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A CASE REPORT ON ATROPINE INDUCED PSYCHOSIS

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ABSTRACT: The administration of atropine to a large population for treatment of intoxication carries the risk of allergic or toxic reactions in a small number of patients**.** It has been reported rarely in the literatures .We describe a cases of atropine-induced psychotic disorder in a substance abused patient and different approaches of management. Dryness of the mouth, blurred vision, photophobia and tachycardia commonly occur with chronic administration of doses. In addition psychotic symptoms such as restlessness and excitement, hallucinations, delirium may occur due to atropine. This is a study of a 55 year old female patient who manifested with visual and auditory hallucination, fatigue, anxiety, headache visual disturbances and chest tightness after intake of atropine. To manage this adverse drug reaction the dose of atropine was progressively reduced to 1ml/hr and 0.5ml/hr and discontinued after appearance of signs of complete atropinization. Patient was given with IV morphine 2 mg/hr to manage agitation and IV haloperidol 5mg as required to managing the psychiatric effects. Physostigmine, scopolamine or glycopyrrolate was given in some cases as replacement of therapy in atropine-induced psychosis. In this case, symptomatic treatment is appropriate as it is substance abused patient, no long term therapy is needed for the patient and anti-cholinergic toxicity is likely to resolve within days of discontinuing the offending agent.

INTRODUCTION: Atropine is an anti-cholinergic which inhibits the muscarinic actions of acetylcholine at postganglionic parasympathetic neuroeffector sites including smooth muscle, secretory glands and CNS sites. Atropine Sulfate used as a pre-anesthetic medication in surgical patients to reduce salivation and bronchial secretions and suppress vagal activity associated with the use of halogenated hydrocarbons during inhalation anesthesia and reflex excitation arising from mechanical stimulation during surgery.

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The antispasmodic action of Atropine is useful in pylorospasm and other spastic conditions In poisoning by the organic phosphate cholinesterase inhibitors found in certain insecticides and by chemical warfare nerve gases, large doses of Atropine relieve the muscarinic-like symptoms and some of the central nervous system manifestations. The CNS effects of the atropine are Headache, flushing, nervousness, drowsiness, weakness, dizziness and insomnia.

Objective:

We describe a case of atropine-induced psychotic disorder in a substance abused patient and different approaches of treatment [1].

Case presentation:

A 55 year old male patient was admitted to the hospital with sudden onset of breathlessness and

altered sensorium. He was diagnosed as a case of accidental OPC poisoning .The medical record shows that the patient is a farmer and made a deliberate attempt of suicide after dispute with a fellow member. The amount of insecticide ingested was unknown. On admission the patient was unconscious, disoriented, had various episodes of seizure and respiratory depression. The patient was managed conservatively.

As an initial phase, primary care was given by decontaminating the patient and simultaneously the trachea was intubated. Patient was shifted to ICU and his respiration was supported with mechanical ventilation manage the respiratory distress. Continuous cardiac monitoring and pulse oximetry was established; an ECG was performed. Feature of delirium and parasympathetic shutdown was observed. Patient's vital signs revealed hypertension with BP 140/100mmHg and on observation the patient was agitated, has muscle weakness, fatigue, muscle cramps, anxiety, headache visual disturbances, tightness in chest. Supportive care was given using fluids and blood glucose level was constantly, monitored. The patient was placed in the left lateral position, with the neck extended to reduce risk of aspiration, to help keep the airway patent, and to decrease pyloric emptying and absorption of poison. As maintenance phase the patient the patient was managed with intravenous (IV) IV pralidoxime (PAM) 1g 8 hourly and anticholinergic agent (AChA) atropine with a dose of 2ml/hr after which the patient started experiencing agitation, visual and auditory hallucination, dry mouth and dilated pupils that poorly reacting to light.

All these symptoms post administration of atropine indicated anticholinergic drug induced psychosis and hence a diagnosis of atropine psychosis was considered. To manage this adverse drug reaction the dose of atropine was progressively reduced to 1ml/hr and 0.5ml/hr and discontinued after appearance of signs of complete atropinization. Patient was gradually weaned from ventilator support but required heavy sedation with IV morphine 2 mg/hr to manage agitation and other psychiatric symptoms following atropine psychosis was suspected. IV haloperidol 5mg as required managing the psychiatric effects. Atropine was stopped and the patient remained normal. The patient was discharged in a much improved condition.

The causality assessment of psychosis with atropine using Naranjo causality assessment scale and WHO-Uppsala monitoring is indicated as probable association with atropine. It showed that there is temporal relationship between drug and reaction is present.

DISCUSSION: 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 [2]. Thus, a toxic reaction is manifested by signs of an overdose, even though the doses used were not deemed excessive. The interpersonal variation in relation to atropine toxicity is demonstrated by cases of death that have been reported following doses of 100 mg or less for adults (and 10 mg for children), while on the other hand, people have recovered from intoxication with a 1 g dose of atropine [3]. Patients with Down's syndrome are abnormally sensitive to atropine [4].

Local reaction to atropine may derive from both toxic and allergic origins, which are not easily distinguishable by the clinical presentation alone [5]. In contrast to local reactions, the systemic reaction due to atropine toxicity has features that are clearly different from those stemming from anaphylactic reaction, thus the cause of the reaction can be more easily determined. Local toxic reaction to atropine includes conjunctival injection and periorbital dry, red skin. Atropine systemic toxicity causes tachycardia, tachypnea, elevated body temperature, and CNS stimulation marked by restlessness, confusion, psychotic reactions, delirium and occasionally seizures. A rash may appear on the face or upper trunk. In severe intoxication, central stimulation may cause CNS depression, coma, circulatory and respiratory failure, and death.

Adverse drug reaction is managed with either discontinue the suspected drug or continue the suspected drug with some alteration. While atropine induced psychosis is managed with

discontinuing the suspected drug, it is done by replacement of drug or discontinue the drug without any other alteration whereas continue the suspected drug, it may be dose reduced or addition of some other drug. Replacement of drug mainly done by physostigmine, scopolamine and glycopyrrolate. Antipsychotics and antidepressant can be used as treatment of atropine induced psychosis. In this case, symptomatic treatment is appropriate as it is substance abused patient, no long term therapy is needed for the patient and anti-cholinergic toxicity is likely to resolve within days of discontinuing the offending agent.

Alternative anti-muscarinic drugs:

There are several anti-muscarinic drugs, other than atropine, that can be used to treat OP intoxication. Of those, the three that have been suggested as a replacement for atropine are physostigmine, glycopyrrolate and scopolamine

Physostigmine:

Atropine induced psychosis, a test dose of physostigmine can be administered. Typically a adult patient recevices an intramuscular injection of 1mg or 2mg of physostigmine and then closely observed for 30minutes if the response is dramatic Improvement, the diagnosis is confirmed. Physostigmine has a short half life, generally less than one hour-improvement following each dose is likely to be brief duration. The drug inhibits anticholinesterase and thereby promotes the action of primary neurotransmitter, acetylcholine. The effect of physostigmine can be very complex since at any moment multiple actions of acetylcholine can occur in preganglionic, postganglionic, somatic motor and central nervous receptors [6].

Glycopyrrolate:

Glycopyrrolate is a quaternary ammo-nium anti-cholinergic agent, with anti-muscarinic activity and peripheral action similar to that of atropine. Because of the marked differences in the chemical structure of atropine and glycopyrrolate, patients allergic to atropine will most probably not be allergic to glycopyrrolate.Indications for the use of glycopyrrolate include: reduction of gastric secretion volume and acidity in patients undergoing surgical procedures, as an adjunct in the treatment of peptic ulcer, secretion reduction during anesthesia, and reversal of the effect of muscle relaxants [6]. It can also be used during pregnancy instead of atropine because it does not cross the blood-placental barrier [7]. Glycopyrrolate is twice as potent as atropine for peripheral effects, therefore half the dosage should be given for comparable response [8]. Concentration of glycopyrrolate penetrated across the blood-brain barrier is low [9]. It does not have detectable central anti-cholinergic effects at doses capable of blocking peripheral cholinergic receptor sites. The mean elimination half-life after intramuscular administration is 75.4 minutes, and almost half of the drug is excreted in pharmacologically active form in the urine within 3 hours [10].

Scopolamine:

Scopolamine is an anti-muscarinic agent with central and peripheral actions. It crosses the blood-brain barrier, and its central action differs from that of atropine in that it depresses the cerebral cortex, especially the motor areas, and produces drowsiness and amnesia.It is effective in the prevention and control of motion sickness [11].

Antipsychotics:

While dose reduction and switching antipsychotics may reduce anti-cholinergic symptoms, physicians need to be particularly sensitized to specific neurological disorders that may arise as a result of anti-cholinergic effects. On basis of diagnosis the patient was discontinued with the suspected drug and given 5 mg of haloperidol intramuscularly. Haloperidol, 0.5-2.0 mg, 1 to 4 times daily, has been accepted as the treatment of choice [12]. The use of haloperidol may result in extra-pyramidal symptoms - rigidity in both upper limb and lower limbs and oromandibular dystonia (difficulty in opening/closing of mouth and protrusion of tongue).

Neuroleptic malignant syndrome (NMS) is a life-threatening neurological emergency associated with the use of neuroleptic agents with the "typical" high potency agents (e.g., haloperidol, fluphenazine). Central dopamine receptor blockade in the hypothalamus causes hyperthermia and other signs of dysautonomia and nigrostriatal dopamine pathways leads to rigidity and tremor [13]. The other diagnosis that present similar to NMS are serotonin

syndrome, malignant hyperthermia, malignant catatonia, and other drug-related syndromes. Haloperidol was replaced by newer antipsychotic olanzapine which has similar affects on delirium in ICU patients with fewer adverse events [14].

Following the start of olanzapine, patient's symptoms resolved with complete neurological recovery.

Antidepressants:

One of Benzodiazepine is used as treatment choice for atropine induced psychosis. Diazepam can be given in doses of 5to 10mg four times a day or lorazepam 1mg once or thrice in a day intravenously. as a precautionary measures when mutiple choice of medication must be prescribed,a combination of drugs having marked anticholinergic should be avoided.

TABLE 2: DIFFERENT TREATMENT APPROACHES OF ATROPINE INDUCED PSYCHOSIS

Treatment		Dose	Side Effects
Alternative anti-muscarinic drugs			
Physostigmine		1mg or 2mg IM	vomiting, epigastric pain, miosis, salivation, sweating, lacrimation, bronchospasm
Scopolamine		0.25 mg IM	Drowsiness,amnesia, Blurred vision,dizziness,drowsiness,dry mouth,flushing,
Glycopyrrolate		1mg IM every 30-40 min or 1 mg IV bolus every 10 or 15 minutes until anti-muscarinic effects appear.	Dry mouth, vomiting, mild constipation, stuffy nose, sinus pain; or flushing (warmth, redness, or tingly feeling).
Symptomatic treatment			
Seizure and tremor	Benzodiazepines diazepam lorazepam	5to 10mg QID 1mg IV OD or TID	Shakiness and unsteady walk, unsteadiness, trembling, or other problems with muscle control or coordination
Neuroleptic malignant syndrome	Antipsychotics Haloperidol Olanazepine	0.5-2.0 mg, OD to qid 10 to 15 mg PO OD	Blurred vision,clumsiness, tremor, difficulty in swallowing

CONCLUSION: The administration of atropine to a large population for treatment of intoxication carries the risk of allergic or toxic reactions in a small number of patients. There are several anti-muscarinic drugs, other than atropine, that can be used to treat OP intoxication. Of those, the three that have been suggested as a replacement for atropine are physostigmine, glycopyrrolate and scopolamine. Benzodiazepines and antipsychotics are used as treatment choice for atropine induced psychosis.In this case, symptomatic treatment is appropriate as it is substance abused patient, no long term therapy is needed for the patient and anti-cholinergic toxicity is likely to resolve within days of discontinuing the offending agent.

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