

## The role of plasmapheresis in organophosphate poisoning: Case reports of three pediatric patients

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The aim of the study was to assess the impact of plasmapheresis treatment in the management of three pediatric patients with organophosphate poisoning who did not respond to standard treatment. The treatment of signs and symptoms, and supportive treatment has been evaluated in this paper.

Patients were initially given atropine infusion and 0.05 mg/kg atropine with five-minute intervals. Despite pralidoxime loading and three consecutively infusions clinical symptoms did not respond to the treatment and plasma pseudocholinesterase levels did not decrease. At this point, plasmapheresis was used on three consecutive days. Accordingly, the clinical signs improved and mechanical ventilation was no longer necessary. Patients were discharged on the sixteenth day after their admission to the hospital.

Plasmapheresis may be an option for the patients who do not respond to atropine and pralidoxime treatment in organophosphate poisoning.

*Key words:* organophosphate, poisoning, plasmapheresis.

Organophosphates (OP) are toxic chemicals that are found in most pesticides. Therefore, OP poisoning is quite common in developing countries.<sup>1</sup> These compounds are absorbed by skin, gastrointestinal system and respiratory system. Since absorption by skin is slower and symptoms occur more slowly, patients are usually late for hospital admittance hence skin exposures may have more serious results.<sup>2</sup>

Compounds are classified according to the atoms on the phosphate. Compounds are named as phosphates when their four atoms contain oxygen; as phosphothioates when containing sulfur; as phosphoramides when containing nitrogen; as phosphoramidothionates when containing nitrogen and sulfur; as phosphonates when containing carbon and as phosphothionates when containing carbon and sulfur. Elimination of phosphothioates; because of their lipophilic composition, is slower than phosphates. OP compounds are mainly metabolized in liver by hydrolysis and show variations between compounds.

Compounds like methylparathion and diazinon are highly liposoluble and may cause late toxicity symptoms because of re-release in fat tissue. Compounds are required to be in oxone forms for inhibition. Thioates which are not accepted as important inhibitors, may be activated by metabolism with oxones. The cleansing rate of the oxons vary according to the characteristics of the compound.<sup>2</sup>

OP's cause accumulation of acetylcholine (ACh) in the synapses by inhibiting the enzyme acetylcholinesterase (AChE). Since diethyl organophosphates are inactivated more slowly than dimethyl organophosphates, the reactivation of the enzyme AChE is slower.<sup>3</sup> The traditional approach which is to treat OP poisoning with atropine and oximes, has been shown to be insufficient to prevent morbidity and mortality in former studies.<sup>3-5</sup>

The purpose of plasmapheresis is to separate antibodies, immunocomplexes, endogenous and exogenous toxins from the plasma and

replace them with some plasma proteins and coagulation factors. Plasmapheresis, colloids, fresh frozen plasma and albumin are used for this purpose. Unlike albumin, fresh frozen plasma contains active cholinesterase, and it is used for increasing the cholinesterase level of patients with low plasma cholinesterase levels.<sup>6,7</sup>

In this paper, we aimed to present three patients who recovered with plasmapheresis after OP poisoning.

### Case 1

A 7-year-old female patient, with vomiting, abdominal pain and progressive deterioration of consciousness, was brought to our pediatric emergency service (ES) 3 days after her hair was washed with an agricultural pesticide containing OP for head lice. At admittance, her body temperature was 37°C, respiratory rate was 25/min, blood pressure was 120/80 mmHg, heart rate was 161/min, and SpO<sub>2</sub> was 95%. Her general condition was poor. She was intubated with miotic and pinpoint pupils, rough respiratory sounds and widespread crepitane rales. She had thick secretion in oropharynx and hypopharynx, GCS (Glasgow Coma Scale) was 10/15. Plasma pseudocholinesterase level was 428 U/L (normal range: 3,530-10,800 U/L). The patient was diagnosed with OP poisoning based on clinical and laboratory findings.

Since she had a history of exposure to OP by her hair being washed with an agricultural chemical, her hair was cut and all of her body and the remaining hair were cleansed with soap and water. Monitoring clinical signs, she was given atropine at the dose of 0.05 mg/kg/hour every 5 minutes. Since heavy bronchorrhea and secretions continued despite intermittent atropine infusion, atropine infusion dose was augmented to 0.08 mg/kg/hour and injection of pralidoxime (PAM) at 40 mg/kg/dose was applied, followed by PAM infusion (8 mg/kg/hour) for two days. In spite of sixty hours of intensive therapy, the clinical findings did not improve and plasmapheresis was planned. The patient received plasmapheresis in three consecutive days. On the fourth day, the clinical findings improved and the pseudocholinesterase level of 3922 U/L rose up to 4868 U/L (Fig. 1). Atropine was infused every 20 minutes after the first plasmapheresis, every 30 minutes after the second plasmapheresis, and every hour after the third plasmapheresis. The patient was separated from mechanical ventilation and she gained consciousness. Atropine dose was decreased gradually and terminated on the twelfth day. The patient was discharged on the sixteenth day.

### Case 2

A 5-year-old female patient who was the sibling

**Table I.** Plasma Treatment and Techniques Used in Cases.

	Case-1	Case-2	Case-3
Weight (kg)	20	18	42
Hematocrit (%)	39	34	41
Total blood volume	1,400 ml	1,260 ml	2,520 ml
Technique of the plasma exchange	Centrifugation technique (Spectra Optica; CardianBCT, Lakewood, CO, USA, and Com.Tec; Fresenius HemoCare GmbH, Bad Homburg, Germany)	Centrifugation technique (Spectra Optica; CardianBCT, Lakewood, CO, USA, and Com.Tec; Fresenius HemoCare GmbH, Bad Homburg, Germany)	Continuous filtration technique (Prisma; Gambro, Lund, Sweden)
TPV given on the first day	1281 ml	1247 ml	1486 ml
TPV given on the other days	854 ml	831 ml	1486 ml
Catheter type	Femoral	Femoral	Femoral
Plasmapheresis duration	3 days	3 days	3 days

TPV: total plasma volume [total blood volume x (1-hematocrit)]

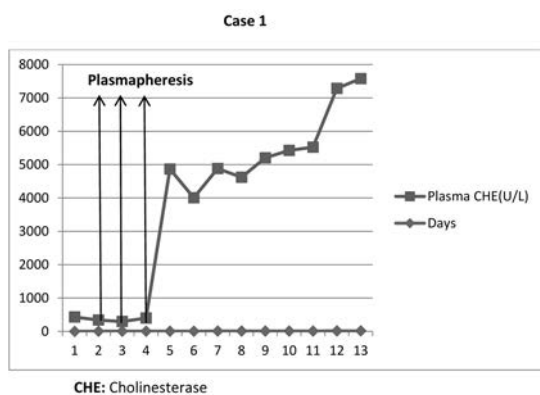


Fig. 1. The level of cholinesterase before and after plasmapheresis in Case 1.

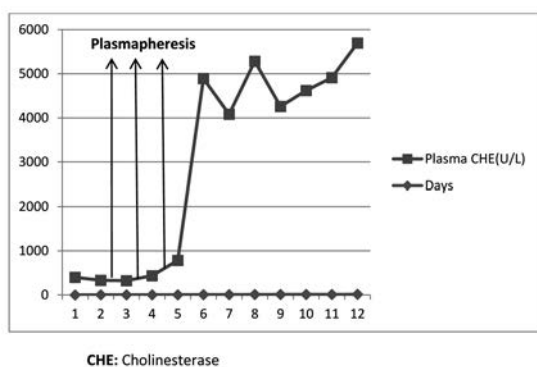


Fig. 2. The level of cholinesterase before and after plasmapheresis in Case 2.

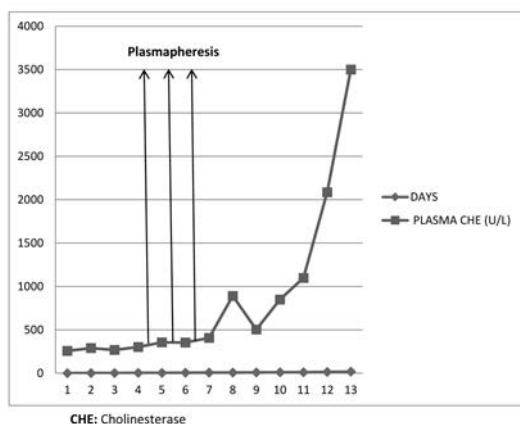


Fig. 3. The level of cholinesterase before and after plasmapheresis in Case 3

of Patient# 1; was brought to our pediatric ES 3 days after her hair was washed with an agricultural pesticide containing OP to fight head lice with vomiting, abdominal pain and progressive deterioration of consciousness. At the admittance, her body temperature was

36.5°C, respiratory rate was 28/min, blood pressure was 110/60 mmHg, heart rate was 156/min, and SpO2 was %97. Her general condition was poor. She was intubated, with miotic and pinpoint pupils, rough lung sounds, widespread crepitane rales, just as her sister. She had thick secretion in oropharynx with GCS 11/15. The level of plasma pseudocholinesterase was 398 U/L. Monitoring clinical signs, she was given atropine at the dose of 0.05 mg / kg/ hour every 5 minutes. Since heavy bronchorrhea and secretions continued despite intermittent atropine infusion, atropine infusion dose was augmented to 0.08 mg/kg/hour and injection of PAM at 40 mg/kg/dose was applied, followed by PAM infusion (8 mg/kg/hour) for two days. In spite of sixty hours of intensive therapy, the clinical findings did not improve and plasmapheresis was planned. The patient received plasmapheresis in three consecutive days. Consequently, the clinical signs improved, and the pseudocholinesterase level reached up to 4,073 U/L (Fig. 2). The patient was separated from mechanical ventilation and she gained consciousness. Atropine was decreased gradually and terminated on the twelfth day. The patient was discharged on the sixteenth day, similarly with her sister.

### Case 3

A 14-year-old male patient admitted to our ES with vomiting, abdominal pain and progressive decline of consciousness after taking an agricultural pesticide (Dimethoate) for committing suicide. At the admittance his body temperature was 36.7°C, blood pressure was 127/76 mmHg, heart rate was 68/min and, SpO2 was 95%. His general condition was poor. He was intubated, with miotic and pinpoint pupils, rough lung sounds and widespread crepitane rales. GCS was found 10/15. Pseudocholinesterase level was found 257 u/L. Monitoring clinical signs, she was given atropine at the dose of 0.05 mg/kg/hour every 5 minutes. Since heavy bronchorrhea and secretions continued despite intermittent atropine infusion, atropine infusion dose was augmented to 0.08 mg/kg/hour and injection of PAM 40 mg/kg/dose was applied, followed by PAM infusion (8 mg/kg/hour) for two days. Plasmapheresis was applied for 3 days when the patient did not clinically improve after 96 hours of medical treatment. Atropine infusion and

intermittent atropine injections were pursued. The patient gained consciousness and on the tenth day of hospitalization atropine injections were applied every 20 minutes. The patient was separated from mechanical ventilation and he gained consciousness. Atropine was decreased gradually and terminated on the sixteenth day. The patient totally recovered with pseudocholinesterase level of 3,630 U/L (Fig. 3). Patient was discharged on the eighteenth day.

Written informed consents were obtained from patients' parents who were mentioned in this paper.

### Discussion

Our case reports show that plasmapheresis may be an option for OP poisoning when medical treatment is insufficient. All three pediatric patients who were exposed to OP totally recovered with plasmapheresis application following failure of medical treatment with atropine and oximes.

Because of the high morbidity and mortality risk of exposure, OP is a major health problem in developing countries.<sup>1</sup> OP compounds are attached to the enzyme AChE and lead to the inactivation of the serine hydroxyl group of the enzyme by phosphorylating it. The reactivation of the phosphorylated enzyme occurs spontaneously (deacetylation, dephosphorylation), hydrolytic and by aging process.<sup>8</sup> Aging is a time dependent process and expresses the loss of reactivation ability of the nucleophilic agents. It occurs by the activation of AChE or BuChE (butyryl cholinesterase) by dealkylation of the phosphoryl group following the phosphorylation of serin.<sup>8</sup>

The inhibition of AChE in OP poisoning leads ACh to cause stimulation in nicotinic receptors (autonomic ganglions and motor end plates) and muscarinic receptors (heart, smooth muscles, glands). Increasing amount of ACh triggers off the clinical effects on the cholinergic synapses such as central nervous system, neuromuscular junction and autonomic ganglion. The first cholinergic crisis requires immediate treatment and the patient needs to be admitted into the intensive care unit.<sup>9,10</sup>

Conventional therapy for OP poisoning includes supportive therapy and antidotal

treatment. Atropine (anticholinergics) and oximes (cholinesterase reactivator) such as pralidoxime and obidoxime are the main medications used for antidotal treatment. Atropine eliminates parasympathetic stimuli by competitively blocking the effect of ACh on muscarinic receptors. Oximes, help in reversing the nicotinic effects which atropine cannot fix and in restoring active cholinesterase while reactivating AChE by dealkylating; removing the phosphoryl group on AChE which the OP binds.<sup>4</sup> In some cases, however, these treatments are not sufficient to prevent morbidity and mortality.<sup>5</sup> In a case series study carried out for the treatment of OP poisoning, the atropine and pralidoxime treatment did not have better results when compared to the atropine only treatment.<sup>7</sup> In a randomized controlled trial, in which patients treated with low-dose and high-dose oximes were compared, it has been observed that high-dose oxime treatment increased mortality.<sup>10</sup> The reasons for the shortage of oxime therapy are as follows: 1- inadequate doses, 2- long half-life of OP compared to oximes with short half-life, 3- timing of the oxime therapy (late start, early finish). Besides, the people with BuChE D70G mutation may also be resistant to the reactivation of the enzyme. In addition, cholinesterase inhibition and hepatotoxicity can be seen as a result of oxime therapy. Because of these reasons, new strategies should be developed for OP poisoning.<sup>11</sup>

Serum cholinesterase activity is a good indicator for evaluating the clinical improvement of a patient. Balali-Mood et al.<sup>12</sup> showed that there was a correlation between the clinical improvement of the patients with OP poisoning and the reactivation of the cholinesterase. If there is no gradual increase in the serum cholinesterase levels, prognosis might be poor with these patients. Cholinesterase reactivators are frequently used in patients with adequate cholinesterase levels, but these agents may be insufficient for some patients. Therefore, it is aimed to increase cholinesterase levels by using blood products. Fresh-frozen plasma contains many plasma proteins including cholinesterase.<sup>13</sup> For some patients with low levels of cholinesterase, fresh frozen plasma is used for replacement.<sup>14</sup> In preventing morbidity and mortality, atropine and / or PAM therapy added to the plasma treatment

has been found more efficient than sole atropine and/or PAM therapy.<sup>15</sup> Guven et al.<sup>16</sup> recently reported an adult patient with OP poisoning who did not respond to atropine and PAM treatment; however, the clinical signs and cholinesterase levels increased after plasmapheresis. Depending on the absence of sepsis, increase in cholinesterase levels after plasmapheresis, improvement in clinical signs and decrease in atropine need, it would be reasonable to tell that our patients had benefited from plasmapheresis.

Plasmapheresis is a nonselective method which is used to dispose hazardous and toxic products from the body circulation. Plasmapheresis provides active cholinesterase by rapidly removing undesired inactive plasma cholinesterase.<sup>17</sup> Two different techniques are used in plasmapheresis treatment: continuous filtration technique (Prisma) and centrifuge technique (Spectra-optica). Spectra-optica system uses tube set and a PL-1 kit in the double needle set.<sup>18</sup> We preferred Spectra-optica system through a double-lumen central catheter, using citrate and heparin for anticoagulation for the plasmapheresis treatment in three consecutive days in patient 1 and patient 2. In patient 3, we used continuous filtration technique (Prisma) and maintained anticoagulation with heparin (Table I).

Yesilbas et al.<sup>17</sup> reported a pediatric patient with OP poisoning who did not respond to atropine and PAM treatment; however, the clinical signs and cholinesterase levels increased after plasmapheresis, high-volume hemodiafiltration, and lipid infusion. They showed that AChE levels increased after this treatment. In a meta-analysis performed in China, six trials including 433 patients were identified. Treatment group including 211 patients adopted traditional physician therapy (atropine and PAM treatment) plus plasma exchange, and control group including 222 patients received physician therapy only. Mortality rates of OP poisoning patients treated with plasmapheresis were found to be lower when compared to the control group<sup>19</sup>.

In conclusion, plasmapheresis can be used in OP poisoning for patients who do not respond to the conventional treatment. However, further randomized controlled studies are necessary to have a clearer idea on this issue.

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