THE EFFECTS OF FRESH FROZEN PLASMA OR ALBUMIN IN THE TREATMENT OF ACUTE ORGANOPHOSPHATE POISONING: WHAT IS THE CLINICAL RELEVANCE?

Vucinic S, Djordjevic D, Jovic-Stosic J, Bokonjic D, Boskovic B

National Poison Control Centre MMA,
Medical Faculty, University of Defence, Belgrade, Serbia
Acute organophosphate poisonings: therapeutic measures

**Standard therapy**

1. Supportive

2. Antidotes

**Adjuncts and alternatives**
Toxicology literature

Likely to be beneficial:
1. Atropine (incremental/bolus)
2. Glycopyrrolate
3. Benzodiazepine
4. External decontamination

Unlikely to be beneficial:
1. Cathartics

Likely to be harmful/ineffective:
1. Induced vomiting
Toxicology literature

Unknown effectiveness:

1. Activated charcoal (single or multiple doses)
2. Alpha$_2$ adrenergic receptor agonists
3. Butyrylcholinesterase replacement therapy
4. Fresh Frozen Plasma
5. Albumin
6. Extracorporeal replacement therapy
7. Gastric lavage
8. Magnesium sulphate
9. N-methyl-D-aspartate receptor antagonists
10. Organophosphorus hydrolases
11. Oximes
12. Sodium bicarbonate
13. Anti-glutamergic compounds
14. Early enteral feeding
**Bioscavengers** are enzymes or antibodies sequestering and neutralizing OPs before they reach biological targets.

Two types of bioscavengers:

1. **Stoichiometric** – stoichiometrically react with OPs (butyrylcholinesterase, antibodies). **Major drawback:** since stoichiometric scavengers bind OP compounds irreversibly in 1:1 ratio, high doses are required for efficient protection against OP poisoning.

2. **Catalytic** – display a turnover with OPs as substrates. This allows similar protection by administering much smaller doses. Catalytic scavengers are thus far more interesting from economics and safety points of view.

Toxicology literature


- BuChE – natural bioscavenger (absorbs and inactivate OP).

- **Advantage of profilactic use of purified human BuChE** - **confirmed** in GA, GB, GD and VX. A single dose of rhBuChR -Th conc. - 4 days, protection from exposure to 2 to 5 LD50’s.

- **Problem**: enzymatic stoichiometric neutralization of OP needs the administration of a huge amount of a costly bioscavenger,(3 mg/kg of highly purified plasma BCHE for challenging several LD50 of OP).

- Experimental study (guinea pigs): nerve agents (GA, GB, GD) phosphorilate adducts with a tyrosine residue on albumin when incubated with human plasma in vitro. Albumin - relatively long-lived biological marker not only of nerve agents, but also of dichlorvos.
# End points and risk factors for OP poisoning

<table>
<thead>
<tr>
<th>End points</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Time elapsed since poisoning</td>
</tr>
<tr>
<td>VAP</td>
<td>Dose of OPI ingested</td>
</tr>
<tr>
<td>Duration of ICU and hospitalization</td>
<td>Type of OPI ingested</td>
</tr>
<tr>
<td>IMS</td>
<td>Antidote/intervention used</td>
</tr>
<tr>
<td>Long term neurologic complications</td>
<td>Availability of ICU</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
</tbody>
</table>
FRESH FROZEN PLASMA

• Blood fraction prepared by removing the cellular components by apheresis. It contains clotting factors, proteins, enzymes and it is used when these components are deficient or lost.

• **HYPOTHESIS:** In OPI poisoning BuChE from FFP will sequester free poison present in blood and remove it from circulation.

• Whether sufficient butyrylcholinesterase can be given to produce clinical benefit is unknown.

There is currently insufficient evidence to recommend the routine use of FFP in OP poisoning.
Guven et al (32/12 FFP):
FFP increases BuChE levels in OP poisonings, prevents the development of IMS and related mortality. May be used as an alternative or adjunctive treatment method in patients with OP poisoning, especially in cases not given pralidoxime. Plasmapheresis using FFP - beneficial effect.

Pichamuthu K, et al - 60 pts - FFP (8 bags), albumin (400 ml) or saline (2L)
No differences regarding: need for ventilation, MV duration, atropin dose, hospitalization, mortality rate. Suggestion: negative outcomes - attributed to BuChE releasing the sequestred OP.

Pazooki et al. 56 (28 FFP)
No significant difference was seen between the two groups on the atropine and pralidoxime dosage, hospitalization length and mortality.

Fulton. “secret ingredient” suggested that possible mechanism is aggressive volume resuscitation with BuChE serving as a scavenger.
### Distribution of patients in different therapeutic groups

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th></th>
<th>ALB</th>
<th></th>
<th>Conv. Ther.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malathion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS 2</td>
<td>2</td>
<td>30</td>
<td></td>
<td></td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>PSS 3</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>33</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>PSS 4</td>
<td></td>
<td></td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td><strong>Dimethoate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS 2</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>PSS 3</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>PSS 4</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td><strong>Dichlorvos</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS 2</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td><strong>Diazinon</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS 2</td>
<td></td>
<td></td>
<td>1</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chlorpyrphos</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS 3</td>
<td></td>
<td></td>
<td>1</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>7</td>
<td>100</td>
<td>3</td>
<td>100</td>
<td>11</td>
<td>100</td>
</tr>
</tbody>
</table>
Patient 1. dichlovos PSS 2

- Emergency room: somnolent, gastric lavage, intubated during transport, 2 mg atropine muscarinic and nicotinic effects on arrival.
- Clinical course in the ICU: FFP (2 doses, 2 days) atropin 22 mg during 3 days, hospitalization 6 days. Bronchopneumonia, rhabdomyolysis.
• Patient 2. dimethoate, PSS 3
• Emergency room: coma, intubated, 6 mg atropine muscarinic and nicotinic effects on arrival.
• Clinical course in the ICU: FFP (2 doses, 2 days) atropin 98 mg during 5 days, hospitalization 16 days due to complications (bronchopneumonia).
• Patient 3. malathion PSS 2
• Emergency room: muscarinic and nicotinic effects on arrival.
• Clinical course in the ICU: FFP (2 doses) atropin 30 mg during 3 days, hospitalization 10 days. Bronchopneumonia, rhabdomyolysis.
FFP

- Patient 4. dimethoate PSS 2
- Emergency room: muscarinic and nicotinic effects on arrival.
- Clinical course in the ICU: FFP (2 doses, 2 days) atropin 94 mg during 3 days, hospitalization 7 days.
FFP

- Patient 5. dimethoate on arrival PSS 2, outcome PSS 4
- Emergency room: muscarinic effects, severe secretion after 12 hours.
- Clinical course in the ICU: FFP (2 doses) atropin 60 mg, pralidoxime 2g loading dose, 500 mg/h. Cardiac and respiratory arrest after 16 hours, exitus letalis. CPK 1678-24266, Le 28,3 AST 55-922 U/L, ALT 25-213 U/L.
- Tox.anal. (blood): dimethoate 35 mg/L, after 6 hr 11,1 mg/L, second dose of plasma 2 ,10 mg/L.
FFP

- Patient 6. malathion PSS 2
- Emergency room: muscarinic and nicotinic effects.
- Clinical course in the ICU: FFP (2 doses, 2 days) atropin 36 mg (5 days), hospitalization 10 days.
FFP

- Patient 7. malathion PSS 3
- Emergency room: muscarinic and nicotinic effects.
- Clinical course in the ICU: FFP (2 doses, 2 days) atropin 735 mg (5 days), PAM 2g + 500 mg/h, hospital. 7 days.
- Tox. analysis in blood: malathion 18,01 mg/L, malaoxon 0,26 mg/L, after 3 hr 11,25 mg/L, malaoxon 0,17 mg/L, second dose of plasma 7,54 mg/L, 3 rd dose 12 hr 0,32 mg/l , malaoxon neg. 24 hr, malathion 0,07 mg/L.
ALBUMIN

- Patient 8, diazinon PSS 2
- Emergency room: muscarinic and nicotinic effects.
- Clinical course in the ICU: albumin (2 doses, 2 days) atropin 23 mg (3 days), hospitalization 6 days.
- Diazinone 0.017 mg/L

[Graph showing ALB and AChE levels over 72 hours with markers at 14% and 39%]
ALBUMIN

- Patient 9. malathion PSS 3
- Emergency room: coma, muscarinic and nicotinic effects, ARI. Intubation, MV (14 days), PAM 2 g + 500 mg/h (5 days)
- Clinical course in the ICU: albumin (2 doses, 2 days) atropin 724 mg (5 days), hospitalization 17 days.
- bronchopneumonia
ALBUMIN

- Patient 10. chlorpyriphos PSS 3
- Emergency room: coma, muscarinic and nicotinic effects, ARI. Intubation, MV (14 days), PAM 2 g +500 mg/h (4 days)
- Clinical course in the ICU: albumin (2 doses, 2 days) atropin 292 mg (4 days), hospitalization 38 days due to complications (bronchopneumonia, rhabdomyolysis, pneumothorax, polyneuropathy).
BuChE and AChE – conventional therapy
Oxime therapy in different therapeutic groups

- FFT: 29% Yes, 71% No
- ALB: 37% Yes, 63% No
- Conventional therapy: 64% Yes, 36% No
Mechanical ventilation in different therapeutic groups

\[X^2 \text{ test (FFT} : \text{Conv. Ther.} \quad p < 0.05)\]
BuChE and AChE levels increase after first dose of FFP

Wilcoxon Matched Pairs Test (buChE – p<0.01 vs pre-FFP value)
The effects of FFP on total atropine dose, duration of ventilation and hospital stay

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FFP</th>
<th>ALB</th>
<th>Conv. Ther.</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSS</td>
<td>2.6 ± 0.8</td>
<td>2.7 ± 0.6</td>
<td>2.7 ± 0.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hospital (days)</td>
<td>8.3 ± 5.0</td>
<td>20.3 ± 16.3</td>
<td>14.1 ± 9.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ventilat. (days)</td>
<td>-</td>
<td>14.0 ± 0.0</td>
<td>7.7 ± 3.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tot. atrop. (mg)</td>
<td>153.6 ± 258.1</td>
<td>346.3 ± 353.6</td>
<td>378.3 ± 299.0</td>
<td>FFP:CT – p &lt; 0.05</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>1/7</td>
<td>0/3</td>
<td>2/11</td>
<td>n.s.</td>
</tr>
<tr>
<td>IMS</td>
<td>0/7</td>
<td>0/3</td>
<td>1/11</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Binding of OP for albumin in FFP and the quantity of OP that was bound

Dichlorvos – 133.6 mg/L
Malathion – 200.8 mg/L
Dimethoate – 139.2 mg/L
Conclusions

- Resuscitation is the mainstay
- ABCD’s include atropine (individual titration-incremental)
- Gastric lavage may be useful within 2-3 hours
- Hypothesized mechanism: quality volume replacement containing albumin, increased level of BuChE, scavenging effect for OP.
- Due to BuChE replacement, albumin content and volume restitution, FFP treatment may be used as an alternative approach in patients with acute organophosphate poisoning especially when oximes are unavailable.