Effectiveness of Combination of Atropine and Glycopyrrolate in the Treatment of Mixed Organophosphorus Poisoning

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Citation

Abstract
A 17 year old boy was brought to emergency department of medicine with alleged history of consumption of mixture of pesticide fenvalerate (20%) with methyl parathion (50%). We reported this case to show effectiveness of atropine and glycopyrrolate combination in the treatment of mixed poisoning which showed better efficacy than atropine alone.

INTRODUCTION
The commonly used household products and pesticides reported in accidental and nonaccidental poisoning include organochlorines, organophosphates, carbamates, pyrethroids, nitrophenols and chlorophenols. Although the large majority of all pesticides are used in the developed world, 99% of all acute pesticide poisoning occurs in developing countries. Attempted suicide accounts for two thirds of all pesticide poisoning fatalities. Acute organophosphorus poisoning is a major clinical and public health problem in developing countries. It accounts for two-third of deaths of all pesticide poisoning. This more in regions where highly toxic pesticides (WHO class I toxicity) are available like Pakistan, India, Srilanka and other developing countries. In India OP compounds cause death in southern and central India. Symptoms of OP poisoning includes salivation, sweating, bradicardia, vomiting, nausea, abdominal pain, urinary incontinence, blurred vision, miosis, anxiety, tremors, fasciculation hyperreflexia, coma etc. The standard treatment involves initial supportive measures followed by gut decontamination and intravenous administration of atropine and pralidoxime.

Pyrethrum and synthetic pyrethrin derivatives belongs to class of insecticides are used in many household and agricultural insecticides and are variously presented as powders, sprays, mosquito coils, and solutions for wood treatment. Generally, pyrethroids are considered safe for human use because of their selective toxicity to the insect nervous system, relatively low toxicity for mammals, poor dermal absorption, and rapid metabolism with little tissue accumulation. Pyrethroid ingestion gives rise within minutes to a sore throat, nausea, vomiting and abdominal pain. There may be mouth ulceration, increased secretions and/or dysphagia. Systemic effects occur 4-48 hours after exposure. Dizziness, headache and fatigue are common, and palpitations, chest tightness and blurred vision less frequent. Coma and convulsions are the principal life-threatening features. Most patients recover within 6 days. Fatal pyrethroid poisoning reports are not common in the toxicology literature. Only a few severe systemic life-threatening pyrethroid-induced illnesses have been reported in developing countries. In recent times, incidence of consumption of these commonly used household insecticides has increased dramatically for suicidal attempts in the developing countries like Nepal and India. The unauthorized pyrethroid/organophosphate mixtures marketed in some developing countries may precipitate human poisoning. Mixing of pesticides not only compromises the safety of marketed insecticides or pesticides but may also pose a clinical diagnostic dilemma. More over treatment given to the patient may be affected due to wrong diagnosis. Reports on management of pesticide mixed poisoning is rarely available. It needed in develop countries like India for proper management of such cases. Here we presented case pesticide mixed poisoning methyl parathion with fenvalerate managed successfully with atropine and glycopyrrolate.
CASE REPORT
A 17 yr old boy was admitted with following alleged consumption of around 250 ml pesticide mixture fenvalerate (20%) with methyl parathion (50%) around 9pm. Immediately with in a hour he was induced vomiting with soap & salt water and taken to the near by hospital where stomach wash was given. Patient has developed general tonic colonic seizures of 2-5 episodes each lasting for about 2 minutes. Injection diazepam, Injection pralidoxime and Injection atropine was given and referred higher center for further management. At the time of admission in this patients was unconscious, not obeying commands, but responding to painful stimuli. Pupils were 2mm, but non reactive to light. Pulse rate was 114/min and blood pressure was 130/80mmHg. Systemic examination was unremarkable. Blood investigations showed normal RFT, LFT but very low cholinesterase levels viz.132 IU/L. The assessment of clinical severity showed that the patient had GCS(Glasgow coma scale) score of 8, APACHE (Acute Physiologial and Chronic Health Evaluation) score of 13 and PSS (Poisoning Severity Score) of 3 with predicted mortality rate of 17%. He had received bowel wash along with single dose of pralidoxime and atropine. Injection diazepam also given for General tonic colonic seizures. In this hospital he was started with injection atropine, injection pralidoxime 1g/6th hourly along with injection ceftriaxone 2g OD and medzolam injection 1ml/hour On the third day ABG showed carbon dioxide retension and saturation was also dropped. He was electively intubated and mechanically ventilated. He was in atropine induced delirium with target heart rate of more than 120. So the dose was reduced and along with glycopyrolate was started from the third day simultaneously with atropine at the rate of 1ml/hour. After 2 days ABG improved he was slowly weaned off from ventilator. Atropine and glycopyrolate were gradually tapered over the period of 2 weeks. Oral feeds were gradually started at the end of second week. Psychiatric consultation was given and started with stalopam 5mg (Citalopram). He was discharged with after asking opinion from the psychiatrist. Patient was reviewed after 2 weeks and stalopam was continued for another week.

DISCUSSION
Pyrethroid insecticides are widely used, but there have been relatively few reports of systemic poisoning. Pyrethrum is regarded as the safest of the insecticides because of its high selectivity and toxicity for the insect nervous system and minimal dermal absorption. These reports have, however, shown that pharmacotherapy is difficult and that the duration of poisoning can be unexpectedly long. Pyrethroids are ion channel toxins prolonging neuronal excitation, but are not directly cytotoxic. Two basic poisoning syndromes are seen. Type I pyrethroids produce reflex hyperexcitability and fine tremor. Type II pyrethroids produce salivation, hyperexicity and seizures. Both produce potent sympathetic activation. The mechanisms by which pyrethroids alone are toxic are complex and become more complicated when they are co-formulated with either piperonyl butoxide or an organophosphorus insecticide, or both, as these compounds inhibit pyrethroid metabolism. The main effects of pyrethroids are on sodium and chloride channels. Pyrethroids modify the gating characteristics of voltage-sensitive sodium channels to delay their closure. A protracted sodium influx (referred to as a sodium 'tail current') ensues which, if it is sufficiently large and/or long, lowers the action potential threshold and causes repetitive firing; this may be the mechanism causing paraesthesia. Organophosphorus compounds are highly potent inhibitors of acetylcholinesterase and these Carbamoyl esterase inhibitors can enhance pyrethroid toxicity in high-dose experimental studies. Hence, the unauthorized pyrethroid/organophosphate mixtures marketed in some developing countries may precipitate human poisoning. Fenvalerate is a synthetic pyrethroid insecticide of moderate to low acute toxicity. An in vitro study has shown that the calcium channel blockade may cause some of the chronic effects of low-level pyrethroid poisoning. However; existing data neither support nor conclusively refute the hypothesis that its effects on voltage-sensitive calcium channel are important in acute pyrethroid-induced neurotoxicity.

Fenvalerate is the first synthetic pyrethroid having no cyclopropane ring in the molecule. It has four stereoisomer and the composition is approximately 1:1:1:1 (racemic) for each isomer. It is type II pyrethroid belongs to WHO class II which is moderate to low acute oral toxicity and LD50 values of this compound differ considerably (82 to >3200 mg/kg) according to animal species. But methyl parathion was highly toxic OP compound belongs WHO class 1a with high lethality. Methyl parathion is highly toxic via the oral route, with reported oral LD50 values of 6 to 50 mg/kg in rats, 14.5 to 19.5 mg/kg in mice, 420 mg/kg in rabbits, 1270 mg/kg in guinea pigs and 90 mg/kg in dogs.

As illegal mixing of compounds in insecticides is becoming
more prevalent, more cases of mixed poisoning will occur. He et al., have shown that a 2-hour exposure to organophosphates, alone or in combination with pyrethroids, will inhibit acetylcholine esterase to a similar extent. Because organophosphates are more potent than pyrethroids mixing of pesticides not only compromises the safety of marketed insecticides or pesticides but may also pose a clinical diagnostic dilemma. The presentation of seizure disorder suspected case of pure organophosphate poisoning should raise the suspicion of the presence of other agents. In this case patient was consumed fenvalerate with organophosphorus compounds. It is a synthetic pyrethroid insecticide of moderate to low acute toxicity. There have been no reports of poisoning in the general population. Experimental studies in animals suggest that neurological signs and symptoms, such as ataxia, tremors, and convulsions, could occur after massive over-exposure or accidental ingestion. But in combination with methyl parathion, the toxicity of the mixture was potentiated.

Here patient admitted with unconscious with excessive salivation and history of convulsion. His GCS score and PSS score suggested that severity of poisoning was high. Patients was treated with medzolam 1mg/ hour as to control convulsion. As patient exposed acute ingestion of organophosphorus and pyrethroid, treatment started with injection atropine, injection pralidoxime and injection medzolam for seizures. The organophosphorus are more potent than pyrethroids and also level of acetylcholinesterase value was also low. Hence the patient was started with pralidoxime and atropine therapy along with medzolam for seizures. The seizure was developed may be either synthetic pyrethroid or by the organophosphorus compound also. It may be synergistic effect of both the agents. He developed respiratory problems on third day he was mechanically ventilated. This is mainly due to effect of organophosphorus compounds and also called as intermediate syndrome usually developed after acute cholinergic crisis. Atropine was continued in this case as cholinergic symptoms were not subsided and dose of atropine gradually increased. As atropine caused delirium and tachycardia on the third day, so the dose of atropine reduced and along with glycopyrrolate was started with the dose 1mg /ml from third day to treat the cholinergic symptoms. The use of glycopyrrolate effectively controlled the cholinergic symptoms and also reduced the atropine requirement. The patient was deventilated after two days and dose of atropine and glycopyrrolate was slowly reduced. Toxic reaction to atropine results from its anti-cholinergic action and includes a variety of peripheral and central manifestations. This reaction is related to the considerable interpersonal variation in susceptibility to atropine (idiosyncrasy), so that toxic effects may occur at the usual therapeutic doses. Thus, a toxic reaction is manifested by signs of an overdose, even though the doses used were not deemed excessive. Glycopyrrolate is quaternary ammonium salt twice as potent as atropine for peripheral effects, therefore half the dosage should be given for comparable response. Penetration of glycopyrrolate across the blood-brain barrier is low and hence less associated with central manifestation. Tracey & Gallagher (1990), report using combination glycopyrrolate and atropine therapy to successfully treat two cases of acute organophosphorus poisoning. Bardin and Van Eeden compared the treatment of insecticide OP poisoning in humans with atropine versus glycopyrrolate. The ratio of atropine and glycopyrrolate was 2:1 and treatment was by continuous infusion. Treatment with atropine and glycopyrrolate was equally effective, except for a trend (not statistically significant) of fewer respiratory infections in the glycopyrrolate group.

So the treatment of atropine in combination with glycopyrrolate not only reduces dose of atropine and also reduces the central adverse effects associated with it. So combination of glycopyrrolate with atropine more beneficial when compared atropine alone and improves the quality of treatment.

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