CASE REPORT / OLGU SUNUMU

Status Epilepticus Development After Organophosphate Intoxication/Midazolam: Case Report

Akut Organofosfat Zehirlenmesi Sonrası Gelişen Status Epilepticus/Midazolam: Olgu Sunumu

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Summary

Onset time and severity of symptoms that develop as a result of acute organophosphate intoxication may vary according to the specific compounds and amount ingested and metabolism rate of the substance. Possible signs are compression of the central nervous system, agitation, confusion, delirium, convulsion, and coma. These conditions are relevant to the mortality and morbidity of organophosphate. In this review, we present a patient who developed status epilepticus after acute organophosphate intake. The 32-year-old male patient was completely healthy before taking the organophosphate substance to attempt suicide. During the mechanical ventilator support in the intensive care unit, tonic convulsions started. The patient was not responsive to the diazepam treatment, and the electroencephalography findings showed generalized tonic-clonic convulsions. The seizures were controlled by starting a 0.1 mg/kg midazolam IV. After confirming that the neurological examination and electromyography results of the patient were normal, the patient was discharged in healthy condition on the 12th day.

Keywords: Organophosphate; poisoning; status epilepticus.

Özet

Akut organofosfat zehirlenmesine bağlı semptomların başlangıç süresi ve ağırlığı, spesifik bileşiğe, alınan miktara, alınan yola ve metabolik bozulmanın hızına bağlı olarak değişmekle birlikte, merkezi sinir sisteminin baskılanması, ajitasyon, konfüzyon, deliryum, konvülsiyon ve koma gibi bulgular ortaya çıkabilir. Bu durum, organofosfat zehirlenmesinin mortalite ve morbititesi ile ilişkilidir. Bu olgu sunumunda, akut organofosfat alımı sonrasında status epileptikus gelişen hastayı rapor ettik. Daha öncesinde sağlıklı olan intihar amacıyla oral organofosfat alan 32 yaşındaki erkek hasta, yoğun bakım ünitesin de mekanik ventilatör desteği altında tonik klonik konvulzyonlar başladı. Diazepam tedavisine yanıt alınamayan hastanın elektroensefalografi bulgusu jeneralize tonik klonik konvülsiyonla uyumlu idi. Hastaya 0.1 mg/kg intravenöz midazolam başlandı ve nöbetleri kontrol altına alındı. On ikinci günde hastanın nörolojik muayenesi ve elektromiyografinin normal olması üzerine sağlıklı bir şekilde taburcu edildi.

Anahtar sözcükler: Organofosfat; zehirlenme; status epileptikus.

Introduction

The organophosphate pesticides (OPs) are commonly used in developing countries; therefore, organophosphate (OP) poisoning cases are being seen more frequently.[1,2] In addition to occupational exposure and accidental ingestions, they are also commonly used to attempt suicide.[3] The clinical presentation of OP poisoning includes muscarinic signs, such as increased amounts of secretion, myosis, nausea-vomiting, urinary incontinence, shortness of breath, tachy-

cardia, bradycardia, hypotension; striated muscle signs, such as muscle weakness and fasciculations; and central nervous system signs, such as confusion, convulsion, and coma. The delayed signs include polyneuropathy starting 2–4 weeks following the poisoning, and also strokes arise from polyneuropathies.[4,5] Acute exposure to OP results in serious, rapid respiratory distress and neural crisis, which are related to mortality and morbidity of the OP.[6,7] In this review, we present a case that developed status epilepticus (SE) resulting from OP poisoning.

Case Report

A 32-year-old male patient was admitted to emergency room service 30 minutes after taking OP to attempt suicide. Nausea, vomiting, hypersalivation, agitation, and respiratory distress were observed in the ER; the Glasgow Coma Score (GCS) of the patient was 7. Muscle fasciculation was also observed. Oxygen treatment was started using a mask.

Atropine treatment was administered as 1 mg intravenously (IV) every five minutes; after administration of 4 mg atropine, the patient was transferred to the Intensive care unit (ICU) with continued oxygen support.

In the ICU, routine laboratory exams, acetylcholinesterase (AChE) level, and arterial blood gasses (ABG) were studied. The pH of was 7.21, PO_2 was 98 mmHg, saturation was 97.5%, PCO_2 was 34.3 mmHg, and the actual base excess (ABE) was -12.5 mmol/L. In addition to the atropine treatment, after administration of bolus 2 gr, 500 mg/h of pralidoxime (2-hydroxyimino methyl-1-methyl pyridinium chloride, 2-PAM-Cl) and diazepam (Diazem, Deva. Turkey) were administered. Activated charcoal at a dose of 1 g/kg was administered through an inserted nasogastric tube to reduce the OP absorption. Vital findings were as follows: pulse, 62/min; arterial tension, 96/46 mmHg; respiratory rate, 28/min; and body temperature, 37.6°C. Myosis, hypersalivation, and
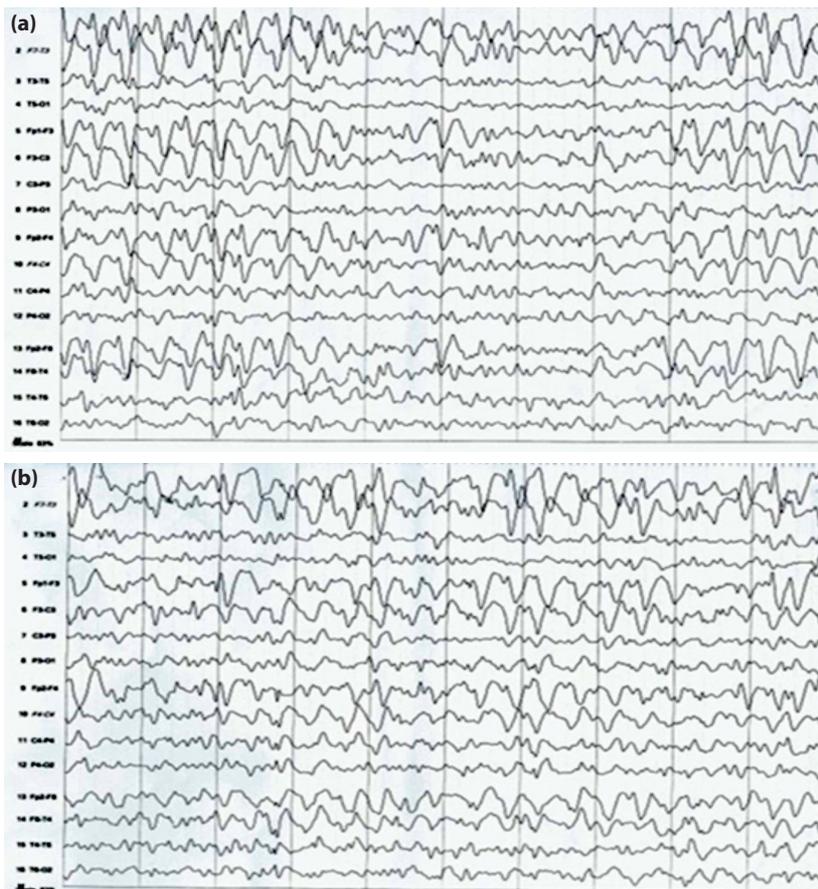

Fig. 1. **(a)** EEG showing the continuation of THE seizure activity between the generalized tonic-clonic seizures. **(b)** EEG showing the continuation of seizure activity between the generalized tonic-clonic seizures.

bilateral pulmonary crepitated rales were detected upon examination. The results of the routine laboratory tests were normal, and the blood AChE level was 1478 IU/L (reference range is 4520–12,000 IU/L).

The patient was connected to the mechanical ventilator by endotracheal intubation to avoid the respiratory distress that developed after three hours of transfer into the ICU. The mechanical ventilator was calibrated to SIMV mode: the positive end-expiratory pressure (PEEP) at 5; tidal volume at 480 ml; and the O_2 fraction of the inhaled air at 50%.

The 2-PAM-Cl infusion was continued along with atropine infusion every five minutes. At the end of the 12th hour, the total amount of 2-PAM-Cl was 2.6 g, and the total amount of atropine was 148 mg. Tonic-clonic convulsions started at the 15th hour of intensive care. Despite the repeated diazepam treatment, the convulsions could not be controlled. An electroencephalography (EEG) examination was conducted. At the EEG, performed between the generalized tonic-clonic

seizures, continuous spike-wave discharges with 2–3 Hz frequency were observed, both at the parasagittal and temporal areas of the brain (Fig. 1). This condition was considered to be SE, and 0.1 mg/kg IV of midazolam (Dormicum, Roche, Germany) treatment was started. The convulsion attacks were brought under control in a short time by the midazolam treatment. The spike waves seen at the previous EEG had improved significantly in the EEG performed after two days (Fig. 2). No pathology was detected in the brain MRI of the patient (Fig. 3).

On the 3rd day of intensive care, the AChE level of the patient was 6493 IU/L. After the 3rd day, the hypersalivation improved. His pupils became isochoric, and his heart rate was 85/min. The 2-PAM-Cl, atropine, and midazolam treatments were continued until the 5th day. At that point, the nicotinic and muscarinic signs had disappeared, and the patient was hemodynamically stable. The patient regained consciousness on the 5th day. The mechanical ventilation support was removed on the 6th day of intensive care, and the patient was extubated. The AChE level was 7890 IU/L upon the con-
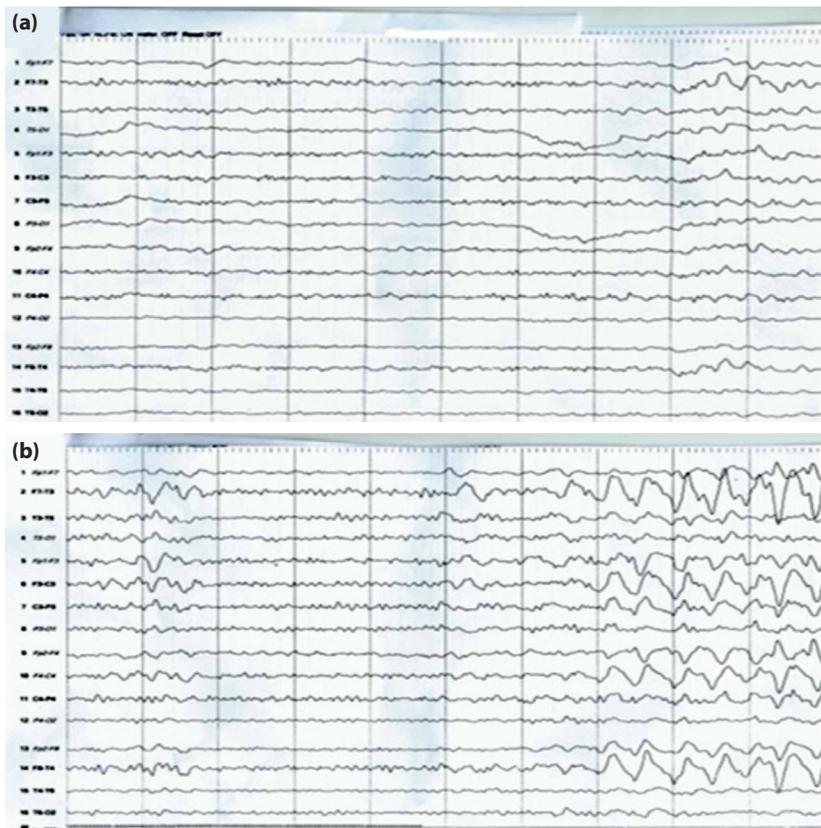

Fig. 2. **(a)** EEG performed after the treatment and controlling the seizures. **(b)** EEG performed after the treatment and controlling the seizures.

Fig. 3. Brain magnetic resonance image.

trol laboratory examination. After stating that the patient's neurological examination and electromyography (EMG) results were normal, the patient was discharged in a healthy condition on the 12th day, supported by the physical therapy and psychiatric treatment.

Discussion

OP is used very commonly in different formulations for various purposes, such as treating domestic areas and as industrial agricultural insecticides, herbicides, fungicides, and rodenticides. Many OP substances are toxic to herbs, animals, and humans. During the metabolism of OP, approximately 75% of the substance is metabolized to dialkyl-phosphate. This metabolite causes OP neurotoxicity and chronic diseases.[7] The main mechanism of the OP is the irreversible inhibition of AChE enzyme: it acts as a neurotoxin by causing Ach accumulation at both muscarinic and nicotinic cholinergic synapses in both the central and peripheral nervous systems.[7,8] Reduced red blood cell Ach esterase or/and plasma pseudocholinesterase levels are the markers of excess OP absorption; these markers may show acute OP intoxication. Seizures are not common in the adult cases of OP poisoning, although they are common in pediatric cases and are diagnosed early with different diagnostic methods. The onset of the acute OP intoxication symptoms may start immediately or may be delayed until hours after exposure.

Medical treatment of acute OP intoxication starts with airway control that assures complete oxygenation. Respiratory distress may develop in these cases: due to laryngospasm, bronchospasm, and seizure, intubation may be necessary. Intubation can be avoided by applying aggressive atropine treatment. Succinylcholine is not recommended because the plasma level of cholinesterase is low; it causes prolonged paralysis. Specific antidotes, such as atropine sulfate (a muscarinic receptor antagonist), blocks the hyperstimulation at the central and muscarinic cholinergic synapses, which is induced by OP. 2-PAM-Cl (a drug to regenerate acetylcholine esterase activity-a cholinesterase reactivator) helps the respiratory system to recover and strengthens the skeletal muscles. However, it does not cross the brain-blood barrier, so it cannot reverse the effects in the central nervous system.[7,9]

The central nervous system symptoms of the acute OP poisoning are nonspecific among them are irritability, restlessness, disorientation, and confusion; SE and generalized seizure may also develop.[7,10] SE may last for a few hours due to serious brain damage. The severity of neuronal damage is related to the duration and severity of the SE.[11] If the seizures are controlled immediately, much of the neuronal damage can be avoided.

The onset and early expression of seizures are cholinergic phenomena. At this stage, anticholinergics easily terminate seizures, and neuropathology is not clear. However, if not controlled, a transitional phase occurs in which the neuronal stimulation of the seizure disrupts the other neurotransmitter systems: the levels of the excitatory amino acid (EAA) increase seizure activity; control with anticholinergics is less effective; mild neuropathology is sometimes observed. With long-term epileptiform activity, the seizure mainly enters a non-cholinergic phase: it is refractory to some anticholinergics; benzodiazepines and N-methyl-d-aspartate (NMDA) antagonists remain effective as anticonvulsants, but require anticholinergic co-administration; mild neuropathology is evident in multiple brain regions. [11] Midazolam is effective in preventing OP-induced chronic epilepsy if administered 1 min after seizures onset, but not 30 min thereafter. Midazolam, together with classical OP antidotes, should be noted in OP poisoning treatment.[10]

Benzodiazepines, such as diazepam (a benzodiazepine anticonvulsant), are recommended for seizure control of.[7,9] However, the anticonvulsant effects of the diazepam de-

crease over time if the management of the seizure is delayed (after the onset of seizure). Studies in which neuropathology was examined, diazepam was unable to afford absolute protection against the incidence of nerve agent-induced brain damage. This is in agreement with the clinical literature regarding the transient effectiveness of diazepam in controlling status epilepticus and relates to the recent findings that nerve agent-induced seizures may recur after benzodiazepine treatment. This transient effectiveness of diazepam may be primarily due to pharmacokinetic factors since brain levels drop within 30 min of IV administration.[11] In addition, if anticholinergic drugs are not administered concomitantly or concurrently with diazepam, there may be serious toxic and fatal interactions between them. Therefore, there is a need for better drugs to treat seizures arise from the poisoning of the OP nerve agent. Midazolam is a new drug that is preferred in acute seizures and SE that arise from neurotoxic OP. The acute seizures and SE may be controlled by the intramuscular administration of midazolam. Due to its favorable pharmacokinetic features, midazolam should be considered instead of diazepam. Hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant effects are the dominant effects of midazolam, rapid-acting, water solubility, and extended shelf life benzodiazepine. Due to its favorable pharmacokinetics, midazolam is a promising alternative to diazepam.[12] The antiseizure activity of midazolam is thought to arise from its allosteric potentiation of the synaptic c-aminobutyric acid (GABA) A receptor.[9]

In our case, the convulsion was not responsive to the diazepam treatment as administered in the early phase. We found that midazolam is effective at controlling seizures in the early phase. Midazolam shows better anticonvulsant activity than diazepam in acute seizures.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Informed Consent
Written informed consent was obtained from of the patient for the publication of the case report and the accompanying images.

Peer-review
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Conflict of interest
The authors declare that they have no conflict of interest.

Authorship Contributions
Concept: Ş.A.; Design: F.Ç.; Supervision: Ş.A.; Materials: M.K.; Data collection &/or processing: Ş.A.; Analysis and/or interpretation: F.Ç.; Literature search: M.K.; Writing: Ş.A.; Critical review: M.K.

References

1. Dong H, Peng X, Qiu Z. A rare case of bullous contact dermatitis caused by severe organophosphorus pesticides poisoning. Int J Dermatol 2013;52(12):1533–4.

2. Wang W, Chen QF, Ruan HL, Chen K, Chen B, Wen JM. Can anisodamine be a potential substitute for high-dose atropine in cases of organophosphate poisoning? Hum Exp Toxicol 2014;33(11):1186–90.

3. Joshi P, Manoria P, Joseph D, Gandhi Z. Acute myocardial infarction: can it be a complication of acute organophosphorus compound poisoning? J Postgrad Med 2013;59(2):142–4.

4. Kayaalp O. Rasyonel Tedavi Yönünden Tıbbi Farmakoloji. 10th ed. Ankara: Hacettepe Taş; 2002. p. 1089–92.

5. Koçak A, Şenol E, Kök HO, Aktaş Ö. Neuropathy Developing After Organophosphate (Tamaron) Poisoning Journal Forensic Medicine 2005;2(3):109–12.

6. Moin-Azad Tehrani MS, Soltaninejad K, Yazdani S, Nelson LS, Shadnia S. Bilateral loculated pleural effusion as a manifestation of acute parenteral organophosphate intoxication: a case report. J Emerg Med 2011;41(6):630–4.

7. Detweiler MB. Organophosphate intermediate syndrome with neurological complications of extrapyramidal symptoms in clinical practice. J Neurosci Rural Pract 2014;5(3):298–301.

8. Chowdhury FR, Bari MS, Alam MM, Rahman MM, Bhattacharjee B, Qayyum JA, et al. Organophosphate poisoning presenting with muscular weakness and abdominal pain--a case report. BMC Res Notes 2014;7:140.

9. Reddy SD, Reddy DS. Midazolam as an anticonvulsant antidote for organophosphate intoxication--A pharmacotherapeutic appraisal. Epilepsia 2015;56(6):813–21.

10. Shrot S, Ramaty E, Biala Y, Bar-Klein G, Daninos M, Kamintsky L, et al. Prevention of organophosphate-induced chronic epilepsy by early benzodiazepine treatment. Toxicology 2014;323:19–25.

11. McDonough JH Jr, Shih TM. Neuropharmacological mechanisms of nerve agent-induced seizure and neuropathology. Neurosci Biobehav Rev 1997;21(5):559–79.

12. Drexler B, Seeger T, Worek F, Thiermann H, Antkowiak B, Grasshoff C. Midazolam is effective to reduce cortical network activity in organotypic cultures during severe cholinergic overstimulation with soman. Toxicol Lett 2018;297:19–23.