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REVIEW ARTICLE

Intermediate Syndrome Following Organophosphate Poisoning; Review Article

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Abstract

Background: Organophosphates (OPs) are regularly utilized as pesticides all over the world. Exposures to OPs cause countless cases of poisoning and death annually. Organophosphates inebriation generates a range of muscarinic, nicotinic, and cholinergic side effects including both central and peripheral nervous systems. OP compound's simple accessibility is responsible for expanding rates of pesticide poisoning and the fact that it is a noteworthy reason for morbidity and mortality that presents general medical issues in a growing district.
Methods: I performed a review of the published literature. The databases Medline, Embase, Scopus and Google Scholar were searched using the terms intermediate syndrome, organophosphate induces intermediate syndrome and organophosphate poisoning. Databases were merged and a duplicate was removed.
Results: In intense organophosphate poisoning, serious and delayed acetylcholinesterase restraint comes with oxidative stress, identified in erythrocyte membranes, that takes place in the initial phases of poisoning and may add to the progress and seriousness of intermediate syndrome (IMS).
Conclusion: It normally appears 2-4 days after presentation when the side effects and indications of the intense cholinergic disorder (e.g., muscle fasciculations, muscarinic signs) are not evident anymore. However, IMS has been considered as a noteworthy causative factor of organophosphate-related morbidity and mortality due to its incessant presence and potential occurrence of breathing malfunction. The aim of the article is to bring down the clear idea about the IMS.

Keywords: Cholinergic Crisis; Intermediate Syndrome; Organophosphate Poisoning

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INTRODUCTION

Organophosphate poisoning is the most widely recognized pesticide poisoning in developing nations (1, 2). Prevalence of OP was accounted for as 10-36.2% in developed nations, 40-60% in African nations and 65-79.2% in developing nations (3). However, in the eastern part of Sri Lanka, prevalence was 27.3% (4, 5). The intermediate syndrome (IMS) following organophosphorus (OP) insecticide poisoning was first depicted in the mid-1980s. The OP poisonings are related with a few disorders, including intense cholinergic difficulties, the intermediate syndrome (IMS), and organophosphate-induced postponed neuropathy (OPIPN). The disorder was characterized as specific signs and side effects happening after evident recuperation from the intense cholinergic disorder (6-8). In any case, IMS has been considered as a noteworthy causative factor of organophosphate-related morbidity and mortality as a result of its incessant incidence and potential breathing disorders (9). In spite of a high frequency, the pathophysiology of IMS is still unknown. The IMS mechanisms that have been proposed before incorporate distinctive vulnerability of different cholinergic receptors, muscle corruption, delayed acetylcholinesterase hindrance, deficient oxime treatment, downregulation or desensitization of postsynaptic acetylcholine receptors, postsynaptic acetylcholine discharge disorder, and oxidative stress-related myopathy (10).

The IMS takes place in relatively 20% of patients following oral intake of OP pesticides, with no reasonable relationship between the specific OP pesticide included and the advancement of the disorder. It normally appears 2-4 days after presentation when the side effects and indications of the intense cholinergic disorder (e.g., muscle fasciculations, muscarinic signs) are not evident anymore. The specific characteristics of the IMS are breathing muscle weaknesses, for example, diaphragm, intercostal muscles and accessory muscles including neck muscles and proximal muscles. Therefore, some patients may only feel weakness in their neck muscles while others may suffer from weakness in both their neck muscles and proximal limb muscles. Such patients may not be in need for ventilatory considerations, however careful controlling of breathing system is obligatory. Basically, where breathing disorders and difficulties grow quickly, treatment measures should be

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taken. In case of untimely breathing treatments, the patient may die. The aim of the article is to bring down the clear idea about the IMS and also emphasize that early identification and early intervention prevent the respiratory arrest.

METHODS

The databases Medline, Embase, Scopus and Google Scholar were searched using the terms Intermediate syndrome, Organophosphate induces Intermediate syndrome and organophosphate poisoning. Databases were merged and a duplicate was removed. Finally, 54 articles were selected and reviewed.

Pharmacology:

Organophosphorus compounds are irreversible inhibitors of the enzyme acetylcholinesterase (AchE). They hinder both cholinesterase and pseudo-cholinesterase action. The hindrance of acetylcholinesterase leads to development of acetylcholine at neurotransmitters with resultant overstimulation of neurotransmission. The clinical characteristics are because of abundant acetylcholine at the muscarinic and nicotinic receptors which prompts primary activation and final enervation of cholinergic neural connections. Pralidoxime (PAM) recovers utilitarian AChE after it has been stopped by OP, while atropine obstructs the development of abundant acetylcholine. Nonetheless, the additional advantage of utilizing PAM along with atropine stays indistinct. Such discoveries in this manner question past examinations that address the importance of PAM in the OP poisoning treatment (9). Additionally, they propose WHO principles for the utilization of PAM ought to be refreshed to consider an adaptable dosing system dependent upon the seriousness of poisoning, albeit any such changes to suggestions should initially be approved in a larger sample size (11).

Pathogenesis of intermediate syndrome:

The pathogenic mechanisms leading to IMS have not been unmistakably clarified. An investigation proposed that the moderate arrival of organophosphates from profound tissues and the industrious hindrance of acetylcholinesterase may be the basis of the IMS advancement (12). Electrophysiological studies demonstrated that both pre and post-synaptic defects have been observed in OP poisoning (13). However, Avasthi et al suggested that desensitization of acetylcholine receptors is responsible for the IMS (14). Furthermore, a study conducted by Yang et al demonstrated that interruption of energy metabolism and calcium homeostasis played a role in the incidence of IMS (15). However, Mathew et al stated that extreme muscle destruction in OP poisoning patients with the extent of muscle destruction that happens amid the cholinergic extremities decide the incidence and seriousness of IMS (16). However, magnitude of muscle damage is not sufficient to explain the muscle weakness in IMS (12, 17). In intense OP poisoning, extreme and delayed acetylcholinesterase hindrance is related with oxidative stress, identified in erythrocyte membranes, that takes place in the initial phases of poisoning and may add to the progress and seriousness of intermediate syndrome (18).

The hindrance of cholinesterase performance prompts the development of acetylcholine at neural connections, causing over invigoration of both central and peripheral nervous systems. Moreover, OP will meddle with synaptic transmission incidentally at muscarinic receptors and nicotinic receptors. Nicotinic indications incorporate expanded or diminished muscle ability and skeletal muscle fasciculations. Muscarinic signs incorporate extreme salivation, meiosis and diarrhea. The most continuous signs are accounted for to be meiosis, retching, hypersalivation, breathing difficulty, stomach torment, lowered consciousness and muscle fasciculation (19). The magnitude and level of AChE restraint is reliant on the structure of the OP. Oxon type of OPs, such as dichlorvos, are naturally dynamic and fit for restraining AChE soon after dispensation. On the other hand, thion type of OPs, such as diazinon and parathion, are naturally latent and require hepatic actuation to the equivalent oxon structure to deliver an AChE inhibitory impact. Accordingly, the inhibitory impacts of a thion OP can be deferred when contrasted with an oxon OP. OPs at first structure a non-covalent electrostatic connection where the dynamic AChE is located. At the point when the principal alkyl chain is separated from OP, a moderately feeble covalent connection will be established. In this manner, both the electrostatic and primary covalent connection are reversible in nature and the rate of unconstrained reactivation is reliant on the OP's chemical features (20). The nature of the disease is so because of the hindrance of an inadequately described esterase called the neuropathy target esterase (21).

Cholinergic phase:

The cholinergic stage often goes off in 48-72 hours; however, total clinical recuperation from every one of the impacts may take as long as seven days. Ordinarily, these impacts are gathered dependent on the influenced receptors and incorporate muscarinic, nicotinic and central nervous system (CNS) impacts (20). The side effects are because of invigoration of the muscarinic and nicotinic receptors. The nicotinic characteristics of intense OP poisoning take place because of aggregation of acetylcholine at nicotinic acetylcholine receptors, including expanded or diminished muscle control and skeletal muscle fasciculations. Unnecessary muscarinic receptor invigoration creates the traditional indications of OP poisoning, including inordinate salivation, miosis, looseness of the bowels, bronchorrhoea, bronchospasm, bradycardia, and urination. More indications incorporate heaving, breathing difficulty, stomach torment, lowered awareness, muscle fasciculations and muscle loss of motion. Following serious poisoning, summed up weakness can incorporate the breathing muscles and assisted ventilation might be essential. It is significant that various muscarinic and nicotinic characteristics may have the same features because of activity at the ganglia. Subsequently, patients may give a blended situation. Development of motion loss can influence the breathing muscles requiring ventilatory help. With oximes, atropine and mechanical ventilation, as well as gastric lavage and purification, the treatment will be of a supportive nature.

Intermediate Syndrome:

Roughly 10 to 40% of intense OP damages create deferred weaknesses in the proximal body parts, neck flexors and breathing muscles (19, 22). This group of manifestations is recognized as the intermediate syndrome

(IMS), and its cause is ineffectively comprehended. Some scholars have referred to lack of pralidoxime treatments and tissue redistribution as possible causes, however these suppositions are not spread all over the world (11). Following the intense cholinergic stage, a second phase of weakness happens after 1-4 days with or without an indication free interim, and, in case it remains unknown, can prompt deadly breathing disorders (23). OP poison-induced IMS was first described in 1987 (6). IMS occurred following recuperation from the intense cholinergic difficulty but prior to OPIPN. It is usually observed 12–72 hours following OP poisoning and may last up to 5–6 days. This syndrome is characterized by a muscle weakness that starts suddenly, incorporating the respiratory muscles (the diaphragm, in particular), as well as lack of movement in the neck muscles (lack of ability to lift the head from the pillow) and weakness of proximal limb muscles. Infrequently, certain cranial nerve palsies, such as external ocular, jaw, facial and palatal muscles, may be detected (24). Intubation and mechanical ventilation is needed if respiratory failure occurs. One of the destructive cholinergic characteristics in organophosphate poisoning is breathing difficulty. The duration of ventilatory care varies between 7 and 21 days. There are quite a few clarifications for breathing disorder; both central and peripheral functions contribute to this fact. In any case, research has proposed that the main components controlling the breathing difficulty related with OP ingestion play the key role (25).

DeferredOrganophosphate-Induced Polyneuropathy:

Organophosphate-induced delayed neuropathy (OPIDN) is an extraordinary clinical issue. It happens in relationship with the ingestion of a lot of organophosphate and presents with body parts tiresome enduring for a long time after the intense cholinergic side effects have died down. Albeit intense impacts of organophosphate inebriation have all the earmarks of being straightforwardly identified with cholinergic over action, the pathophysiology of the accompanying neuropathy is less known and is not identified with cholinesterase restraint (26). The clinical picture is portrayed by a distal paresis in lower body parts. Frequent or long hours of closeness to OPs, even at fairly low amounts and with no intense side effects, can likewise lead to neuropathy (27). Ataxia and loss of motion are the usual manifestations of OPIDN.

Determination of organophosphate-indued neuropathy lays on acknowledgment of a suitable closeness in a patient with dynamic motor shortfall more noteworthy than sensory neuropathy. Electrodiagnostic research shows an axonal neuropathy (28). Research on nerve conduction assumes an imperative contribution to the determination of this uncommon clinical situation, which may uncover distal-dominant sensory motor axonal polyneuropathy (29).

There are no particular characteristics and nerve biopsy uncovers axonal degeneration with auxiliary demyelination. Toxic neuropathic features might be described by a distal paresis in the lower limbs related with delicate side effects. Association of the central nervous system might take place. Pyramidal tract malfunction might be present in the upper limbs at a later time (30). Repetitive or delayed introduction of OPs, even at moderately low dimensions and with no intense side effects, might likewise lead to neuropathy.

These inconveniences quickly advance into a rising loss of motion that appears to happen all the more every now and again in the lower limbs. In the long run, the flabby loss of motion resolves, and hypertonicity is observed. Verifiably, these side effects are called “Ginger Jake Paralysis”, because a great many Americans amid denial ended up feeble or lost motion power in the wake of drinking a liquor containing ginger concentrate (Ginger Jake) that had been sullied with the OP triorthocresyl phosphate (TOPC) (31). They normally experienced constant spasticity and an irregular stride called “Jake leg” or “Jake walk” (32). The present examination proposes TRPA1 is the significant go-between of OPIDN and focusing on Transient receptor potential cation channel, part A1 (TRPA1) is an efficient method for the treatment of OPIDN (33).

Clinical characteristics of intermediate syndrome

IMS, which was first named by Wadia et al in 1974 as type II loss of motion, is a disorder portrayed by muscle loss of motion when the intense cholinergic stage is followed. The phrasing was then altered by Senanayake and Karalliedde in 1987 to intermediate syndrome because it emerges between the time of early cholinergic disorder and the late beginning of fringe neuropathy. IMS progresses 12-96 hours following presentation and mirrors a long-time activity of acetylcholine on the nicotinic receptors. The clinical characteristics are feeble muscles in the eyes (34), neck, bulbar, proximal body parts, as well as breathing muscles with incidental dystonic acting, which would require mechanical ventilation in an emergency unit for a few days. Cranial-nerve paralyses are normal. The possibility of death in the event of intermediate syndrome is because of breathing recession. The sensory capacities distinctively stay typical and full recuperation is obvious in 4-18 days (34).

Types of organophosphate poisoning

Numerous organophosphate mixes are presently accessible to consume as insect killers. Measurably, parathion was the responsible for IMS in up to 75% of the cases in previous examinations led by Mahieu P et al (35). Fenthion, dimethoate, monocrotophos, methamidophos and malathion were also reported to cause IMS but no reported case developed IMS after phenthoate ingestion according to the study conducted by *Gadoth N*(36). In the World Health Organization (WHO) categorization of OP pesticides, phenthoate and parathion are categorized as class II-relatively dangerous and class-Ia, extremely dangerous, respectively. LD50 (LD: lethal dosage) in rats for phenthoate and parathion mentioned on the online material safety data sheet (MSDS) is > 600 mg/kg and 20–30 mg/kg, respectively. This information shows that the fewer phenthoate IMS cases might be due to its lower toxicity.

Diagnosis of organophosphate poisoning

Many physicians use serum or RBC AChE activity to monitor OP poisoning. Serum AChE, also called pseudocholinesterase or butyryl-cholinesterase (BuChE), is found in the serum, liver, pancreas, heart and brain. It is liable to a high level of variety influenced by many conditions, such as liver dysfunction, decompensated heart

disease, malnutrition, allergic disease and malignant neoplasm. Further, no detectible distinction in the serum AChE between day 1 and day 3 after OP poisoning has been observed in IMS patients (37). Hence, there is no predictive value of serum AChE for IMS. In contrast, RBC AChE is more reliable, with better correlation in terms of clinical presentations (38). Increased RBC AChE was noted when the patient recovered from IMS and was successfully weaned off mechanical ventilation (39).

Electrophysiological studies may offer some hints regarding the development of IMS. Three phenomena of electrophysiological studies were observed in IMS: (a) repeated terminating following a solitary boost; (b) moderate decrease in twitch height or compound muscle activity potential pursued by an expansion, with repeated invigoration of ≥ 20 Hz (decrease-increase reaction); and (c) continuous decrease in twitch height or compound muscle activity potential with repeated invigoration (decreasing reaction) (40). The decreasing reaction is the most continuous discovering amid IMS resulting from a marked downregulation of acetylcholine receptors (AChRs) at the post-junctional layer, alongside a break of the pre-junctional ACh mobilization receptor. Downregulation of AChRs is due to a compensatory response after prolonged exposure to ACh followed by decrease of AChRs resulting from endocytosis (41).

Treatment

Treatment of OP poisoning is a basic and belligerent procedure which incorporates purification, antitoxin intake (atropine and oximes), mechanical ventilation helps and extracorporeal disposal strategies if necessary. Cleaning is basic in the underlying monitoring of an intensely harmed OP patient. All clothes ought to be taken out, and forceful water system ought to be carried out if topical introduction is conjectured. Materials containing leather ought to be disposed of, as OPs cannot be separated from these items. Similar proportions of forceful purification ought to likewise be considered after an oral intake, because OPs will often be discharged in the body's liquid. Gut disinfecting by means of gastric lavage might be considered if the introduction happened in 30 minutes of introduction and the patient is not spewing yet. Initiated charcoal might constrain more ingestion and might be considered if the patient has a secured aviation route.

Moderate-to-serious poisoning might need more oxygen and, in outrageous conditions, endotracheal intubation. Abundant discharges can be controlled by threatening the OP's muscarinic impacts with an anticholinergic factor like atropine. A doubling portion procedure (atropine 1 – 3 mg IV, doubling the portion at regular 5-minute intervals until impact) is appeared to decrease death possibility more adequately when contrasted with a fixed-portion procedure (atropine 2 – 5 mg each 10 – 15 minutes).

Atropine does not turn around the nicotinic side effects related with OP poisoning. Pralidoxime re-triggers OP-repressed AChE by expelling the OP from the enzyme, re-triggering the AChE enzyme and bettering as well as impeding nicotinic manifestations. The World Health Organization (WHO) recommends that pralidoxime be measured as a 30 mg/kg bolus pursued by an 8 mg/kg/hr administration in grown-ups (42). An ongoing Cochrane Review reasoned that there is not enough proof to show whether pralidoxime is advantageous or hurtful. Pralidoxime is utilized to treat nicotinic side effects and to bring down the atropine prerequisite. Clearly, the WHO's prescribed PAM blood level is not perfect for the controlling of organophosphate poisoning (43) (44). As suggested by Eyer and different researchers, the rule for the injection of 4 mg/L PAM ought to be additionally updated and talked about (45). Pawar et al recommended that a high-portion routine of PAM that comprises of a consistent administration of 1 g/h for 48 h after a 2 g loading portion decreases the risk of death in tolerably extreme instances of intense organophosphorus pesticide damage (46). Proof proposes, notwithstanding, that the centralization of pralidoxime in the blood may require to be higher to estrange the dangerous impacts of numerous insect killers. Accordingly, a bolus-loading administration pursued by an upkeep administration might be the best routine (47).

Hong-Xiang Liu et al suggested that persistent micropump of atropine and pralidoxime chloride consolidated is more powerful than the utilization of repetitive bolus infusion in the treatment of extreme intense organophosphorus insect killer poisoning (48). It has been accounted for that constant micropump infusion of atropine can altogether diminish the patient casualty rate in extreme OP damages (49). Deterioration indications can be observed following introduction to exceedingly lipophilic organophosphates (50). Sometime, a decrease in clinical condition was noticed when the patient had all the earmarks of being improving. All the prominent side effects could conceivably be clarified by OP redistribution from fat stores, as they were either cholinergic or nicotinic by nature. In such instances, pralidoxime ought to start again, alongside extra portions of atropine, as shown by clinical indications. The expansion of intranasally injected oximes to the present treatment routine for organophosphate damage would better adequacy, lessening both brain harm and risk of death. Oximes are utilized to neutralize the impacts of organophosphate damage, yet they do not promptly go through the blood rain barrier (BBB) when administered intravenously. In any case, risk of death by OP damage is straightforwardly relative to the age, seriousness of damage and length of mechanical ventilation and conversely corresponding to serum cholinesterase level (51).

Both hemodialysis and hemoperfusion can be used to shut down OP mixes from blood. There are numerous instances revealing the adequacy of such strategies. Plasmapheresis is another disposal procedure that has been utilized to evacuate invulnerable structures. Plasmapheresis is powerful in disposal of substances with high plasma protein restricting limit (>80%) and low allocation volume (<0.2 L/kg) (52). Plasmapheresis is the technique in which under 15% of complete plasma is evacuated and not supplanted. Therapeutic plasma exchange (TPE) is another technique in which isolated plasma is supplanted with albumin or plasma and crystalloids freshly frozen. Not just the removal of OP, but rather substitution of cholinesterase

by fresh frozen plasma through plasma trade might contribute to clinical betterment in patients damaged by OP (52). There exist some studies that support the viability of plasmapheresis in OP poisoning and intermediate syndrome (53).

CONCLUSION

Organophosphate poisoning is the most widely recognized pesticide damage in developing nations. It has a high death rate: its being deadly is frequently identified with a deferral in determination or an inappropriate treatment. Neuromuscular weakness resulting from OP poisoning is divided into three types; firstly, type I paralysis in which muscle weakness occurs in the first admission day related with cholinergic indications; secondly, type II loss of motion or IMS where deferred muscle weakness occurs after the acute cholinergic phase of OP poisoning; and thirdly, type III paralysis, in which polyneuropathy occurs 2–3 weeks after OP poisoning. Early determination and proper treatment, on the other hand, are regularly lifesaving, despite the fact that the clinical course of OP poisonings may be very extreme and require escalated care control. Moreover, the WHO rules for the utilization of PAM ought to be refreshed to consider an adaptable dosing procedure dependent on seriousness of poisoning, however these changes to suggestions should initially be approved in a bigger sample size.

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