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Invited Review Article

A comprehensive review on experimental and clinical findings in intermediate syndrome caused by organophosphate poisoning

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ABSTRACT

Acute organophosphate (OP) intoxication is important because of its high morbidity and mortality and occurrence of muscular paralysis associated by inhibition of acetylcholinesterase (AChE) activity at the neuromuscular junction. Cholinergic crisis, intermediate syndrome (IMS), and OP-induced delayed neuropathy (OPIDN) are the evidences that can be observed in OP intoxication. The main cause of morbidity due to OP poisoning is IMS that occurs 24–96 h after poisoning. Mechanisms underlying the IMS are not fully known. Although the electrophysiological aspects of delayed neuropathy are best characterized, the IMS remain very little studied. The aim of this study was to revisit current knowledge related to OP and the IMS. For this purpose, a systematic review without date limitation was performed. A total of 599 relevant articles were found and reviewed. Data were categorized according to experimental and clinical studies. Occurrences of persistent AChE inhibition, electromyography changes, muscle cell injury, and oxidative stress are the most important pieces of evidence for involvement of IMS in OP toxicity.

Delayed AChE inhibition, muscle necrosis, down regulation or desensitization of postsynaptic ACh receptors, failure of postsynaptic ACh release, and oxidative stress-related myopathy are involved in IMS. Toxicokinetic factors, such as a high lipid-solubility, duration of AChE inhibition and metabolite excretion, evolution of alterations on repetitive nerve stimulation (RNS), type and frequency of muscle lesions can estimate the probability of the IMS. Plasma AChE of less than 200 units is a predictor and the 30 Hz RNS decremental response could be a useful marker for the IMS.

Contents

Introduction

Organophosphate (OP) poisoning is a major global health problem. This poisoning produces various forms of acute, subacute, or delayed neurotoxicity that causes life-threatening acute neurological complications such as seizures, paralysis, neuromuscular and cardiac conduction

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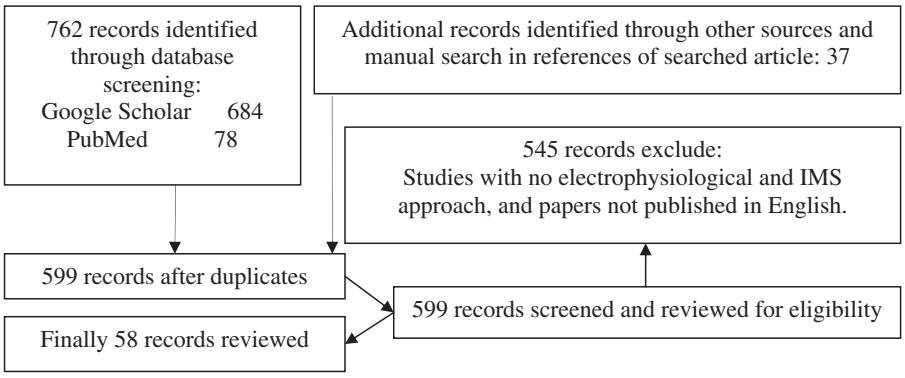

Fig. 1. Flow diagram of the literature reviewing process.

disorders. The neurotoxic effects of OP in human range from neurobehavioral and electroencephalographic changes to increase in the variability of action potential (AP) latencies in skeletal muscles. Cholinergic crisis, intermediate syndrome (IMS), and OP-induced delayed neuropathy (OPIDN) can be observed in OP intoxication (Dettbern et al., 2006). OPIDN, a sensory-motor distal axonopathy is believed to be a result of inhibition of neuropathy target esterase (Lotti and Moretto, 2005; Vasconcellos et al., 2002). The IMS following OP poisoning has been described in the mid-1980s by Senanayake and Karalliedde (1987). Approximately 20% of patients following exposure to OP pesticides may experience IMS (Karalliedde et al., 2006). The late onset of respiratory failure associated with IMS is a major contributor to the high morbidity, mortality, and cost of OP poisoning treatment. The IMS is clinically characterized by weakness in the cranial nerves, weakness of respiratory, neck and proximal limb muscles, and depressed deep tendon reflexes. These symptoms appear within 24 to 96 h post OP exposure in two types of paralysis. The type 1 paralysis responds to atropine while type 2 does not. Fasciculation that is seen in type 1 is not part of IMS. Delayed polyneuropathy develops within 1 to 3 weeks but duration of the IMS varies from a few days to several weeks (Van den Neucker et al., 1991).

Clinical and experimental electrophysiological studies in the IMS show that subclinical electrophysiological abnormalities are common and progressive. Studies demonstrate a repetitive firing following a single stimulus, gradual reduction in twitch height or compound muscle action potential (CMAP) followed by an increase with repetitive stimulation (decrement–increment phenomenon), and continued reduction in twitch height or CMAP with repetitive simulation (Jayawardane et al., 2009; Karalliedde et al., 2006).

The aim of this study was to gather all data related to IMS and electromyographic changes that may occur after OP poisoning to clarify understanding the involved mechanisms.

Methods

Bibliographic databases including PubMed and Google Scholar were searched between years 1953 to 2011 for the keywords "organophosphate, organophosphorous, intermediate syndrome, myopathy, neuropathy, and electromyography". In the first step, 599 articles were found, after elimination of duplicates or irrelevant papers, 58 papers were selected and reviewed. Reference lists of published articles were hand-searched to ensure inclusion of all possible studies (Fig. 1).

Results and discussion

IMS description

This syndrome was described in patients who develop proximal muscle weakness and cranial nerve lesions after recovery from a cholinergic crisis. It is apparent that all patients who develop such weakness have progressive neuromuscular junction dysfunction since the time of acute exposure. This phenomenon is thought to be due to primary motor endplate dysfunction resulting from prolonged inhibition of AChE. This involves both presynaptic and postsynaptic failures. Patients who develop weakness of proximal muscles, neck flexion of MRC (Medical Research Council) score of 3/5 or less are at risk of late respiratory failure. An incomplete IMS is described with less severe weakness and initial decrement increment progressing to severe decrement in RNS but not progressing to respiratory failure (Jayawardane et al., 2008). Clinical weakness of IMS is experienced in 65.55% of patient as reported by Avasthi and Singh (2000), 20% by Poojara et al. (2003), 42% by De Bleecker et al. (1993), and 49% by Wadia et al. (1987), with no clear association between the particular OP pesticide involved and the development of the syndrome. IMS occurring after poisoning by fenthion, monocrotophos, dimethoate, methylparathion, phosmet, chlorpyrifos, phenthoate, dichlorvos and methamidophos (De Bleecker et al., 1992, 1993; De Wilde et al., 1991; Good et al., 1993; Jayawardane et al., 2008; Jin et al., 2008; Karademir et al., 1990; Senanayake and Karalliedde, 1987; Van den Neucker et al., 1991; Van den Neucker et al., 1991).

Respiratory failure caused by IMS

The respiratory failure is mostly a consequence of nicotinic paralysis of the respiratory muscles. The diaphragm is involved out of proportion to other muscles in IMS. Studies of acute OP poisoning in experimental animals have revealed that muscle necrosis is much more severe in the diaphragm in comparison to other skeletal muscles (Ariens et al., 1969; Wadia et al., 1974). However, the respiratory failure may occur in acute OP intoxication because of muscarinic hyperactivity that can lead to excessive airway secretions and a central respiratory depression. Also, respiratory failure as a complication of endotracheal intubation can be caused by arytenoid dislocation or subluxation, or compression injury (Jin et al., 2008). Phrenic nerve conduction study in one patient with impending respiratory failure revealed an unstimulable phrenic nerve (Singh et al., 1998). Isolated bilateral vocal cord paralysis that recorded by laryngeal electromyography should be excluded as a cause, if dysphonia or respiratory distress occurs after extubation in patients with IMS (Jin et al., 2008).

Electrophysiological changes during IMS

The electrophysiological aspects of delayed neuropathy are best characterized, but those of crisis and IMS remain very little studied. There are several electrodiagnostic testing in the better management of patients with OP poisoning. RNS studies can help in understanding the abnormalities observed during the progression and development of IMS. Single fiber electromyography (SFEMG) is another electrodiagnostic technique that allows evaluation of single

Table 1
Electromyographic findings reported in the clinical and animal studies appeared in close relationships with cases of IMS.

Clinical and animal studies	Human/animal	Pesticide	Electromyographic finding
Maselli et al. (1986)	Human	Methyl parathion	Repetitive CMAP & ↓response at higher rates of stimulation in SNS
Senanayake and Karalliedde (1987)	Human	Fenthion Monocrotophos Dimethoate Methamidophos	Fade on tetanic stimulation, absence of fade on low frequency stimulation, and post-tetanic facilitation, suggestive of a postsynaptic defect
Wadia et al. (1987)	Human	Diazinon Malathion Fenthion Sumithion	↓CMAP & repetitive CMAP in RNS
Besser-Gutmann et al. (1989)	Human	Unknown	↓Evoked CMAP, decrement–increment phenomenon in RNS
De Wilde et al. (1991)	Human	Fenthion	Fade on tetanic stimulation, absence of fade on low frequency stimulation, and post-tetanic facilitation
Maselli and Soliven (1991)	Rat	DPFP	Repetitive CMAPs in response to a single stimulus; ↓response to RNS
Van den Neucker et al. (1991)	Human	Fenthion	Neuromuscular junctional dysfunction
De Bleecker et al. (1992)	Human	Dimethoate	↓Response at low rates of RNS, ↑at a high rate
De Bleecker et al. (1993)	Human	Methylparathion Fenthion Dimethoate	Decrement–increment phenomenon in RNS
Good et al. (1993)	Human	Phosmet	↓Response at low and high rates of RNS, MEPP, ↓mean ACh sensitivity and normal MP
De Bleecker et al. (1994)	Rat	Paraoxon Fenthion	Repetitive activity in RNS ↓Amplitude in SNS
Baker and Sedgwick (1996)	Human	Sarin	Small changes in SFEMG with no clinical neuromuscular symptoms
Camara et al. (1997)	Rat	Methamidophos	↑Amplitude, prolonged the decay phase of nerve-evoked and spontaneous MEPP
Singh et al. (1998)	Human	Monocrotophos Phorate	Repetitive responses & decrement–increment phenomenon in RNS
Dongren et al. (1999)	Rat	Dimethoate	Prolongation of MCD, ↓CMAP
de Blaquiere et al. (2000)	Mouse	Diazinon 1—Single dose 2—Multiple dose	1—↑Jitter of AP but not EP 2—↑Jitter of EP
Yang et al. (2001)	Rat	1—Phoxim 2—Methomyl, fenvalerate	1—↑MCD of SFAP blocking of NMT, jitter abnormalities 2—Jitter abnormalities
Jayawardane et al. (2008)	Human	Chlorpyrifos Dimethoate Phenthoate Diazinon	Combination of decrement–increment and repetitive fade or severe decrement at high frequencies
Jin et al. (2008)	Human	Dichlorvos	1—Widespread fibrillation, positive sharp waves, and ↓AP

Abbreviations: action potentials (AP), compound muscle action potentials (CMAP), diisopropylfluorophosphate (DIFP), end-plate potential (EP), mean consecutive difference (MCD), membrane potentials (MP), miniature end-plate potentials (MEPP), motor nerve conduction velocity (MNCV), repetitive nerve stimulation (RNS), single fiber electromyography (SFEMG), single muscle fiber potentials (SFAP), sensory nerve action potentials (SNAP), single nerve stimulation (SNS).

muscle fibers within a motor unit. SFEMG allows the quantitation of the parameters of fiber density, jitter (variability of latencies), and blocking. Fiber density is an indirect estimate of the number of muscle fibers per unit volume belonging to a single motor unit (Stalberg and Trontelj, 1979) and is a more sensitive electrophysiological method in the detection of neuromuscular transmission (NMT) (Baker and Sedgwick, 1996; Dongren et al., 1999; Yang et al., 2001). Several authors have recorded the clinical and electrodiagnostic features of the OP-induced nicotinic syndrome (Besser-Gutmann et al., 1989; Roberts, 1976; Vasconcellos et al., 2002; Wadia et al., 1974; Wadia et al., 1987) that are summarized in Table 1. Electrodiagnostic hallmarks of this condition include supramaximal electrical stimulus-induced repetitive responses and either a decremental response, i.e. tetanic fade or a decrement–increment response at higher frequencies of RNS (Besser-Gutmann et al., 1989; Jayawardane et al., 2008). A large cohort of OP-poisoned patients was studied with RNS in the proximal muscle groups that showed clear progression of electrophysiological changes in parallel with the development of IMS (Aaron, 2008; Jayawardane et al., 2008). IMS can be explained by combined pre- and post-synaptic dysfunctions of NMT (De Bleecker et al., 1993, De Bleecker, 1995; Senanayake and Karalliedde, 1987). The nature of the NMT failure that is observed in IMS includes potential mechanisms of presynaptic feedback which may reduce ACh release and postsynaptic receptor desensitization because of the continual nicotinic receptor stimulation (Jayawardane et al., 2009; Karalliedde et al., 2006). Possible causes of muscular fatigue are NMT defects, myopathy, and fiber type disproportion (Perry et al., 1988). Normal nerve conduction velocities (Jayawardane et al., 2008; Maselli et al., 1986), distal latency (Wadia et al., 1987), fade on tetanic stimulation (a change in the type of neuromuscular block to a non-depolarization block) (Baker and Sedgwick, 1996), absence of fade on low-frequency stimulation, and absence of post-tetanic facilitation (Senanayake and Karalliedde, 1987) suggest that a postsynaptic defect is the predominant cause of paralytic symptoms. It was shown that decrement–increment responses at RNS are indicative of a depolarization block due to inactivation of AChE at the motor end-plate (Singh et al., 1998). Prolonged end-plate potential or repetitive end-plate potentials or a combination of both can cause a muscle twitch in single nerve stimulation (SNS) (Clark et al., 1984). A reduction in amplitude of RNS was observed in weak rats with severe end-plate AChE inhibition (De Bleecker et al., 1994). Interestingly, sustained end-plate depolarization results in decrement and weakness in acute OP exposure (Maselli and Soliven, 1991). Electrophysiological studies have shown that paraoxon increases neurotransmitter release and causes spontaneous and impulse-related antidromic nerve activity that induce skeletal muscle fiber necrosis (Wecker et al., 1978).

The possible causes of IMS

Acetylcholinesterase (AChE) inhibition. To produce a muscle fiber contraction, acetylcholine (ACh) is released from the depolarized motor neuron terminal enters into the synaptic cleft where it binds to receptors to depolarize the muscle end-plate and muscle fiber sarcolemma. This action results in a calcium-dependent myofiber

contraction. To allow end-plate repolarization, ACh is rapidly hydrolyzed by the enzyme AChE. The acute toxicity of OP is attributable to the inhibition of AChE and the consequent accumulation of ACh in the central and peripheral nervous system synapses. The nicotinic manifestation of OP poisoning is characterized by skeletal muscle involvement in the form of fasciculation and limb and respiratory muscle weakness. Most studies confirm that the pathophysiology of IMS is not clearly known but the role of persistent excess of ACh at the neuromuscular junction cannot be ignored. This persistent severe inhibition of AChE through the course of poisoning by dimethoate, fenthion, parathion, and paraoxon underlies the cholinergic crises and IMS (De Bleecker, 1995; Khan et al., 2001).

In a prospective study in 1993, a delayed and severe AChE inhibition and relapse of muscarinic symptoms were observed during development of IMS in OP-poisoned patients (De Bleecker et al., 1993). Fenthion and chlorpyrifos were found to produce a gradual increase of cholinergic signs with IMS lasting several days after exposure (De Bleecker, 1995; Lotti et al., 1986). IMS usually occurs 2–4 days after exposure when the symptoms and signs of the acute cholinergic syndrome are no longer obvious (Karalliedde et al., 2006). However, failure of AChE to improve the muscle power in one hand and the similar levels of inhibited AChE between patients who developed IMS and those who did not on the other hand implicate additional mechanisms in the development of IMS. Of course, the presence of only nicotinic signs during IMS cannot be explained by the 'AChE inhibition theory' (Aygun et al., 2003; Khan et al., 2001). AChE inhibition, therefore may initiate other processes which result in cellular dysfunction. Also reduction of AChE and nicotinic ACh receptor mRNA expression occurs after oral poisoning with disulfoton in rat (Matsuda et al. 2000).

Muscle disorders. The distribution of the weakness in human cases and experimental animals with IMS can be ascribed to necrosis of muscle fibers and development of myopathy. However, myopathy and the IMS have a common origin in ACh accumulation (Karalliedde et al., 2006) and this has led to speculation that myopathy is involved in induction of IMS. The fall in amplitude of the AP associated with normal velocity can be explained by a reversible lesion at the neuromuscular junction and perhaps also at the anterior horn cell. The anterior horn cell is associated with nicotinic ACh receptors (Wadia et al., 1987). In this regard, De Bleecker et al. (1994) stated that myopathy is not aggravated by a further decline in AChE activity in fenthion poisoning suggesting that the role for persistent AChE inhibition as the cause of IMS. Transient weakness is actually muscular fatigue and other causes such as atrophy or loss of muscle bulk may be related to IMS.

Severe muscle damage in OP-poisoned patients was shown during the cholinergic crises and IMS (Mathew et al., 2002). In experimental animals, acute excess of ACh produces overstimulation of muscle fibers that leads to muscle degeneration known as acute myopathy. The severity of the myopathy is positively correlated with the degree and duration of AChE inhibition (De Bleecker et al., 1991; Dettbarn, 1984; Wecker et al., 1978). The induction of skeletal muscle fiber necrosis is triggered by inhibition of a neurally regulated fraction of AChE (Wecker et al., 1978). The maximal necrotizing myopathy in rats occurred within the first 24 to 48 h of the poisoning with paraoxon and mipafox, or fenthion. Also fenthion caused a limited rhabdomyolysis that correlated with AChE inhibition (De Wilde et al., 1991). Thirty minutes after single administration of paraoxon to rats, a dose-dependent necrosis in skeletal muscle fibers occurred that initiated at the motor end-plate region and characterized by dilated mitochondria, expanded sarcoplasmic reticulum, fused and widened subsynaptic folds, and coated cleft vesicles. By 24 h, a generalized breakdown of muscle fiber architecture was evident with an accompanying infiltration of phagocytes (Wecker et al., 1978). Electron microscopy revealed degeneration and regeneration of the end-plates in phosmet human poisoning (Good et al., 1993). In a prospective study, necrotic fibers in muscle biopsies were too sparse to explain severe muscle weakness (De Bleecker et al., 1993). A single sublethal dose of sarin in rats induced a non-Wallerian-type axonal degeneration of the neuromuscular synapse in the slow twitch, soleus muscle than in the fast extensor digitorum longus muscle. This study demonstrates a direct cytotoxic effect of sarin in muscles (Kawabuchi et al., 1991). Muscle is composed of two types of muscle fibers which differ in their enzymatic composition, speed of contraction, and fatigability. Type I fibers have more oxidative enzymes, are less susceptible to fatigue, and are slow twitch fibers. Type II muscle fibers have a higher proportion of glycolytic enzymes and are more-easily fatigued and fast twitch fibers. So we can conclude that sarin may affect the oxidative cycle in muscles cells.

Oxidative damage. The events following acute OP poisoning provide a favorable setting for free radical generation. Free radicals mediate muscle damage and inflammation after strenuous exercise as well as the cellular injury of ischemia reperfusion (Abdollahi et al., 2004; Soltaninejad and Abdollahi, 2009). Therefore, the extensive muscle fasciculation and muscle overactivity that occur in the cholinergic crisis of acute OP poisoning and the paralysis which simulates ischemia reperfusion can both lead to production of free radicals, cellular lipid peroxidation and muscle damage (Shadnia et al., 2007; Yang and Dettbarn, 1998). Similar injury on muscle may take place in acute OP poisoning that contributes to the development of muscle weakness and IMS (Dandapani et al., 2003). One of the sources of free radical generation in acute OP poisoning is probably muscles (Amirkabirian et al., 2007). Pretreatment of mice with alpha-tocopherol and N-acetylcysteine prevented ecothiophate-induced myopathy that supports the role of oxidative stress in IMS (Kelly et al., 1992). Also, mechanisms other than ACh-induced oxidative stress may be involved in the progression of type I to type II paralysis (Venkatesh et al., 2006).

Other factors. Some OP are metabolized in the liver to much more active metabolites. These poisons such as parathion, fenthion, chlorpyrifos are also usually highly lipid soluble (Davies et al., 1975; de Blaquiere et al., 2000; De Bleecker et al., 1993) and thus are widely distributed into fat. This helps in the occurrence of delayed and prolonged ChE inhibitions and consequently occurrence of IMS. Impairment of systemic functions (cardiovascular, hepatic, and renal) during OP poisoning that prolongs their metabolisms (De Bleecker et al., 1993; Jin et al., 2008) can probably lead to IMS. Disruption of energy metabolism and calcium homeostasis implicates in the occurrence of IMS (Yang et al., 2002). Another issue is the genetic polymorphisms in biotransformation of enzymes such as glutathione S-transferases, cytochromes P450, paraoxonase (Li et al., 2000) or target molecules that might increase or decrease sensitivity to certain pesticides and influence their toxicity (Eaton, 2000). OP-poisoned patients with genotype of variant allele at 55 codon of PON1, GSTM1 null and both GSTM1 and GSTT1 null have probably higher risk for IMS (Xiao et al., 2003). Parathion, phosmet, methylparathion, diazinon, phoxim, fenthion, and dimethoate with P═S bond are poor AChE inhibitors in comparison to methamidophos, dichlorvos, phenthoate, and monocrotophos with P═O bond. This is because the P═S bond is less polarized than the P═O bond that results in a phosphorus atom with low reactivity and minimal capacity to inhibit the enzyme. This happens mostly through the metabolic oxidation of P═S to P═O by oxidative desulfuration and causing AChE inhibition (Fukuto, 1990). Although IMS is more likely to occur with some OP, it is not confined to a few distinct compounds. It seems that IMS relates to the severity of poisoning not of the specific OP (Dettbern et al., 2006).

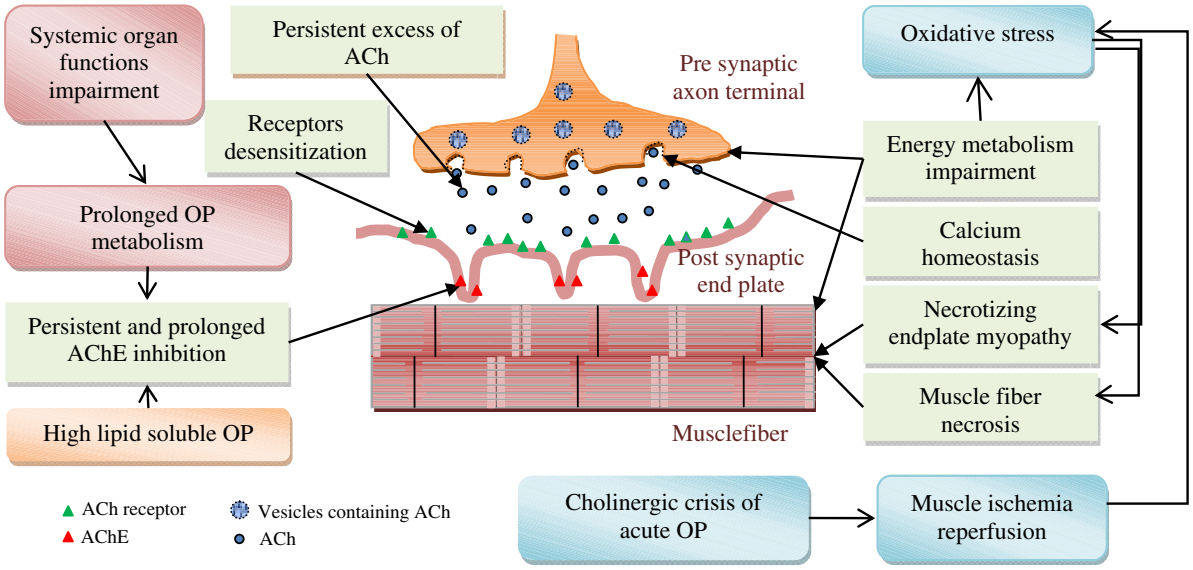

Fig. 2. A simplified model outlining potential of mechanisms of neuromuscular junction impairment during IMS caused by OP poisoning.

Conclusion

Taking collectively, the mechanisms playing the role in induction and progress of IMS in OP poisoning are summarized and drawn in Fig. 2. We can conclude that mechanisms of IMS include prolonged AChE inhibition, muscle necrosis, down regulation or desensitization of postsynaptic ACh receptors, failure of postsynaptic ACh release, and oxidative stress-related myopathy. Toxicokinetic factors, such as a high lipid-solubility, duration of AChE inhibition and metabolite excretion, evolution of alterations on RNS, type and frequency of muscle lesions can estimate the probability of the IMS. Due to potential dangers of IMS, physicians should be aware of the occurrence of neurotoxic effects and should perform neuromuscular studies to rule out other causes and predict severity of OP intoxication. Plasma AChE of less than 200 units is a predictor and the 30 Hz RNS decremental response could be a useful marker for the IMS (Avasthi and Singh, 2000).

Conflict of interest

The authors declare that there are no conflicts of interest.

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References

Aaron, C.K., 2008. Organophosphate poisoning-induced intermediate syndrome: can electrophysiological changes help predict outcome? PLoS Med. 5, e154.
Abdollahi, M., Ranjbar, A., Shadnia, S., Nikfar, S., Rezaie, A., 2004. Pesticides and oxidative stress: a review. Med. Sci. Monit. 10, 141–147.
Amirkabirian, N., Teimouri, F., Esmaily, H., Mohammadirad, A., Aliahmadi, A., Abdollahi, M., 2007. Protection by pentoxifylline of diazinon-induced toxic stress in rat liver and muscle. Toxicol. Mech. Methods 17, 215–221.
Ariens, A.T., Meeter, E., Wolthuis, O.L., Van Benthem, R.M.J., 1969. Reversible necrosis at the end plate region in striated muscle of rat poisoned with cholinesterase inhibitors. Experentia 25, 57–59.
Avasthi, G., Singh, G., 2000. Serial neuro-electrophysiological studies in acute organophosphate poisoning—correlation with clinical findings, serum cholinesterase levels and atropine dosages. J. Assoc. Physicians India 48, 794–799.
Aygun, D., Onar, M.K., Altintop, B.L., 2003. The clinical and electrophysiological features of a delayed polyneuropathy developing subsequently after acute organophosphate poisoning and it's correlation with the serum acetylcholinesterase. Electromyogr. Clin. Neurophysiol. 43, 421–427.
Baker, D.J., Sedgwick, E.M., 1996. Single fibre electromyographic changes in man after organophosphate exposure. Hum. Exp. Toxicol. 15, 369–375.
Besser-Gutmann, L., Dillmann, U., Weilemann, L.S., Hopf, H.C., 1989. End-plate dysfunction in acute organophosphate intoxication. Neurology 39, 561–567.
Camara, A.L., Braga, M.F., Rocha, E.S., Santos, M.D., Cortes, W.S., Cintra, W.M., et al., 1997. Methamidophos: an anticholinesterase without significant effects on postsynaptic receptors or transmitter release. Neurotoxicology 18, 589–602.
Clark, A.L., Hobbiger, F., Terrar, D., 1984. Nature of the anticholinesterase-induced repetitive response of rat and mouse striated muscle to single nerve stimuli. J. Physiol. 349, 157.
Dandapani, M., Zachariah, A., Kavitha, M.R., Jeyaseelan, L., Oommen, A., 2003. Oxidative damage in intermediate syndrome of acute organophosphorous poisoning. Indian J. Med. Res. 117, 253–259.
Davies, J.E., Barquet, A., Freed, V.H., 1975. Human pesticide poisonings by a fat-soluble organophosphate insecticide. Arch. Environ. Health 30, 608–613.
de Blaquiere, G.E., Waters, L., Blain, P.G., Williams, F.M., 2000. Electrophysiological and biochemical effects of single and multiple doses of the organophosphate diazinon in the mouse. Toxicol. Appl. Pharmacol. 166, 81–91.
De Bleecker, J.L., 1995. The intermediate syndrome in organophosphate poisoning: an overview of experimental and clinical observations. Clin. Toxicol. 33, 683–686.
De Bleecker, J., Willems, J., De Reuck, J., Santens, P., Lison, D., 1991. Histological and histochemical study of paraoxon myopathy in the rat. Acta Neurol. Belg. 91, 255–270.
De Bleecker, J., Van Den Neucker, K., Willems, J., 1992. The intermediate syndrome in organophosphate poisoning: presentation of a case and review of the literature. J. Toxicol. Clin. Toxicol. 30, 321–329.
De Bleecker, J., Van den Neucker, K., Colardyn, F., 1993. Intermediate syndrome in organophosphorus poisoning: a prospective study. Crit. Care Med. 21, 1706–1711.
De Bleecker, J., Van Den Abeele, K., De Reuck, J., 1994. Electromyography in relation to end-plate acetylcholinesterase in rats poisoned by different organophosphates. Neurotoxicology 15, 331–340.
De Wilde, V., Vogelaers, D., Colardyn, F., Vanderstraeten, G., Van den Neucker, K., De Bleecker, J., et al., 1991. Postsynaptic neuromuscular dysfunction in organophosphate induced intermediate syndrome. Klin. Wochenschr. 69, 177–183.
Dettbarn, W.D., 1984. Pesticide induced muscle necrosis: mechanisms and prevention. Fundam. Appl. Toxicol. 4, 18–26.
Dettbern, W.D., Milatovic, D., Gupta, R.C., 2006. Toxicology of Organophosphate and Carbamate Compounds. Academic Press, London.
Dongren, Y., Tao, L., Fengsheng, H., 1999. Electroneurophysiological studies in rats of acute dimethoate poisoning. Toxicol. Lett. 107, 249–254.
Eaton, D.L., 2000. Biotransformation enzyme polymorphism and pesticide susceptibility. Neurotoxicology 21, 101–111.
Fukuto, T., 1990. Mechanism of action of organophosphorus and carbamate insecticides. Environ. Health Perspect. 87, 245–254.
Good, J.L., Khurana, R.K., Mayer, R.F., Cintra, W.M., Albuquerque, E.X., 1993. Pathophysiological studies of neuromuscular function in subacute organophosphate poisoning induced by phosmet. J. Neurol. Neurosurg. Psychiatry 56, 290–294.
Jayawardane, P., Dawson, A.H., Weerasinghe, V., Karalliedde, L., Buckley, N.A., Senanayake, N., 2008. The spectrum of intermediate syndrome following acute organophosphate poisoning: a prospective cohort study from Sri Lanka. PLoS Med. 5, 1143–1153.
Jayawardane, P., Senanayake, N., Dawson, A., 2009. Electrophysiological correlates of intermediate syndrome following acute organophosphate poisoning. Clin. Toxicol. (Phila.) 47, 193–205.
Jin, Y.-H., Jeong, T.-O., Lee, J.-B., 2008. Isolated bilateral vocal cord paralysis with intermediate syndrome after organophosphate poisoning. Clin. Toxicol. 46, 482–484.
Karademir, M., Erturk, F., Kocak, R., 1990. Two cases of organophosphate poisoning with development of intermediate syndrome. Hum. Exp. Toxicol. 9, 187–189.

Karalliedde, L., Baker, D., Marrs, T.C., 2006. Organophosphate-induced intermediate syndrome: aetiology and relationships with myopathy. Toxicol. Rev. 25, 1–14.
Kawabuchi, M., Cintra, W.M., Deshpande, S.S., Albuquerque, E.X., 1991. Morphological and electrophysiological study of distal motor nerve fiber degeneration and sprouting after irreversible cholinesterase inhibition. Synapse 8, 218–228.
Kelly, S., Ferry, C.B., Bamforth, J.P., Das, S.K., 1992. Protection against the effects of anticholinesterases on the latencies of action potentials in mouse skeletal muscles. Br. J. Pharmacol. 107, 867–872.
Khan, S., Hemalatha, R., Jeyaseelan, L., Oommen, A., Zachariah, A., 2001. Neuroparalysis and oxime efficacy in organophosphate poisoning: a study of butyrylcholinesterase. Hum. Exp. Toxicol. 20, 169–174.
Li, W.F., Costa, L.G., Richter, R.J., et al., 2000. Catalytic efficiency determines the in vivo efficacy of PON1 for detoxifying organophosphates. Pharmacogenetics 10, 767–799.
Lotti, M., Moretto, A., 2005. Organophosphate-induced delayed polyneuropathy. Toxicol. Rev. 24, 37–49.
Lotti, M., Moretto, A., Zoppellari, R., Dainese, R., Rizzuto, N., Barusco, G., 1986. Inhibition of lymphocytic neuropathy target esterase predicts the development of organophosphate-induced delayed polyneuropathy. Arch. Toxicol. 59, 176–179.
Maselli, R.A., Soliven, B.C., 1991. Analysis of the organophosphate-induced electromyographic response to repetitive nerve stimulation: paradoxical response to edrophonium and D-tubocurarine. Muscle Nerve 14, 1182–1188.
Maselli, R., Jacobsen, J.H., Spire, J.P., 1986. Edrophonium: an aid in the diagnosis of acute organophosphate poisoning. Ann. Neurol. 19, 508–510.
Mathew, J., Oommen, A., Zachariah, A., 2002. Muscle injury in organophosphorous poisoning and its role in the development of intermediate syndrome. Neurotoxicology 172, 1–11.
Matsuda, H., Seo, Y., Kakizaki, E., Takahama, K., 2000. Changes in mRNA expression levels of synaptic- and target tissue-specific proteins after organophosphate exposure. Leg. Med. 2, 55–63.
Perry, J., Barnes, G., Gronley, J.K., 1988. The post-polio syndrome: an overuse phenomenon. Clin. Orthop. 233, 145–162.
Poojara, L., Vasudevan, D., Arun Kumar, A., Kamat, V., 2003. Organophosphate poisoning: diagnosis of intermediate syndrome. Ind. J. Crit. Care Med. 7, 94–102.
Roberts, D.V., 1976. E.M.G. voltage and motor nerve conduction velocity in organophosphorus pesticide factory workers. Int. Arch. Occup. Environ. Health 36, 267–274.
Senanayake, N., Karalliedde, L., 1987. Neurotoxic effects of organophosphorus insecticide. An intermediate syndrome. N. Engl. J. Med. 316, 761–763.
Shadnia, S., Dasgar, M., Taghikhani, S., Mohammadirad, A., Khorasani, R., Abdollahi, M., 2007. Protective effects of alpha-tocopherol and N-acetyl-cysteine on diazinon-induced oxidative stress and acetylcholinesterase inhibition in rats. Toxicol. Mech. Methods 17, 109–115.
Singh, G., Mahajan, R., Whig, J., 1998. The importance of electrodiagnostic studies in acute organophosphate poisoning. J. Neurol. Sci. 157, 191–200.
Soltaninejad, K., Abdollahi, M., 2009. Current opinion on the science of organophosphate pesticides and toxic stress: a systematic review. Med. Sci. Monit. 15, 75–90.
Stalberg, E., Trontelj, J., 1979. Single Fiber Electromyography. Mirvalle Press, Woking, England.
Van den Neucker, K., Vanderstraeten, G., De Muynck, M., De Wilde, V., 1991. The neurophysiologic examination in organophosphate ester poisoning. Case report and review of the literature. Electromyogr. Clin. Neurophysiol. 31, 507–511.
Vasconcellos, L.F., Leite, A.C., Nascimento, O.J., 2002. Organophosphate-induced delayed neuropathy: case report. Arq. Neuropsiquiatr. 60, 1003–1007.
Venkatesh, S., Kavitha, M.L., Zachariah, A., Oommen, A., 2006. Progression of type I to type II paralysis in acute organophosphorous poisoning: is oxidative stress significant? Arch. Toxicol. 80, 354–361.
Wadia, R.S., Sadagopan, C., Amin, R.B., Sardesai, H.V., 1974. Neurological manifestations of organophosphate insecticide poisoning. J. Neurol. Neurosurg. Psychiatry 37, 841–847.
Wadia, R.S., Chitra, S., Amin, R.B., Kiwalkar, R.S., Sardesai, H.V., 1987. Electrophysiological studies in acute organophosphate poisoning. J. Neurol. Neurosurg. Psychiatry 50, 1442–1448.
Wecker, L., Laskowski, B., Dettbarn, W.D., 1978. Neuromuscular dysfunction induced by acetylcholinesterase inhibition. Fed. Proc. 37, 2818–2822.
Xiao, C., He, F.S., Zheng, Y.X., Leng, S.G., Qin, F.K., Niu, Y., et al., 2003. Genetic susceptibility to intermediate myasthenia syndrome following organophosphate insecticides poisoning. Zhonghua Yu Fang Yi Xue Za Zhi 37, 259–262.
Yang, Z.P., Dettbarn, W.D., 1998. Lipid peroxidation and changes in cytochrome c oxidase and xanthine oxidase activity in organophosphorus anticholinesterase induced myopathy. J. Physiol. Paris 92, 157–161.
Yang, D., He, F., Li, T., 2001. Repetitive nerve stimulation and stimulation single fiber electromyography studies in rats intoxicated with single or mixed insecticides. Toxicology 161, 111–116.
Yang, D., Lu, X., Hang, W., He, F., 2002. Biochemical changes in primary culture of skeletal muscle cells following dimethoate exposure. Toxicology 174, 79–85.