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CASE REPORT

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Sublingual administration of atropine eye drops for treating organophosphorus poisoning

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Key Clinical Message

An 89-year-old patient with fenitrothion toxicity received sublingual atropine eye drops, reducing the intravenous atropine requirement. This alternative method enabled rapid rehabilitation, and he walked unaided, leading to discharge.

KEYWORDS

atropine, eye drops, organophosphorus, poisoning, sublingual

1 | INTRODUCTION

Each year, approximately 3 million people worldwide experience organophosphorus (OP) poisoning, resulting in an estimated 300,000 deaths.[1] Atropine, an antimuscarinic, is the antidote of choice according to clinical guidelines.[1] Atropine is administered intravenously until atropinization, defined as normal lung sounds on auscultation, a systolic blood pressure >80 mmHg, a heart rate >80 beats/min, dry axillae, and resolution of pinpoint pupils.[2] In the currently recommended regimen, many atropine doses are needed.[2] Most hospitals have an insufficient supply of intravenous atropine for OP poisoning treatment. Therefore, other regimens for OP poisoning treatment are needed to reduce intravenous atropine use. In previous reports, alternative treatment agents were discussed, including scopolamine, which can be transdermally administered, and glycopyrrolate, which does not cross the blood–brain barrier.[3] In addition, reports have described the use of highly concentrated atropine doses created from bulk atropine powder.[4]

Salivation is an OP poisoning symptom, and excessive salivation can lead to airway obstruction. To diminish airway secretions, atropine eye drops have been administered sublingually to patients with terminal pancreatic cancer[5] and pediatric patients with metachromatic leukodystrophy receiving palliative care.[6]

Here, we report an 89-year-old man with OP poisoning who was administered sublingual atropine eye drops, rather than intravenous atropine, during a prolonged clinical course of OP poisoning treatment.

2 | CASE HISTORY

An 89-year-old man was brought to our hospital after ingesting approximately 50 mL of 50% fenitrothion following an altercation with his wife. He ingested fenitrothion 2 h before arriving at the hospital. His vital signs on arrival were as follows: blood pressure, 208/101 mmHg; pulse, 85 beats per minute; respiratory rate, 25 breaths per minute; oxyhemoglobin

saturation, 99% with O_2 supplemented at 10 L/min; body temperature, 33.9°C; and Glasgow coma scale, E4V4M6. On physical examination, his pupils measured 1.0/1.0 mm. In addition, he demonstrated salivation, lacrimation, and incontinence of stool and urine. He was diagnosed with OP poisoning. Initially, 1 g of pralidoxime was administered, followed by the initiation of continuous intravenous atropine injection within 30 min. He was admitted to our hospital and was treated in the intensive care unit 2 h later.

2.1 | Differential diagnosis, investigation, and treatment

Although the patient received an intravenous atropine injection immediately after OP poisoning was diagnosed, his pupil size remained constricted (1.0/1.0 mm), and he had copious secretions into the airway. Therefore, he was intubated to secure his airway. On day 4, his muscles weakened and tendon reflexes decreased, indicating the presence of an intermediate syndrome. On day 12, his pupil size began to recover (Figure 1). However, intravenous atropine doses were still required because of copious salivation, and this substantially interfered with his rehabilitation. On day 16, a tracheostomy was performed, and he was weaned from ventilatory support. On day 23, his cholinesterase level began to increase (Figure 1). When the intravenous atropine dose was slightly reduced, salivation increased substantially. Therefore, on day 27, we began the administration of 1% atropine eye drops sublingually, one drop at a time. The dosing of intravenous atropine was reduced and was discontinued on day 31. Change in atropine administration approach is shown in Figure 1.

2.2 | Outcome and follow-up

The patient's rehabilitation rapidly progressed, and he could walk unaided on day 37. On day 58, the tracheostomy was occluded and removed. On day 62, sublingual administration of atropine eye drops was terminated. On day 74, he was discharged from the hospital.

3 | DISCUSSION

In our patient, atropine eye drops—administered sublingually—were effective for treating OP poisoning. When symptoms of OP poisoning persist, transitioning from intravenous atropine injection to sublingually administered atropine eye drops can become a trigger for the patient's rehabilitation progress.

The first symptoms observed in patients with OP poisoning are salivation, lacrimation, emesis, miosis,

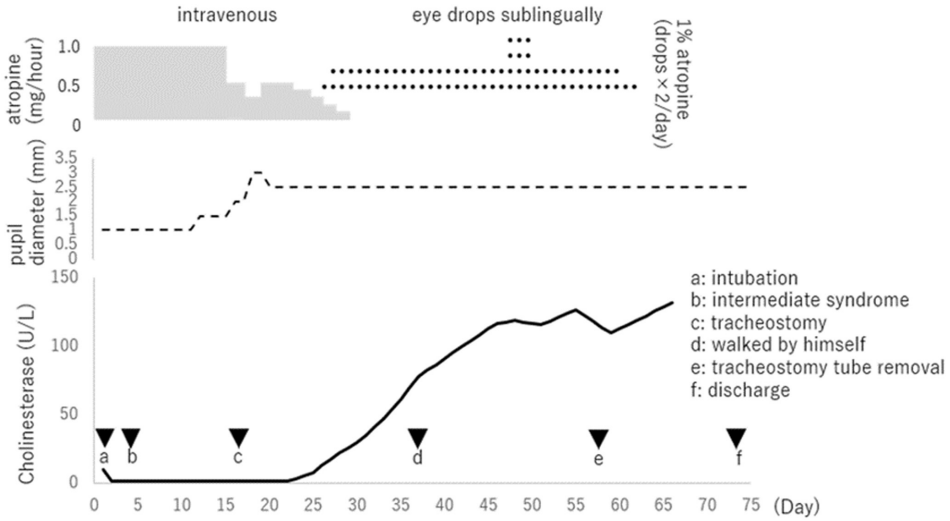

FIGURE 1 Change in atropine administration approach and time course of cholinesterase levels and pupil diameter. Organophosphorus poisoning (OP) was diagnosed and intravenous atropine injections were administered. From day 0 to day 15, atropine continuous intravenous injections were administered at a rate of 1 mg/h. On day 12, his pupil size started to recover, and on day 23, his cholinesterase levels started to increase. From day 16, the dosage of continuous intravenous atropine was reduced gradually, however from day 27 onwards, atropine eye drops sublingual administration (twice daily at 10:00 AM and 10:00 PM) were introduced because the symptoms of OP poisoning persisted. A combination of continuous intravenous injection and sublingual administration was utilized, making it possible to discontinue the continuous intravenous injection. The dosage of sublingual administration was adjusted based on saliva production and eventually, it was discontinued on day 63.

bradycardia, hypotension, bronchoconstriction, and convulsions.[7] The patients may require endotracheal intubation to prevent airway obstruction by secretions. Within 24–96 h after intake, intermediate syndrome occurs, characterized by muscle weakness, respiratory insufficiency, and decreased deep tendon reflexes.[1] Intermediate syndrome refers to the recurrence of toxic symptoms in patients with OP poisoning after the acute phase symptoms have temporarily subsided, and it occurs due to the excessive accumulation of acetylcholine at neuronal synapses. In this patient, miosis, salivation, urinary and fecal incontinence were muscarinic symptoms, while hypertension observed at the time of admission, muscle weakness, and decreased tendon reflexes were nicotinic symptoms.

The antidote of choice for OP poisoning is atropine, which is antimuscarinic. Recently, the appropriate dosage and duration of atropine therapy were determined.[2] Atropine is initiated at 1–2 mg, and the dose is doubled every 5 min until atropinization. After atropinization, the patients are administered approximately 20%–30% of the total dose needed for atropinization per hour. This incremental dosage regimen is recommended worldwide.[8] Drying of secretions indicates the start of atropinization and the endpoint of atropine administration.[1] The usual duration is 48–72 h.[2] In our patient, atropinization was impossible owing to a lack of atropine stock. This patient was administered 1 g of pralidoxime, another treatment for OP poisoning, however, continuous administration could not be also carried out, due to the lack of stock. These factors may have contributed to the development of his intermediate syndrome. In addition, there is another reason that prolonged the necessity for atropine administration. In cases of fenitrothion toxicity, the required duration of atropine administration could be longer. Two reasons for these prolonged toxic symptoms are the high lipid solubility of fenitrothion, which continues the cholinergic phase, and bioactivation of its sulfur moiety.[9] In our patient, salivation did not decrease; therefore, the patient needed long-term airway management and intravenous atropine administration.

Sialorrhea, defined as drooling or the excessive flow of saliva from the mouth, is observed in patients with cerebral palsy, amyotrophic lateral sclerosis, and Parkinson's disease.[10] The treatment of sialorrhea is often the off-label use of atropine eye drops administered sublingually. The novelty of our patient's treatment is that sublingual administration of atropine eye drops was used for prolonged OP poisoning symptoms, and the patient had a good outcome. Using the intravenous method, an indwelling intravenous catheter is required to administer atropine, preventing rehabilitation and the resumption of daily living activities. Administration of atropine eye drops decreased our patient's salivation and allowed removal of the intravenous catheter. This facilitated his rehabilitation, and he could walk independently at discharge from our hospital. The use of oral atropine is also beneficial in fostering rehabilitation, unfortunately, it could not be prescribed in our case immediately. Due to the lack of a control group, it cannot be definitively stated that rapid progress in rehabilitation was solely attributed to the sublingual administration of atropine eye drops. However, we consider it to be one contributing factor to the advancement of rehabilitation.

Although atropine eye drops administered sublingually may be an effective alternative to intravenous injection, it is important to note that atropine dose adjustment is difficult. An overdose of atropine leads to symptoms that include nausea, vomiting, dry mouth, mydriasis, blurred vision, fever, rash, tachycardia, confusion, urinary retention, hallucinations, and delirium.[10] We suggest that while decreasing the intravenous atropine dose, a gradual increase in the sublingual administration of atropine eye drops (0.5 mg per drop) may be necessary until only sublingual atropine is required. The anticipated adverse effects of atropine eye drop sublingual administration were not observed in this patient. Although it was not used in our patient, the use of glycopyrrolate can avoid the central nervous system side effects of an excessive dose of atropine. Hallucinations and delirium should not occur; however, the peripheral effects of tachycardia, dry mouth, mydriasis, and urinary retention may still occur.

4 | CONCLUSION

When prolonged intravenous atropine administration is required because of persistent OP poisoning symptoms, sublingual administration of atropine eye drops can replace intravenous atropine and promote rehabilitation.

AUTHOR CONTRIBUTIONS

Ichiro Hirayama: Conceptualization; writing – original draft. **Yoshito Kamijo:** Supervision. **Minaho Nonaka:** Resources. **Tetsuhiro Yano:** Visualization. **Mitsuru Ishii:** Data curation. **Yoshiteru Tominaga:** Project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest in this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Our institution does not require ethical approval for reporting individual cases.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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