Case Report

Reversible Parkinsonism in Profofenos and Cypermethrin compound poisoning – A Case Report

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Abstract

Organophosphorus insecticide (OPI) poisoning is a major health problem in India. These are irreversible inhibitors of acetyl cholinesterase which produce a well-established triphasic effect. The first phase which is a cholinergic phase due to increased action of acetylcholine at muscarinic, nicotinic and central nervous system synapses produces symptoms like Miosis, Blurred Vision, Nausea, Vomiting, Diarrhea, Salivation, Lacrimation, Bradycardia, Abdominal Pain (Muscarinic), Fasciculations, Paralysis, Pallor, Muscle Weakness, Hypertension, Tachycardia, Mydriasis (Nicotinic), Confusion, Toxic Psychosis, Seizure, Fatigue, Respiratory Depression, Dysarthria, Unconsciousness, Ataxia, Anxiety (Central Effects). The second phase is intermediate syndrome which sets in 2-4 days after initial exposure, the signs and symptoms comprise of muscle fasciculations and neuromuscular paralysis involving the respiratory, bulbar and limb muscles. The third phase is Organophosphorus Induced Delayed Polyneuropathy (OPIDN), which is often noted after 7-21 days of exposure, initial symptoms include paraesthesias, pain in calves, foot drop etc. In addition, extrapyramidal manifestations are also described after acute organophosphorus poisoning such as Dystonia, Rest Tremors, Cog Wheel Rigidity And Choreathetosis. Cypermethrin is a synthetic pyrethroid used as an insecticide. Studies suggested that long term exposure to cypermethrin induces nigrostriatal dopaminergic neurodegeneration in adult rats. Acute ingestion of cypermethrin will cause nausea, vomiting, stomach pain, convulsions, coma and death in humans. The etiology of parkinsonism is multi factorial with genetic, environmental and toxic determinants, development of typical parkinsonism after brief exposure to organophosphorus compounds is a rare phenomena and there are only few reports in literature. We report a 40 year old female who presented with cholinergic crisis following acute ingestion of Profofenos and Cypermethrin mixed compound, developed

parkinsonism on day 5 of admission and recovered completely after 2 days of treatment with Amantidine.

Key words

Organophosphorus insecticide, Profofenos, Cypermethrin, Parkinsonism, Amantidine.

Introduction

Organophosphorus insecticide (OPI) refers to heterogeneous group of chemical compounds with an ability to inhibit the enzymes, acetyl cholinesterase (AChE) and neuropathy target esterase. The action of OPI on AChE results in accumulation of acetylcholine and over stimulation of Acetylcholine receptors in the synapses results of Autonomic Nervous System (ANS), Neuro-Muscular Junctions, and Central Nervous system(CNS) which results in nicotinic, muscarinic and central effects [1]. The first phase which is a cholinergic phase due to increased action of acetylcholine at muscarinic, nicotinic and central nervous system synapses produces symptoms like Miosis, Blurred Vision, Nausea, Vomiting, Diarrhoea, Salivation, Lacrimation, Bradycardia, Abdominal Pain (Muscurinic), Fasciculations, Paralysis, Pallor, Muscle Weakness, Hypertension, Tachycardia, Mydriasis (Nicotinic), Confusion, Toxic Psychosis, Seizure, Fatigue, Respiratory Depression, Dysarthria, Unconsciousness, Ataxia, Anxiety (Central). The second phase is intermediate syndrome which sets in 2-4 days after initial exposure, the signs and symptoms comprise of muscle fasciculations and neuromuscular paralysis involving the respiratory, bulbar and limb muscles. The third phase is Organophosphorus Induced Delayed Polyneuropathy (OPIDN), which is often noted after 7-21 days of exposure, initial symptoms include paraesthesia, pain in calves, foot drop etc. In addition, extrapyramidal manifestations are also described after acute organophosphorus poisoning such as dystonia, rest tremors, cog wheel rigidity and choreathetosis. Profofenos is a widely used organophosphate insecticide which may undergo rapid aging of AchE. Cypermethrin is a class II pyrethroid pesticide, used to control insects in the household and agricultural fields. It crosses the blood-brain barrier and induces neurotoxcity and motor defecits. Cypermethrin cause neurotoxicity by the following mechanisms: 1) By hyper-excitation of central nervous system by extending the opening of Sodium (Na) channels in the CNS leading to hypopolarization and hyper-excitation of the neurons [14, 15, 16]. 2) By modulating the levels of GABA (Gamma Amino Butyric Acid) [17]. 3) Cypermethrin readily enters the brain and induces oxidative stress leading to dopaminergic toxicity [18] (**Table – 1**). Since oxidative stress critically contributes to the nigrostriatal dopaminergic neurodegeneration, cypermethrin could be considered as one of the most relevant pesticides, which possibly implicated in Parkinson's disease (PD) pathogenesis [19]. An altered level of dopamine and its metabolites is reported in animals, which were exposed to cypermethrin for short-term study. Low doses of cypermethrin (5 and 10 mg/kg body weight) did not alter the major indices of the nigrostriatal dopaminergic neurodegeneration in adult animals [19]. Alteration in the levels of dopamine and its metabolites and loss of tyrosine hydroxylase positive cells in the nigrostriatal tissues and impaired motor behavior was observed in the animals after prolonged exposure to cypermethrin at moderate doses [19, 20]. GABA is one of the most common targets of class II pyrethroids, including cypermethrin and regulates the chloride channels. Cypermethrin suppresses the open state of voltage-gated chloride channels and inhibits GABA dependent uptake of chloride ions [21, 22], leading to hyper-excitability and neurotoxicity symptoms [23].

GABA neurotransmitter is one of the most predominating neurotransmitters, which regulates chloride channels in brain.

Cypermethrin effectively suppressed the open state of voltage-gated chloride channel and inhibits GABA dependent chloride uptake at higher concentrations [22, 23, 24]. Cypermethrin mediated inhibition of chloride channel is known to produce minor tremors, depression, grinding of teeth, hyperesthesia, spastic paralysis and sunken eyes, etc., in a dose dependent manner [23]. Cypermethrin mediated neurotoxicity seems to arise from excitability disturbance is further evidenced from its ability to inhibit the activity of acetyl cholinesterase maximally in the brain as compared with other organs leading to decreased cholinergic transmission and consequent accumulation of neurotransmitter acetylcholine resulting in the termination of nerve impulses [25]. Cypermethrin alters the activity of delayed-rectifier voltage-dependent potassium channel and potassium ion transport across synaptosomes, which regulate the neuronal excitability and ultimately leads to neurotoxicity [26, 27]. Potassium current is one of the main targets of cypermethrin, which causes neurotoxic effects in many neurons [28]. Cypermethrin mediates neurotoxicity owing to its potential to modify the performance of potassium channel leading to an alteration in the activation potential. Delayed rectifier voltage-dependent potassium channel regulates diverse aspects of neuronal excitability. Cypermethrin delays the function of this channel at lower concentrations; however, at higher concentrations, it inactivates potassium current [28].

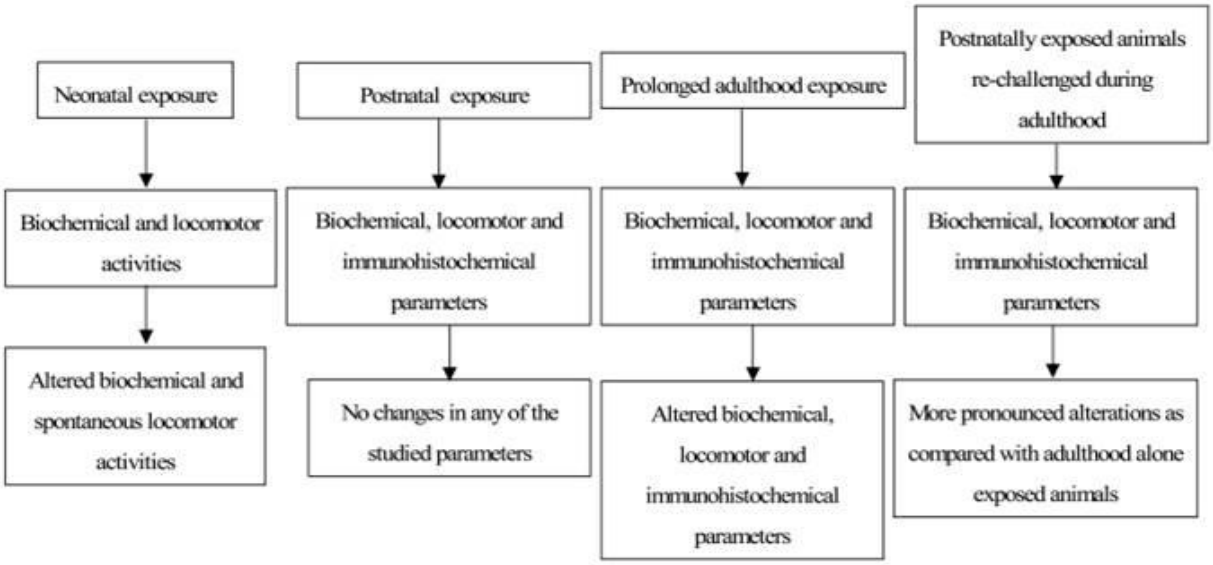
Table – 1: Cypermethrin mediated Adult Neurotoxicity [17, 8, 19].

Model animal	Dose and Route of Exposure	Exposure Time	Neurotoxic Effects
Sprague-Dawley rats [18]	15 mg/kg, oral	15 days	No change in the dopaminergic neuronal system
	75 mg/kg, oral		Induced appearance of abnormal behavior i.e., severe convulsive movement, salivation after a few hours of exposure
	15 mg/kg, oral to 6-OHDA pre-exposed		Reduced the number of dopaminergic neurons in the substantia nigra and number of forepaw adjusting steps
Wistar rats [17]	145 mg/kg and 14.5 mg/kg, oral	One dose	Ataxia after a few hours of exposure Potentiated the pentobarbitone-induced sleeping time Enhanced convulsion in pentylenetetrazole co-treated rats
Wistar rats [19]	15 mg/kg, intraperitoneal	Twice a week for 12 weeks, 24 doses	Decreased locomotor activity, dopamine and its metabolites levels and tyrosine hydroxylase-positive cells. No change in serotonin level and glutamic acid decorbaxylase-positive cells in the nigrostriatal tissues.

The salient findings which have shown the effects of cypermethrin in nigrostrial dopaminergic pathways were as per **Figure – 1**. The oxidative stress is implicated in the cypermethrin mediated neurotoxicity. The major contributors of oxidative stress are excessive production of Reactive Oxygen Species (ROS) and reactive nitrogen species in the cells or tissues exposed to cypermethrin or reduced level of components of the antioxidant machinery.

Cytochrome P450 2E1 (CYP2E1) is recognized as one of the major contributors involved in cypermethrin metabolism leading to generation of ROS and oxidative stress via mixed function oxidase [20, 29, 32].

Figure – 1: The salient findings which have shown the effects of cypermethrin in nigrostrial dopaminergic pathways [5, 19, 20, 31].



Amantidine, a Glutamate (non-competitive inhibitor of NMDA receptor) antagonist and Dopamine facilitator. It is developed as an antiviral drug for prophylaxis of influenza A2, it was found serendipitiously to benefit parkinsonism. It acts rapidly but has lower efficacy than levodopa, which is equivalent to or higher than anticholinergics. Amantidine may act both presynaptically and postsynaptically. Presynaptically, it enhances the release of stored catecholamines from intact dopaminergic terminals by an amphetamine like mechanism [36], and also inhibits the reuptake of catecholamines in the presynaptic termina. Post synaptically it directly activates dopamine receptor [36] and can produce changes in DA receptor conformation that fixates the receptor in a high affinity (agonist like) configuration [36]. About 2/3rd patients derive some benefit. However, tolerance develops over months and the efficacy is gradually lost. Amantadine promotes presynaptic synthesis and release of DA in the brain and has anticholinergic property. These were believed to explain all its beneficial effect in parkinsonism. However, an antagonistic action on NMDA type of glutamate receptors, through which the striatal dopaminergic system exerts its influence is now considered to be more important.

Case report

A 40 year female presented to the emergency department with a history of consumption of unknown quantity of Organophosphorus compound (profofenos 40% and cypermethrin 4%) with complaints of vomiting, profuse sweating, increased salivation and altered sensorium. On examining the patient her B.P was 100/60 mmHg, pulse - 98/min, Temp - 98.5 ^{0}F, pupils-pinpoint with normal vesicular breath sounds and normal heart sounds. The patient was admitted and treated with Inj. Atropine 2 mg I.V. every 15 min till signs of atropinisation were seen and Inj. PAM (PRALLIDOXIME) 1.5 g in 100 ml normal saline given over 30 min in the first Day followed by 1.5 g over 1 hour for 2 days.

On Day 2 - Patient was conscious and irritable with no signs and symptoms of cholinergic crisis and with normal vitals. All the blood

investigations were normal except for decrease in S. Cholinesterase levels - 148 U/L (normal - 1080-3040 IU/L). Complete blood picture – Hemoglobin - 11.2 g/dl, RBC Count - 2.5 millions/micro litre, Total WBC count - 8500/ microliter, Platelet count - 2.5 Lakhs/micro litre with normocytic normochromic blood picture Blood Urea – 28 mg/dl, S. creatinine - 0.8 mg/dl, Random Blood Sugar - 114 m Eq/L, S. Sodium - 114 m Eq/L, S. Potassium - 3.0 mEq/L, S. Chloride-94 mEq/L and Liver function tests were with in normal limits, ECG – WNL, X-Ray Chest Pa View – NAD.

On Day 3 - Patient developed dysphagia, aphonia and quadriparesis (LMN type). On examination, Intellectual Functions were normal, all the cranial nerves were normal, there was no vocal cord palsy, all deep tendon reflexes were normal and there were no fasciculations. Plantars had flexor response.

On Day 5 - Patient developed rigidity, bradykinesia, tremors in both hands. On examination, she had an expressionless face, monotonous speech, decreased rate of eye blinking, resting tremors in both hands and cog wheel rigidity which are the features of Parkinsonism. Bilateral Deep tendon reflexes were normal and with flexor plantar response. Hence, we diagnosed the case as Parkinsonism secondary to OP Compound or Cypermethrin Exposure. The patient was treated with Tab. Amantidine 100 mg T.I.D, and the patient was completely recovered from the symptoms in 2 days of duration.

Discussion

This patient, who ingested Organophosphorus and cypermethrin compound manifested parkinsonism-like features on day 5 and recovered completely with 2 days of treatment with Amantidine. There was no family history of Parkinsonism, so we attribute her extrapyramidal manifestations to acute OPI and Cypermethrin exposure. The central nervous system manifestations of acute OPI exposure are anxiety, restlessness, ataxia, convulsions, respiratory depression, and coma, apart from the usual neurological complications. Neurological manifestations of OPI exposure may also include choreoathetosis, opisthotonos, torticollis, facial grimacing, tongue protrusion, extrapyramidal symptoms, and typical parkinsonism [6, 7, 8]. Parkinsonism following OPI exposure was first reported in 1978 by Davis, et al. [9]. In 1999 Bhatt, et al. [8] reported five patients with OPI-induced parkinsonism, among whom four cases occurred following exposure to OPI. The excessive acetylcholine activity due to prolonged and irreversible inhibition of acetyl cholinesterase during OPI poisoning may alter the dopamine activity within the basal ganglia and substantia nigra, resulting in the exposed person exhibiting parkinsonism-like features [6]. Bhatt, et al. [8] suggested that the lack of response to levodopa–carbidopa in their patients might imply dopamine receptor blockade rather than mere deficiency of dopamine production [8]. OPI-induced acute parkinsonism is a reversible phenomenon. The drugs reported to be effective in case reports of OPI-induced parkinsonism are bromocriptine, benzhexol [10], amantadine [11, 12], and biperidine [13]. According to Bhatt, et al. [8], levodopa was not effective in the treatment of OPI-induced parkinsonism in their series. Cypermethrin induced nigrostriatal neurodegeneration follows the slow and progressive neurodegeneration. The main mechanism implicated in the nigrostriatal dopaminergic neuronal death has been oxidative stress and cypermethrin also induces oxidative stress [4, 19, 20, 29]. Cypermethrin induces the nigrostriatal dopaminergic neurodegeneration and behavioral deficits, as the result of slow and progressive loss of dopaminergic neuronal cells, one of the specific hallmarks of sporadic PD [31]. Cypermethrin like rotenone, causes neurotoxicity in many parts of brain, however, its preferential target in the nigrostriatal region remains dopaminergic neurons [19]. This drawback is not only for cypermethrin, as non-selective responses of Paraquat, MPTP and 6-OHDA due to mitochondrial injury result into lesions in many parts of the brain, including

hippocampus, in addition to the nigrostriatal dopaminergic neurons [32, 33, 35]. Cypermethrin induces neurodegeneration only after long-term exposure (12 weeks), if it mimics with sporadic etiology at molecular and epidemiological levels, the system could be more relevant to humans as compared with other model systems [19, 31].

Conclusion

Organophosphate and cypermethrin compounds poisoning inducing Parkinsonism is very rare. Here, we are reporting a case which presented with parkinsonism after 3 days of Organophosphate and cypermethrin compound poisoning. THE Clinical features of parkinsonism are completely resolved after treatment with Amantidine 100 mg T.I.D. for 2 days.

References

1. Birinder S. Paul, Gagandeep Singh. Neurology in Tropics. 2nd edition. Jagjit S. Chopra, Inder M.S. Sawhney; 2016, Chapter 43, Organophosphorous poisoning; p. 473-482.
2. Wadia RS, Sadagopan C, Amin RB, Sardesai HV. Neurological manifestations of Organophosphorus insecticide poisoning. J Neurol Neurosurg Psychiatry, 1974; 37: 841–7.
3. Kirby ML, Castagnoli K, Bloomquist JR. In vivo effects of deltamethrin on dopamine neurochemistry and the role of augmented neurotransmitter release. Pestic. Biochem. Physiol., 1999; 65: 160–168.
4. Kale M, Rathore N, John S, Bhatnagar D. Lipid peroxidative damage on pyrethroid exposure and alterations in antioxidant status in rat erythrocytes: a possible involvement of reactive oxygen species. Toxicol Lett., 1999 Apr 12; 105(3): 197-205.
5. Nasuti C, Gabbianelli R, Falcioni ML, Di Stefano A, Sozio P, Cantalamessa F. Dopaminergic system modulation, behavioral changes, and oxidative stress after neonatal administration of pyrethroids. Toxicology, 2007 Jan 18; 229(3): 194-205.
6. Hsieh BH, Deng JF, Ger J, Tsai WJ. Acetylcholinesterase Inhibition and the Extrapyramidal Syndrome: A Review of the Neurotoxicity of Organophosphate. Neuro Toxicology, 2001; 22: 423-7.
7. Karunanithi K, Annadurai A, Krishnamoorthy M, Elumalai P, Manivasagam T. 1-methyl 4 -phenyl 1,2,3,6-tetrahydropyridine is a potent neurotoxin: Gamma-tocopherol recuperate behavior, dopamine, and oxidative stress on Parkinsonic mice. Int J Nutr Pharmacol Neurol Dis., 2011; 1: 139-45.
8. Bhatt MH, Elias MA, Mankodi AK. Acute and reversible Parkinsonism due to organophosphate pesticide intoxication: Five cases. Neurology, 1999; 52: 1467-71.
9. Davis KL, Yesavage JA, Berger PA. Single case study: Possible organophosphate-induced Parkinsonism. J Nerv Ment Dis., 1978; 166: 222-5.
10. Joubert J, Joubert PH. Chorea and psychiatric changes in organophosphate poisoning. A report of 2 further cases. S Afr Med J., 1988; 74: 39-40,
11. Shahar E, Andraws J. Extra-pyramidal Parkinsonism complicating organophosphate insecticide poisoning. Eur J Paediatr Neurol., 2001; 5: 261-4.
12. Muller-Vahl KR, Kolbe H, Dengler R. Transient severe Parkinsonism after acute organophosphate poisoning. J Neurol Neurosurg Psychiatry, 1999; 66: 253-4.
13. Arima H, Sobue K, So M, Morishima T, Ando H, Katsuya H. Transient and reversible Parkinsonism after acute organophosphate poisoning. Clin Toxicol., 2003; 41: 67-70.
14. Eells JT, Dubocovich ML. Pyrethroid insecticides evoke neurotransmitter release from rabbit striatal slices. J.

Pharmacol. Exp. Ther., 1988; 246: 514–521.

15. Narahashi T, Frey JM, Ginsburg KS, Roy ML. Sodium and GABA-activated channels as the targets of pyrethroids and cyclodienes. Toxicol. Lett., 1992; 64: 429–436.
16. Kirby ML, Castagnoli K, Bloomquist JR. In vivo effects of deltamethrin on dopamine neurochemistry and the role of augmented neurotransmitter release. Pestic. Biochem. Physiol., 1999; 65: 160–168.
17. Manna S, Bhattacharyya D, Mandal TK, Dey S. Neuropharmacological effects of alfa-cypermethrin in rats. Indian J. Pharmacol., 2005; 37: 18–20.
18. Mun JY, Lee WY, Han SS. Effects of cypermethrin on the dopaminergic neurons in the progressive hemiparkinsonian rats. Toxicol. Mech. Methods, 2005; 15: 399–404.
19. Singh AK, Tiwari MN, Upadhyay G, Patel DK, Singh D, Prakash O, Singh MP. Long-term exposure to cypermethrin induces the nigrostriatal dopaminergic neurodegeneration in adult rats: Postnatal exposure enhances the susceptibility during adulthood. Neurobiol. Aging., 2012; 33(2): 404-15.
20. Tiwari MN, Singh AK, Israr A, Upadhyay G, Singh D, Patel DK, Singh C, Prakash O, Singh MP. Effects of cypermethrin on monoamine transporters, xenobiotic metabolizing enzymes and lipid peroxidation in the rat nigrostriatal system. Free Radic. Res., 2010; 44: 1416–1424.
21. Bloomquist JR, Soderlund DM. Neurotoxic insecticides inhibit GABA-dependent chloride uptake by mouse brain vesicles. Biochem. Biophys. Res. Commun., 1985; 133: 37–43.
22. Ray DE, Sutharsan S, Forshaw PJ. Actions of pyrethroid insecticides on voltage-gated chloride channels in neuroblastoma cells. Neurotoxicology, 1997; 18: 755–760.
23. Ullah MS, Ahmad M, Ahmad N, Khan MZ, Ahmad I. Toxic effects of cypermethrin in female rabbits. Pakistan Vet. J., 2006; 26: 193–196
24. Burr SA, Ray DE. Structure-activity and interaction effects of 14 different pyrethroids on voltage-gated chloride ion channels. Toxicol. Sci., 2004; 77: 341–346.
25. Marigoudar SR, Ahmed RN, David M. Cypermethrin induced respiratory and behavioural responses of the freshwater teleost, Labeo rohita (Hamilton) Veterinarski Arhiv., 2009; 79: 583–590.
26. Murakoshi H, Trimmer JS. Identification of the Kv2.1 K channel as a major component of the delayed rectifier K current in rat hippocampal neurons. J. Neurosci., 1999; 19: 1728 –1735.
27. Rao GV, Rao KS. Modulation of K+ transport across synaptosomes of rat brain by synthetic pyrethroids. J. Neurol. Sci., 1997; 147: 127–133.
28. Peele DB, Crofton KM. Pyrethroid effects on schedule-controlled behavior: time and doses relationship. Neurotoxicol. Teratol., 1987; 9: 387–394.
29. Giray B, Gurbay A, Hincal F. Cypermethrin-induced oxidative stress in rat brain and liver is prevented by Vitamin E or allopurinol. Toxicol. Lett., 2001; 18: 139–146.
30. Anwar K. Cypermethrin, a pyrethroid insecticide induces teratological and biological changes in young chick embryos. Pakistan J. Biol. Sci., 2003; 6: 1698–1705.
31. Singh AK, Tiwari MN, Dixit A, Upadhyay G, Patel DK, Singh D, Prakash O, Singh MP. Nigrostriatal proteomics of cypermethrin-induced dopaminergic neurodegeneration: Microglial activation dependent and

independent regulations. Toxicol. Sci., 2011; 122: 526–538.

32. Calo M, Iannone M, Passafaro M, Nistico G. Selective vulnerability of hippocampal CA3 neurones after microinfusion of paraquat into the rat substantia nigra or into the ventral tegmental area. J. Comp. Pathol., 1990; 103: 73–78.
33. Acuna-Castroviejo D, Coto-Montes A, Gaia Monti M, Ortiz GG, Reiter RJ. Melatonin is protective against MPTP-induced striatal and hippocampal lesions. Life Sci., 1997: 60: 23–29.
34. Winnicka MM, Wisniewski K. Bilateral 6-OHDA lesions to the hippocampus attenuate the facilitatory effect of CCK-8 us and caerulein on memory in rats. Pharmacol. Res., 2000; 41: 347–353.
35. Chen Q, Niu Y, Zhang R, Guo H, Gao Y, Li Y, Liu R. The toxic influence of paraquat on hippocampus of mice: involvement of oxidative stress. Neurotoxicology, 2010; 31: 310–316.
36. Joseph Jancovic, Eduardo Tolosa. Parkinson's Disease & movement Disorders. 6th edition, Philadelphia. Wolters Kluwer; 2015, Chapter 10, Pharmacological Management of Parkinson's disease; p. 99-100.