Clinical Presentation, Consecutive Measurements of Serum Butyryl-Cholinesterase Activity and Treatment of a Dog Intoxicated by Anticholinesterase and Presented Acute Cholinergic Crisis Followed by Intermediate Syndrome. Case Report and Review of the Literature

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ABSTRACT

The article describes the clinical signs, laboratory findings, including consecutive serum butyryl-cholinesterase (sBuChE) activity measurements, treatment and outcome of a dog diagnosed with intermediate syndrome (IMS) of organophosphate intoxication. A 2-year old neutered female mixed-breed dog was presented with acute cholinergic crisis (ACC) due to anticholinesterase intoxication. sBuChE activity upon admission was markedly low [382 U/L; reference interval, (RI) 2,660-11,00 U/L]. The dog was treated with atropine sulfate, diphenhydramine, 2-pyridine aldoxime-methyl-chloride and supportive care. The muscarinic signs resolved, but 24 hrs post-admission the dog sustained a grand-mal seizure and developed quadriparalysis and severe weakness, including respiratory muscle weakness, necessitating positive pressure mechanical ventilation (PPMV). The dog recovered slowly, presenting signs of ventroflexion, front limb muscle weakness and absent swallow reflex of several days, which gradually improved. During ventilation sBuChE activity was 2735 U/L, and later on during hospitalization, remained mildly less than the RI. The dog was discharged on day 8 of hospitalization. IMS has previously been diagnosed based on the history of a previous case of ACC, with deterioration to classic IMS clinical signs, requiring PPMV. Interestingly, sBuChE was within or mildly below RI during the course of the IMS, which highlighted the possibility of a diagnosis of IMS in face of normal sBuChE activity. The authors conclude that IMS should be suspected in dogs showing cranial nerve, respiratory, neck and proximal limb muscle weakness or paralysis, especially in face of prior ACC, but even in the absence of preceding ACC signs.

Key words: Organophosphate; Carbamates; Canine; Positive Pressure Ventilation, Ventroflexion.

INTRODUCTION

Organophosphates are commonly used in agriculture, industry and home environmental pest control, and as chemical warfare agents (1-3). Organophosphate intoxication induces several neurological syndromes, including acute cholinergic crisis (ACC; type-1 syndrome) (1, 4-6), intermediate syndrome (IMS; type-2 syndrome) (7, 8) and organophosphate-induced delayed polyneuropathy

(OPIDP), myopathy and central nervous system (CNS) impairment (9, 19). Cases of organophosphate intoxication in humans, describing signs of ambulation difficulty, ataxia and muscle weakness have been recorded during the 1960's and 1970's, and were then categorized as intoxication "type-2 signs" (11), and later termed IMS (12). Since then, IMS has been reported extensively in humans, with only few reports in animals (13-19). IMS presented as paralysis, occurring 7 to 96 hours post-ACC, but before the typical onset time of OPIDP. It was clinically characterized by muscular weakness, predominantly of proximal limb muscles, neck flexors, muscles innervated by motor cranial nerves or respiratory muscles (7, 8, 12-14). IMS was also characterized by prolonged cholinesterase inhibition (7, 8, 20-24).

Herein, we describe a dog that sustained ACC, which later developed to IMS, requiring positive pressure mechanical ventilation (PPMV). Interestingly, serum butyrylcholinesterase activity (sBuChE) normalized during the IMS period, although no clinical improvement was noted.

CASE REPORT

A 2-year old, 25-kg, neutered female mixed-breed dog was referred to the Veterinary Teaching Hospital. On admission day, the dog roamed unleashed in a vineyard, when ataxia, hypersalivation and diarrhea were observed. It was rushed to the referring veterinarian, where tremors, facial twitches and hyperthermia [rectal temperature (RT), 40°C] were noted. Treatment included intravenous (IV) lactated Ringer's solution with 5% dextrose, atropine-sulphate (4 mg intra-muscular) diazepam (10mg IV, repeated twice) and apomorphine (0.5 mg, IV). The dog vomited a foamy vomitus in response to apomorphine. Then, activated charcoal suspension (60 mL) was administered by gastric tube.

Upon admission to the hospital, the dog was non-ambulatory, and showed depression, hyperesthesia, tremors, hypersalivation, panting and diarrhea. Heart rate was 140 bpm, and RT was 39°C. Hematological (Advia 2120i, Siemens Medical Solutions Diagnostics GmbH, Erlangen, Germany) and serum chemistry (Cobas 6000, Roche, Mannheim, Germany (at 37°C)) abnormalities included mild neutrophilic leukocytosis, increased muscle enzyme and amylase activities and mildly increased serum creatinine, phosphorus and bilirubin concentrations (Table 1), while sBuChE activity (Cobas 6000, Roche, Mannheim, Germany (at 37°C)) was markedly low [382 U/L; reference interval (RI), 2,660-11,000].

Based on the latter, the medical history and clinical signs, ACC of anticholinesterase intoxication was tentatively diagnosed. Treatment included IV balanced electrolyte solution (Lactated Ringer's solution. Bieffe Medital SA, Sabinarigo, Spain) (5 mL/kg/h), metoclopramide (Pramin, RAFA laboratories, Jerusalem, Israel) (1 mg/kg/day IV at constant rate infusion (CRI)], atropine-sulphate (Atropine-sulfate, S.A.L.E.p.A. Cenate Sotto, Italy) (1mg, IV), diazepam (Diazepam, Hameln Pharmaceuticals, Gloucester, UK) (2 mg, IV), diphenhydramine (Diphenhydramine-hydrochloridium, Fagron, Capelleaan den Ijssel, Netherlands) (4 mg/kg, SC), 2-pyridine aldoxime-methyl-chloride 2-PAM; (Pralidoxime). Pyridine-2 Aldoxim, The Veterinary Teaching Hospital Pharmacy, Rishon Lezion, Israel) (2-PAM; 500 mg, intramuscular), methocarbamol (Ortoton, Recordati Pharma, Ulm, Germany) (1150 mg, IV) and activated charcoal (Charcodote, Pharmascience Inc., Montréal, Canada). Over the next 24 hours, most muscarinic signs waned, and the dog ate, but exhibited general weakness. The dog sustained a *grand mal* seizure 24 hours post-admission, and received levetiracetam (Keppra, CTS, UCB Pharma S.A., Braine-l'Alleud Belgium) (loading dose, 60 mg/kg IV, followed by 20 mg/kg IV q8h) and midazolam (Midolam, RAFA Laboratories, Jerusalem, Israel) (0.2 mg/kg/h IV CRI, for 8 hours).

Twelve hours later, the dog was in lateral recumbency, unresponsive, with very shallow breathing and was assessed with respiratory failure, manifested also by severe arterial hypoxemia (OmniC or Cobas b221, Roche, Mannheim, Germany) [PaO_2, 62 mmHg; RI, 85-100]. Oxygen (150 mL/kg/min) was then administered by nasal prongs. The RT increased (40.7°C). Lipid emulsion (Lipofundin, B. Braun Melsungen AG, Melsangn, Germany) was administered at 4 mL/kg IV bolus, followed by 15 mL/kg for1 hour followed by flumazenil (Flumazenil, Hamlen pharma plus gmbh, Hameln, Germany) (0.01 mg/kg IV). The dog's mental status remained unchanged. Arterial hypoxemia did not improve with nasal oxygen (PaO_2, 61.9 mmHg), while thoracic breathing movements became progressively weaker and shallower. Therefore, the dog was intubated, and PPMV (synchronized intermittent mandatory ventila-

Table 1: Laboratory analytes at presentation and during hospitalization of a dog intoxicated by anticholinesterase.

Analyte	Reference interval (units)	Admission	Day1	Day2	Day3	Day4	Day5	Day6	Day7
Leukocytes	5.2-13.9 ($x10^3/\mu L$)	15.3							
Hematocrit	37.1-57.0 (%)	47.2							
Hemoglobin	12.9-18.4 (g/L)	15.6							
MCV	58.8-71.2 (fL)	71.6							
MCHC	31.0-36.2 (g/dL)	33.10							
Platelets	143.3-400 ($x10^3/\mu L$)	255.0							
Neutrophils	3.9-8.0 ($x10^3/\mu L$)	11.55							
Lymphocytes	1.3-4.1 ($x10^3/\mu L$)	1.33							
Monocytes	0.2-1.1 ($x10^3/\mu L$)	2.21							
Eosinophils	0-0.6 ($x10^3/\mu L$)	0.06							
Basophils	0-0.1 ($x10^3/\mu L$)	0.04							
Packed cell volume	37-55.0 (%)	45	47			45	39		
Total plasma protein[1]	5.5-7.7 (g/dL)	6.6	6.2			6.2	6.0		
Albumin	3.0-4.4 (g/dL)	4.3	4.0			3.5			
Alkaline phosphatase	21-170 (U/L)	52							
Alanine transaminase	19-67 (U/L)	335							
Amylase	103-1510 (U/L)	3832							
Aspartate transaminase	19-42 (U/L)	463							
Total bilirubin	0.0-0.2 (mg/dL)	0.22	0						
Calcium (total)	9.7-11.5 (mg/dL)	9.7							
Cholesterol	135-361 (mg/dL)	204							
Creatine kinase	51-399 (U/L)	1756							
Total CO_2	16.0-22.0 (mmol/L)	23.0							
Creatinine	0.3-1.2 (mg/dL)	1.28	0.67			0.67			
GGT	0-6 (U/L)	4							
Glucose	64-123 (mg/dL)	114							
Potassium	3.6-5.3 (mEq/L)	4.04	3.62	3.86		3.92			
Phosphorus	3.0-6.2 (mg/dL)	2.29							
Sodium	145-154 (mEq/L)	147	151.8						
Chloride	108-118 (mEq/L)	111.6	116.8						
Total protein	5.4-7.6 (g/dL)	6.09							
Triglycerides	19-133 (mg/dL)	20							
Urea	10.7-53.5 (mg/dL)	35.5							
BuChE	2660-11000 (U/L)	382			2735	2376	2107	1792	2178
pH	7.35-7.45		7.365	7.405[2]	7.372	7.316			
PaO_2	>x4 inspired O_2 (mmHg)		62 (21%)	587[2] (100%)	76.6 (60%)	125.5 (40%)			
$PaCO_2$	35-45 (mmHg)		38.2	34.5[2]	29.6	31.5			
HCO_3	18-24 (mmol/L)		21.4	21.1[2]	16.8	15.7			
BE	(-4)-4 (mmol/L)		-3.5	-2.8[2]	-7.0	-4.8			

MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; GGT, gamma-glutamyl transpeptidase; BuChE, butyrylcholine esterase; BE, Base excess; [1], measured by refractometry [2], while on positive pressure ventilation.

tion with 100% O_2) was instituted, which led to improved arterial PaO_2 (587.2 mmHg). As a result, delivered O_2 concentration was then reduced to 60%. PPMV was ceased after 40 hours and replaced by nasal oxygen. The dog then showed obtundation, tetraparesis and marked neck flexor weakness. Serum BuChE activity was 2735 U/L at this point.

The mental status normalized 24 hours later (Day 4 of hospitalization), but the dog was still weak, showing severe ventroflexion, front limb muscle weakness and an absent swallowing reflex, and was therefore fed via nasogastric tube. The dog became progressively stronger over the next 2 days, although marked ventroflexion and proximal limb weakness persisted. Nevertheless, the dog became ambulatory, with support, showing stiff, short-stride gait, requiring rests after every few steps. On Day 7, the dog was more ambulatory, was able to swallow, drink and eat, although marked ventroflexion persisted. Further improvement was noted by Day 8, and the dog was discharged, despite having mild cervical ventroflexion. Serum BuChE activity, which was markedly decreased during the APP, had normalized during the IMS but was later mildly below the reference interval (RI) during hospitalization. One-week post discharge, the owners reported that the dog had normalized, and was bright alert and responsive.

DISCUSSION

To the best of the knowledge of the authors, only two IMS cases in dogs were previously reported (16, 19). In this third case, atypically, cholinesterase activity was within RI, or nearly so, during the IMS period. Although acute organophosphate intoxication generally induces the typical muscarinic, nicotinic and CNS symptoms (i.e., ACC), up to 20% of intoxicated humans demonstrate delayed (approximately 7-96 hours) onset of additional symptoms, including cranial nerve, cervical and proximal limb neuropathy, respiratory muscle weakness, up to paralysis and depressed deep tendon reflexes, which characterize the IMS or "type 2 paralysis" (11, 12, 25). Most evidence, including the typical onset time and clinical signs, support that IMS is a distinct syndrome of organophosphate intoxication, different from both ACC and OPIDP. Similar to ACC, but unlike OPIDP, IMS likely results from the anticholinesterase action of organophosphates, unlinked to particular compound exposure (25).

There is no information regarding the incidence or prevalence of IMS in small animals. Nevertheless, in the scarce published data (2 dogs, 2 cats and a caracal) (14, 16, 18, 19), the recorded history and clinical signs, along with low acetylcholine-esterase (AChE) or BuChE activity (when measured) (14, 16, 18), were similar to those in humans with IMS. The same is true for the present case, where the history of organophosphate intoxication is circumstantial (i.e., acute clinical signs consistent with ACC, occurring while walking in an agricultural area), with markedly low sBuChE activity, followed by severe muscular weakness, noted 36 hours post-admission, consisting predominantly of proximal limb, neck flexor, and respiratory muscle weakness, necessitating PPMV. Decreased BuChE (7, 26-28) or AChE (7, 21, 27) activities were recorded in humans with IMS. Organophosphates inhibit cholinesterase in the autonomic nervous system, parasympathetic neurons in smooth muscle, cardiac muscle or exocrine glands, in somatic nervous system neuromuscular junctions and in CNS cholinergic synapses. AChE (or "true cholinesterase") is the enzyme responsible for acetyl-choline cleavage in these sites (1, 20). It is also present on red blood cell surface (20). BuChE, resembling AChE, is present in the serum, pancreas, brain, and intestinal mucosa (29, 30). Ordinarily, serum BuChE activity is slightly higher than that of AChE. Low sBuChE activity is a diagnostic marker used to confirm anticholinesterase intoxication (31). In acute cholinesterase inhibition or anticholinesterase intoxication, sBuChE activity decreases, but is restored usually within a few days from the initial organophosphate exposure, while AChE recovery is much slower, up to several months post intoxication (32). Therefore, sBuChE activity is a more sensitive, but less specific for confirming anticholinesterase intoxication (33).

The clinical symptoms of IMS emerge within hours to days following the anticholinesterase exposure, as one of two paralysis types. Type-1 paralysis, but not type-2 (i.e., IMS) paralysis, is atropine-responsive, while fasciculations, commonly seen in type-1 syndrome, do not occur in IMS. The duration of the IMS varies from several days to several weeks (23, 24). Its pathogenesis is yet to be clarified, but it is suggested to be caused by prolonged AChE inhibition, resulting in impaired neuromuscular signal transduction (16). Early electromyography studies in humans localized the lesion as a neuromuscular end-plate to post-synaptic

space junctionopathy (12). Several causes of IMS have been suggested; 1) Failure of post-synaptic acetylcholine release, impairing neuromuscular transmission; 2) Cholinergic receptor down-regulation through their internalization or postsynaptic receptor desensitization after prolonged acetylcholine stimulation. Muscarinic receptors are more prone to down-regulation under tolerance situations, while skeletal muscle nicotinic receptors cannot develop acetylcholine tolerance, thereby becoming the primarily ones affected in IMS (35-37); 3) Occurrence of muscular disorders, including myopathy, muscle degeneration, rhabdomyolysis and muscle necrosis (22, 26); 4) The post-ACC events provide favorable scenery for free radical generation, which may mediate muscle cellular lipid peroxidation, damage and inflammation after strenuous exercise, as well as ischemia-reperfusion cellular injury, potentially occurring following extensive muscle fasciculation and overactivity during ACC (38-39). In addition, several contributing factors to IMS were suggested. Lipid solubility of the organophosphates prior to and following their hepatic metabolism, promote their wide distribution into fat, might increase the occurrence of delayed, prolonged cholinesterase inhibition, ultimately inducing IMS (7, 40). Impairment of systemic hepatic, cardiovascular and hormonal functions through organophosphate toxicity possibly prolongs organophosphate metabolism (7), thereby contributing to IMS. Genetic polymorphisms in biotransformation of enzymes or target molecules may also influence the sensitivity to certain pesticides and their toxicity (41, 42).

Regardless of the mechanism, IMS is reportedly characterized by prolonged cholinesterase inhibition (7, 16, 20-24). Interestingly, in the present dog, sBuChE activity was either within, or slightly below RI during the IMS period. Moreover, sBuChE activity was extremely low during the ACC, normalizing while the dog was being ventilated, and later became slightly below RI, when clinical improvement was noted. Normal sBuChE activity has been noted by the authors in other dogs suspected with IMS (S.K., unpublished data). This finding might result from prolonged organophosphate influence through one or several of the above-mentioned mechanisms, which potentially persist in the face of normal or near normal cholinesterase activity. Cholinergic receptor down-regulation might persist despite cholinesterase activity regeneration. As the acetyl-choline receptor half-life is 10 days (43), possibly, heavily stimulated receptors (post-intoxication) become desensitized and more readily endocytosed. This process may be related to increased post-junctional non-contractile calcium ion concentration (44). The rather prolonged recovery from IMS is explainable in terms of the acetylcholine receptor production, and may not be directly related to cholinesterase activity. The same is true to the other possible pathophysiological mechanisms of IMS. Recovery of muscle damage may still be prolonged in the face of normal or near normal cholinesterase activity.

The definition criteria of IMS in humans are based on clinical findings of proximal limb, extraocular, neck and respiratory muscle weakness to paralysis, hours to days following exposure to an organophosphate, with or without requirement of PPMV (11, 12, 25). In some reports, BuChE (7, 26-28) or AChE (7, 21, 27) activity was recorded, and was always markedly below the RI, and in limited studies, when remeasured, remained markedly below RI (45-47).

In the present case, the dog was diagnosed with organophosphate intoxication based on compatible history, classic ACC clinical signs and markedly low sBuChE activity. IMS was diagnosed by the deterioration of the dog to classic IMS clinical signs and requirement of PPMV 36 hours post admission, although interestingly sBuChE activity was normal or near normal BuChE during the course of the IMS. The latter finding might be important when considering IMS in face of sBuChE activity within RI. IMS should be suspected in any case of cranial nerve, respiratory, neck and proximal limb muscle weakness or paralysis, especially post ACC-related signs, but even in the absence of preceding ACC signs.

REFERENCES

1. Gupta, R.C. and Milatovic, D.: Organophosphates and Carbamates. In: Gupta RC, editor. Veterinary Toxicology: Basic and Clinical Principals. 2nd ed. London: Saunders-Elsevier; pp. 573-585, 2012.
2. Ballantyne, B. and Marrs, T.C.: Clinical and Experimental Toxicology of Organophosphates and Carbamates. Oxford: Butterworth-Heinemann; 2017.
3. Adeyinka, A. and Pierre, L.: [internet]. Organophosphates. Stat Pearls Publishing LLC. 2020. https://www.ncbi.nlm.nih.gov/books/NBK499860/ (Accessed at 15 Nov. 2021).
4. Marrs, T.C.: Organophosphate poisoning. Pharmacol. Ther. 58: 51-66, 1993.
5. Fukuto, T.: Mechanism of action of organophosphorus and carbamate insecticides. Environ. Health Perspect. 87:245-254, 1990.

6. Bardin, P.G., van Eeden, S.F. Moolman, J.A., Foden, A.P. and Joubert, J.R.: Organophosphate and carbamate poisoning. Arch. Intern. Med. 154:1433-1441, 1994.
7. De Bleecker, J., van Den Neucker, K. and Colardyn, F.: Intermediate syndrome in organophosphorus poisoning: A prospective study. Crit. Care Med.; 21:1706-1711, 1993.
8. De Bleecker, J.L.: The intermediate syndrome in organophosphate poisoning: an overview of experimental and clinical observations. J. Toxicol. Clin. Toxicol. 33:683-686, 1995.
9. Lotti, M and Moretto, A.: Organophosphate-induced delayed polyneuropathy. Toxicol. Rev. 24:37-49, 2005.
10. Jokanović, M., Kosanović, M., Brkić, D. and Vukomanović, P.: Organophosphate induced delayed polyneuropathy in man: an overview. Clin. Neurol. Neurosurg. 113:7-10, 2011
11. Wadia, R.S., Sadagopan, C., Amin, R.B. and Sardesai, H.V.: Neurological manifestations of organophosphorous insecticide poisoning. J. Neurol. Neurosurg. Psychiatry. 37:841-847, 1974.
12. Senanayake, N. and Karalliedde, L.: Neurotoxic effects of organohosphorus insecticides. N. Engl. J. Med. 316:761-763, 1987.
13. Smalley, H.E., O'Hara, P.J., Bridges, C.H. and Radeleff, R.D.: The effects of chronic carbaryl administration on the neuromuscular system of swine. Toxic. Appl. Pharmacol. 14:409-419, 1969.
14. Jaggy, A, Oliver JE. Chlorpyrifos toxicosis in two cats. J Vet Intern Med. 1990;4(3):135-139.
15. Levy J.K.: Chronic chlorpyrifos toxicosis in a cat. J. Am. Vet. Med. Assoc.203:1684-1686, 1993.
16. Hopper, K., Aldrich, J. and Haskins S.C.: The recognition and treatment of the intermediate syndrome of organophosphate poisoning in a dog. J. Vet. Emerg. Crit. Care. 12:99-103, 2002.
17. Myers, C.J., Aleman, M., Heidmann, P., Wilson, W.D. and Madigan, J.E.: Myopathy in American miniature horses. Equine Vet. J. 38, 272-276, 2006.
18. Merbl, Y., Aroch, I., Klainbart, S., Aizenberg, Z. and Kelmer, E.: Intermediate syndrome of chlorpyrifos toxicity (Polaris®) in a caracal (*Caracal caracal*). J. Zoo WildL. Med. 42:144-148, 2011.
19. Tinson, E., Boller, E. and Davis, M.: A suspected case of intermediate syndrome in a dog with carbamate toxicosis. Aust. Vet. J. 95:201-206, 2017.
20. Blodgett, D.J. and Means, C.: Organophosphate and Carbamate Insecticides. In: Peterson, M.E., Talcott, P.A. (eds). Small Animal Toxicology - 3rd ed. St. Louis: Saunders-Elsevier, pp. 715-724, 2013.
21. Yang, C.C. and Deng, J.F.: Intermediate syndrome following organophosphate insecticide poisoning. J. Chin. Med. Assoc. 70: 467-472, 2007.
22. Karalliedde, L., Baker, D. and Marrs, T.C.: Organophosphate-induced intermediate syndrome aetiology and relationships with myopathy. Toxicol. Rev. 25:1-14, 2006.
23. Abdollahi, M. and Karami-Mohajeri, S.: A comprehensive review on experimental and clinical findings in intermediate syndrome caused by organophosphate poisoning. Toxicol. Appl. Pharmacol. 258:309-314, 2012.
24. Alahakoon, C., Dassanayake, T.L., Gawarammana, I.B. and Weerasinghe, V.S.: Can we predict intermediate syndrome? A review. Neurotoxicol. 69: 209-216, 2018.
25. Morris, C.M., Savy, C., Judge, S.J. and Blain, P.G.: Acute Toxicity of Organophosphorus Compounds. In: Balali-Mood, M., Abdollahi, M. (eds). Basic and Clinical Toxicology of Organophosphorus Compounds. London: Springer. pp. 45-78, 2014.
26. John, M., Oommen, A. and Zachariah, A.: Muscle injury in organophosphorous poisoning and its role in the development of intermediate syndrome. Neurotoxicol. 24:43-53, 2003.
27. De Bleecker, J., Willems, J., Van den Neucker, K, De Reuck, J. and Vogelaers, D.: Prolonged toxicity with intermediate syndrome after combined parathion and methyl parathion poisoning. J. Toxicol. Clin. Toxicol. 30:333-345, 1992.
28. Khan, S., Hemalatha, R., Jeyaseelan, L, Oommen, A. and Zachariah, A.: Neuroparalysis and oxime efficacy in organophosphate poisoning: a study of butyryicholinesterase. Hum. Exp. Toxicol. 20:169-174, 2001.
29. Fikes, J.D.: Organophosphorus and carbamate insecticides. Vet. Clin. N. Am. Small Anim. Pract. 20:353-367, 1990.
30. Tecles, F. and Ceron, J.J.: Determination of whole blood cholinesterase in different animal species using specific substrates. Res. Vet. Sci.70:233-238, 2001.
31. Hooser, S.B., Beasley, V.R., Sundberg, J.P. and Harlin, K.: Toxicologic evaluation of chlorpyrifos in cats. Am. J. Vet, Res. 49:1371-1375, 1989.
32. Tafuri, J. and Roberts, J.: Organophosphate poisoning. Ann. Emerg. Med. 16:193-202, 1987.
33. Bajgar, J.: Laboratory diagnosis of organophosphates/nerve agent poisoning. Klin. Biochem. Metab. 13:40-47, 2005.
34. Van den Neucker, K., Vanderstraeten, G., DeMuynck, M., and De Wilde, V.: The neurophysiologic examination in organophosphate ester poisoning. Case report and review of the literature. Electromyogr. Clin. Neurophysiol. 31:507-511, 1992.
35. Schwab, B.W., Costa, L.G. and Murphy, S.D.: Muscarinic receptor alterations as a mechanism of anticholinesterase tolerance. Toxic. Appl. Pharmacol. 71:14-23, 1983.
36. Costa, L.G., Schwab, B.W. and Murphy, S.D.: Differential alterations of cholinergic muscarinic receptors during chronic and acute tolerance to organophosphorus insecticides. Biochem. Pharmacol. 31:3407-3413, 1982.
37. Costa, L.G., Schwab, B.W. and Murphy, S.D.: Tolerance to anticholinesterase compounds in mammals. Toxicol. 25:79-97, 1982.
38. Abdollahi, M., Ranjbar, A., Shadnia, S., Nikfar, S. and Rezire, A.; Pesticides and oxidative stress: a review. Med. Sci. Monit. 10, 141-147, 2004.
39. Yang, Z.P. and Dettbarn, W.D.: Lipid peroxidation and changes in cytochrome c oxidase andxanthine oxidase activity in organophosphorus anticholinesterase induced myopathy. J. Physiol. (Paris) 92:157-161, 1998.
40. Davies, J.E., Barquet, A. and Freed, V.H.: Human pesticide poisonings by a fat-soluble organophosphate insecticide. Arch. Environ. Health. 30:608-613, 1975.
41. Li W.F., Costa, L.G., Richter, R.J., Hagen, T., Shih, D.M., Tward, A., Lusis, A.J. and Furlong, C.E.: Catalytic efficiency determines the in vivo efficacy of PON1 for detoxifying organophosphates. Pharmacogenet. 10:767-799, 2000.
42. Eaton, D.L.: Biotransformation enzyme polymorphism and pesticide susceptibility. Neurotoxicol. 21:101-111, 2000.

43. Duclert, A. and Changeux, J-P.: Acetylcholine receptor gene expression at the developing neuromuscular junction. Physiol. Rev.75:339-368, 1995.
44. Tsuneki, H., Kimura, I. and Kimura, M.: Independent regulation of activation and inactivation phases in non-contractile Ca^{+2} transients by nicotinic receptor at the mouse neuromuscular junction. Brain Res. 650:299-304, 1994.
45. Sudakin, D.L., Mullins, M.E., Horowitz, B.Z., Abshier, V. and Letzig, L.: Intermediate syndrome after malathion ingestion despite continuous infusion of pralidoxime. J. Toxicol. Clin. Toxicol. 38:47-50, 2000.
46. De Bleecker, J.L.: Intermediate syndrome: prolonged cholinesterase inhibition. J. Toxicol. Clin. Toxicol. 31:197-199, 1993.
47. Soummer, A., Megarbane, B., Boroli, F., Arbelot, C., Saleh, M., Moesch, C., Fournier, E. and Rouby, J.J.: Severe and prolonged neurologic toxicity following subcutaneous chlorpyrifos self-administration: a case report. Clin. Toxicol. 49:124-127, 2011.