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ORGANOPHOSPHATE-INDUCED DELAYED POLYNEUROPATHY- A REVIEW

Medicine

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ABSTRACT

Organophosphates are used mainly in the fields as pesticides and herbicides but are also used as petroleum additives, lubricants,antioxidants and plastic modifiers. Most cases of organophosphate toxicity result from exposure in an agricultural setting, not only among those mixing or spraying the pesticide or herbicide but also among workers returning prematurely to sprayed fields. Absorption may occur through the skin, by inhalation, or through the gastrointestinal tract.Organophosphates compounds inhibit the enzyme acetylcholinesterase by phosphorylation, resulting in acute cholinergic symptoms, with both central and neuromuscular manifestations. This review will focus on organophosphates induced delayed polyneuropathy, which is a relatively rare and less known manifestation of organophosphate poisoning.The review will discuss about the clinical presentation, pathogenesis, molecular mechanisms of OPIDP in man and the possibilities of treatment.

KEYWORDS

Neuropathy target esterase, Organophosphates, Polyneuropathy.

INTRODUCTION-

Although a number of organic phosphorus (OP) compounds were synthesized in the 1800s, their development as insecticides only occurred in the late 1930s and early 1940s[1,2]. First commercialized OP insecticide was synthesized by the German chemist Gerhard Schroeder (Bladan, containing TEPP [tetraethyl pyrophosphate] as the active ingredient), and he also synthesized one of the most known OP insecticide, parathion, in 1944. Since then, hundreds of OP compounds have been made and are used worldwide. As of 2007, the most commonly used organophosphate in both the agricultural sector and in all other sectors was chlorpyrifos, followed by acephate and malathion[3].According to the World Health Organization statistics, about 1 million accidental and 2 million suicidal poisonings with organophosphorus insecticides are reported every year, with more than 300000 fatalities and the average mortality of more than 15%[4,5].Organophosphate poisoning can lead to acute cholinergic syndrome, intermediate syndrome, organophosphate-Induced delayed polyneuropathy, the syndrome of dipper's flu and chronic effects i.e. persisting behavioral and neurological dysfunction.

Organophosphate-Induced Delayed Polyneuropathy(OPIDP)-

Certain organophosphates cause a delayed polyneuropathy that occurs approximately 2 to 3 weeks after acute exposure after , when signs of both the acute cholinergic and the intermediate syndromes have subsided and can occur even in the absence of cholinergic toxicity. In the past, it was seen with contamination of illicit alcohol with triorthocresylphosphate .The delayed syndrome follows exposure only to certain organophosphates such as triorthocresyl phosphate, leptophos, trichlorfon, and mipafox. Organophosphates cause a distal sensorimotor axonopathy . The sign and symptoms of organophosphate-Induced delayed polyneuropathyinclude tingling of the hands and feet, followed by sensory loss, progressive muscle weakness and flaccidity of the distal skeletal muscles of the lower and upper extremities, and ataxia[6,7]. Paresthesias in the feet and cramps in the calf muscles are followed by progressive weakness that typically begins distally in the limbs and then spreads to involve more proximal muscles. The maximal deficit usually develops within 2 weeks. Quadriplegia occurs in severe cases. Although sensory complaints are typically inconspicuous, clinical examination shows sensory deficits. The Achilles reflex is typically lost, and other tendon reflexes may be depressed also; however, in some instances, evidence of central involvement is manifested by brisk tendon reflexes. Cranial nerve function is typically spared. With time, there may be improvement in the peripheral neuropathy, but upper motor neuron involvement then becomes unmasked and often determines the prognosis for functional recovery. There is no specific treatment to arrest progression or hasten recovery.

Neuropathological studies in experimental organophosphate-Induced delayed polyneuropathy have evidenced that the primary lesion is a bilateral degenerative change in distal levels of axons and their terminals, primarily affecting larger/longer myelinated central and peripheral nerve fibers, leading to breakdown of neuritic segments and the myelin sheaths[8]. OPIDP is not related to AChE inhibitionbut it is due to inhibition of an esterase, present in nerve tissues as well as other tissues (e.g., lymphocytes), named neuropathy target esterase (NTE). Several organophosphates, depending on their chemical structure, caninhibit NTE, as do some non-organophosphates, such as certain carbamates and sulfonyl fluorides. Phosphorylation of NTE by organophosphates is similar to that observed for AChE. However, only organophosphates whose chemical structure leads to aging of phosphorylated NTE can cause OPIDP. Other compounds that inhibit NTE but cannot undergo the aging reaction are not neuropathic, indicating that inhibition of NTE catalytic activity is not the mechanism of axonal degeneration, and that the aging of NTE is a key event in the initiation of OPIDP[9]. For organophosphate-Induced delayed polyneuropathy to be initiated, phosphorylation and subsequent aging of at least 70% of NTE is necessary, and this two-step process occurs within hours of poisoning. When the first clinical signs of organophosphate-Induced delayed polyneuropathy are evident some weeks later, NTE activity has recovered.Measurement of lymphocyte NTE has been used to monitor occupational exposure and predict the occurrence of neuropathy.

Despite these recent advances, the most crucial issues in the mechanisms of OPIDP development and progression remain obscure; indeed, though reductions in axonal transport have been found to precede overt clinical signs, the exact chain of events occurring between phosphorylation and aging of NTE and axonal degeneration is still unknown. Several epidemics of organophosphate-Induced delayed polyneuropathy have occurred in the past, but its occurrence in humans is now rare, since before commercialization OPs must undergo specific neurotoxicity testing in the hen (one of the most sensitive species) to determine whether organophosphate-Induced delayed polyneuropathy is produced[10].The prognosis for functional recovery depends on the degree of pyramidal involvement with paralysis and ataxia representing a permanent outcome of severe organophosphate-Induced delayed polyneuropathy[7,11,12]. It appears that clinical signs of organophosphate-Induced delayed polyneuropathy in children are considerably milder than in adults.Medical treatment of OPIDP in humans is symptomatic. Standard treatment used for management of organophosphate poisoning comprising atropine and pralidoxime was not effective in treatment of organophosphate-Induced delayed polyneuropathy . No specific treatment exists to prevent occurrence of the neuropathy following exposure in humans.

CONCLUSION-

From the review it is clear that organophosphatespoisoning not only causes acute cholinergic manifestations but can also lead to organophosphate-Induced delayed polyneuropathy. It is therefore recommended that, every patient of organophosphates poisoning should be followed up for atleast one month. Further research is needed in this area for prevention of organophosphate-Induced delayed polyneuropathy following organophosphates exposure and its effective management.

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