clinical presentations: the classic muscarinic symptoms typically associated with adults may be absent, and the

primary toxic manifestations are those of the central nervous system (**Lifshitz, 1999**).

MECHANISM OF TOXICITY

Acetylcholinesterase is one of the most efficient enzymes, being capable of an extremely rapid rate of hydrolysis of acetylcholine and regeneration of the active enzyme. Acetylcholine attaches itself to the hydroxyl group of serine residue 203 at the active center of acetylcholinesterase to form an enzyme intermediate (**Taylor, 1996**). Breakdown of this intermediate regenerates an active enzyme, and in the process acetylcholine is hydrolyzed. The molecular mechanism of organophosphate and carbamate toxicity lies in the phosphorylation or carbamylation of the same serine residue and the formation of an organophosphorous or carbamyl intermediate with acetylcholinesterase. The phosphorylated or carbamylated enzyme is much more stable and has a lower rate of hydrolysis and regeneration of the active enzyme. For some phosphorylated enzymes, the regeneration rate can be so slow that the phosphorylated acetylcholinesterase is essentially inactive (**Moretto, 1998** and **Taylor, 1996**).

Moreover, some of these phosphorylated enzymes can lose an alkyl group over the next 24 to 48 hours, before active enzymes can be regenerated. This process is referred to as aging. An aged enzyme is permanently phosphorylated and cannot be regenerated by spontaneous hydrolysis or an oxime antidote (**Vale, 1998**). The powerful nerve agents, such as sarin and soman, owe their deadly action to their very rapid rate of aging of the phosphorylated enzyme, rendering the acetylcholinesterase permanently inactivated very quickly (**Taylor, 1996**). Compared with the phosphorylated enzyme intermediate, the

hydrolysis of the carbamylacetylcholinesterase intermediate to regenerate an active enzyme is more rapid. Therefore, carbamate poisoning is not as severe and is self-limiting. In general, the chemical structure of the organophosphate (mostly the side groups) determines the affinity to acetylcholinesterase, time for hydrolysis, and regeneration of the enzyme, and therefore the toxicity and time of onset of symptoms (**Moretto, 1998** and **Vale, 1998)**).

TREATMENT

Because the toxic effects are the consequence of the inhibition of acetylcholinesterase in the nervous system, leading to an accumulation of the neurotransmitter acetylcholine at synapses and myoneural junctions, the standard treatment of acetylcholinesterase pesticide poisoning consists of the use of atropine, a competitive acetylcholine antagonist, to reverse the biochemical abnormalities at the synapses resulting from excess acetylcholine, and the use of nucleophilic oxime, pralidoxime or obidoxime, to regenerate acetylcholinesterase (**Aaron & Howland, 1998)** and **Howland et al., 1998**).

The antidote exerts its antidotal effect by a nucleophilic attack on the phosphate moiety of the phosphorylated enzyme, resulting in phosphate removal and regeneration of an active acetylcholinesterase. Because aged acetylcholinesterase cannot be reactivated by an oxime antidote, oxime therapy should be initiated as soon as possible after the exposure. The structure of the organophosphate side chain is an important determinant of the rates of enzyme aging and pralidoxime reactivation(**Kwong, 2002**).