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DIFFERENT PATTERNS OF ATROPINE INDUCED PSYCHOSIS: PROSPECTIVE OBSERVATIONAL STUDY

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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. Psychotic symptoms such as restlessness and excitement, hallucinations, delirium may occur due to atropine. There were ten patients who manifested slurred speech, flight of ideas, visual hallucinations, emotional lability, and ambivalence after intake of atropine. This was a prospective observational study to assess the incidence and other patterns of atropine-induced psychotic disorder in a substance abused patients. The incidence of ADR amounts to be 31.3 % in medicine wards. Psychosis was occurred on the day of administration of atropine and the mean duration of the ADR was found to be 2.7 days. Mean length of the hospital stay was 6.2 days which shows that ADR causes prolongation of the hospitalisation. The causality assessment of psychosis with atropine using Naranjo causality assessment scale and WHO-Uppsala monitoring is indicated as probable association with atropine and severity as moderate. The preventability was assessed by Schumock thronton scale in which most of them are not preventable. The patient was discontinued with the suspected drug. Physostigmine, scopolamine or glycopyrrolate can be given as replacement of therapy in atropine-induced psychosis. Length of the hospital was increased due to ADR. Patient who is taking higher doses causes more incidences of psychotic symptoms than others. So physician should be vigilant while prescribing the doses.

Key words: Atropine, Psychosis, Adverse drug reaction

INTRODUCTION

Atropine is an anti-cholinergic drug which is indicated for Sinus Bradycardia, Bronchospasm, Cardiac arrest, Stomach ulcer, Uveitis, Epilepsy, Sinoatrial block and Drug Toxicity. Most of the side effects of atropine are directly related to its anti-muscarinic action. Dryness of the mouth, blurred vision, photophobia and tachycardia commonly occur with chronic administration of therapeutic doses. Anhidrosis also may occur and produce heat intolerance or impair temperature regulation in persons living in a hot environment. Constipation and difficulty in micturition may occur in elderly patients. Occasional hypersensitivity reactions have been observed, especially skin rashes which in some instances progressed to exfoliation. In addition psychotic symptoms such as restlessness and excitement, hallucinations, delirium may occur due to atropine.

OBJECTIVE

We describe incidences and different patterns of adverse drug reaction of ten cases with atropine-induced psychotic disorder in a substance abused patients.

METHODOLOGY

This was a prospective observational study which was conducted over a short period of time that is 3 months at tertiary care teaching hospital in Tamilnadu, based on the atropine induced psychoses which were reported in organophosphorus poisoning cases. The approval of the institutional human ethics committee and permission from the head of the institution and the superintendent of the hospital were obtained before the commencement of the study. This study describes the patterns of adverse drug reaction of an atropine induced psychosis cases in the medical wards. All the organophosphorus poisoning cases were included. Patient used with other system of medicine were excluded. All patient related information was collected in a pre-designed case record form (CRF). The data obtained included demographic details, past history, complaints, laboratory investigation reports, diagnosis, and treatment. The patients were identified through routine ward rounds by the principal investigators. A causality analysis of was assessed by WHO-UMC and Naranjo probability score. The severity of each reported ADR was assessed using the criterion developed by modified Hartwig et al., and Siegel scale.Preventability was assessed using the Schumock and Thornton scale. Severity and preventability scores was assessed and entered in the ADR report form. Management of ADR had been analyzed.

RESULTS

A total of 34 patients were admitted during study period of 3months in the medicine wards and 2 patients were excluded as they did not fulfil the inclusion criteria. All patients included in the study were followed up daily. Drug therapy and any changes made in the same were recorded till the patient was discharged. Of the 32 patients, 12 had developed ADR. Out of total two of the patients were developed with constipation due to the pharmacology of the drug. It was not assessed in this study, because it was purely based on the atropine induced psychosis. Incomplete forms with respect to the patient's information, medication details, and inadequate description of the events were excluded from the analysis. Therefore, the incidence of ADR amounts to be 31.3 %(10/32) in medicine wards. Purely based atropine induced psychosis were rare. The reported incidence was very high compared with the other ADR studies. The suspected reactions were recorded in an ADR case report form by a clinical pharmacist for evaluation.

Table 1: patient demographics

Patient demographics	Total patients receiving atropine treatment	Patients with atropine induced psychosis
Age 15-30 31-50 >50	 11(34.4) 18(56.3) 3(9.4)	 6(54.5) 3(16.7) 1(33.3)
Gender Male Female	 17(53.2) 15(46.87)	 7(41.1) 3(20)

The gender distribution among the patients, who experienced ADRs were 7 (70%) males and 3 (30%) females. Taking the whole study population (32), males (41.1%) have experienced more number of ADRs as compared to the females (20%) population. Similarly, among study population, 34.4% were 15-30years, 56.3% were 31-50 years and 9.4% were more than 50 years respectively. In the study group of atropine induced psychosis were more patients in 15-30years age group, and they had 6patients (54.55%in users) and 3 patients (16.7%) were in 31-50 age group and 1 (33.3%in users) patient, respectively (Table1).

This was an assessment of toxic effects of atropine occurring as a result of treatment of substance. Clinical manifestations included hallucination, Agitation, restlessness, insomnia, impaired thought process, Hyperactivity and hyperthermia. On admission the patient was in organophosphorus poisoning. Patient was showed hyperthermia and varied vital signs. Patient had complaints of fever, salivation, lacrimisation, drowsiness and increased urination. On laboratory investigation it showed increased cholinesterase levels (>1500µg/ml). Patients were infused with different rate of infusion one or two days. Then patients were manifested slurred speech, flight of ideas, visual hallucinations, emotional lability, and ambivalence. It was diagnosed as atropine induced psychosis. The diagnosis of the substance induced psychosis is done by the DSM IV – TR. Prominent hallucination or delusion was present in the patient immediately after taking the atropine. No other causes of psychosis were found in patients. Agitation (6 patients) was the most

prominent symptom present in the atropine induced psychosis patients (Fig:1).

Type A (augmented) reactions are predictable through knowledge of the drug's pharmacology and are dose-dependent while by contrast Type B (bizarre) reactions are unpredictable from the known pharmacology of the drug, and do not show a clear dose response relationship. While classifying the ADR, atropine induced psychosis were found to have Type-B, Bizarre with poorly understood pharmacology.

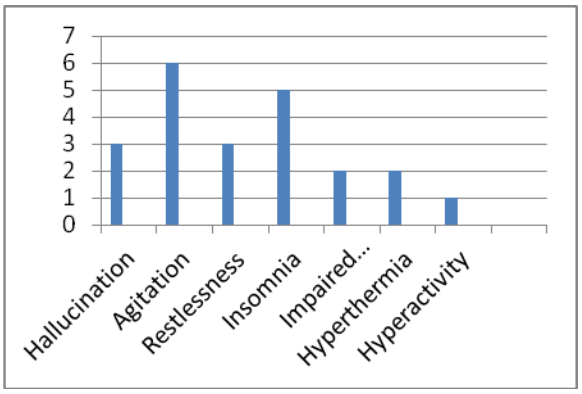

Fig 1: Symptoms of atropine induced psychosis.

Onset and duration of action were assessed in this study; Patients were infused with different rate of infusion one or two days. Then patients were manifested slurred speech, flight of ideas, visual hallucinations, emotional lability, and ambivalence within the day of administration.The mean duration of ADR was found to be 2.7days. Mean length of hospitalisation was found to be 6 days. it causes prolongation of the hospitalisation.

The causality assessment of psychosis with atropine using Naranjo causality assessment scale and WHO-UMC scale. On causality assessment using Naranjo Probability Scale, 30% ADRs were categorized as probable (score ranging from 5-8) and 70% were categorized as possible (scores ranging from 1-4) (Table 5). WHO-Uppsala monitoring centre causality assessment criteria also indicated that most of the cases are probable association with atropine.

Severity assessment was done by the hartwig's scale which classifies severity in to mild, moderate, severe based on scores from 1-2, 3-4 and 5 to 7 respectively. All of the ten cases showed severity as moderate, because it causes the prolongation of hospitalisation and scored 4 by hartwig's scale.

Preventability was assessed by Schumock and Thornton scale where the patient classified as definitely preventable, probably preventable and not preventable. Out of the ten cases, two of them showed as definitely preventable and remaining showed as not preventable.

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, scopalamine and glycopyrrolate. Antipsychotics and antidepressant can b e used as treatment of atropine induced psychosis.On recommendation the patient was discontinued with the suspected drug and given 5 mg of haloperidol intramuscularly or lorazepam 1mg once or thrice in a day intravenously. Atropine-induced psychosis was considered, and glycopyrrolate (0.2 µg/ml intravenously) was given in some cases. Within five minutes the patient returned to his normal mental status. Atropine was stopped and the patient remained normal. The patient was discharged in a much improved condition. In these cases our patient was not re-challenged atropine.

Table 2: Different patterns of atropine induced psychosis

Sl. No	Age/ sex	Complaints	Atropine	Causality	severity	preventability	seriousness	management	outcome
1	M/32	Impaired thought process, agitation, insomnia	10mg/IV/1 ml/hr	Probable	Moderate	Not preventable	Other medical condition	Discontinue suspected drug,T.lorazepam 1mg NG TID	Recovered
2	M/25	Hyperthermia, hallucination	10mg/IV/2 ml/hr	Possible	Moderate	Definitely preventable	Prolonged hospitalisation	continue suspected drug,dose reduced	Recovered
3	F/32	Agitation, restlessness, insomnia,	5mg/IV/1ml /hr	Probable	Moderate	Not preventable	Other medical condition	Discontinue suspected drug,haloperidol5mg im stat	Recovered
4	F/45	Hyperactivity ,agitation, insomnia	5mg/IV/2ml /hr	Probable	Moderate	Not preventable	Prolonged hospitalisation	Continue suspected drug,Dose reduced(1ml/hr),T.lorazepam 1mg IV OD	Recovered
5	F/37	Agitation, insomnia	1ml/hr/IV	Probable	Moderate	Not preventable	Other medical condition	Continue suspected drug,Dose reduced(0.5ml/hr then 0.2ml/hr),T.lorazepam 1mg IV OD	Recovered
6	M/25	Agitation, restlessness, insomnia	30mg/IV/2 ml/hr	Probable	Moderate	Not preventable	Other medical condition	Discontinue suspected drug,haloperidol5mg im stat	Recovered
7	M/26	Agitation, restlessness	15mg/IV/4 ml/hr	Possible	Moderate	Not preventable	Other medical condition	Discontinue suspected drug	Recovered
8	M/32	Impaired thought process	30mg/IV/1 ml/hr	Probable	Moderate	Not preventable	Other medical condition	Discontinue suspected drug,T.lorazepam 1mg NG TID	Recovered
9	M/25	Hyperthermia, hallucination	10mg/IV/2 ml/hr	possible	Moderate	Definitely preventable	Prolonged hospitalisation	Continue suspected drug,Dose reduced(0.1ml/hr then 1ml/hr),then replacement of drug.glycopyrolate0.2µg IV	Recovered
10	55/M	agitation, visual and auditory hallucination, dry mouth, dilated pupils that poorly reacting to light	2ml/hr	Probable	Moderate	Not preventable	Other medical condition	Dose reduced to 1ml/hr and 0.5ml/hr &replacement of drug with IV pralidoxime (PAM) 1g 8 hourly, IV haloperidol 5mg	Recovered

DISCUSSION

Atropine is an anti-cholinergic act by blocking the action of acetylcholine at muscarinic receptors, and also serves as a treatment for organophosphate poisoning. Adverse reactions to atropine include ventricular fibrillation, supraventricular or ventricular tachycardia, dizziness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, dry mouth and potentially extreme confusion, dissociative hallucinations and excitation especially amongst the elderly[1].

From the 32 patients, who were taking treatment, percentage of the male and female were similar; it may depend on the admissions. Since the study site was an agriculture area, the organophosphorus poisoning was more compared to the urban areas. out of 15 female patients, only 3(29.57%) were exposed to adverse drug reactions. But among 17 female patients, 7(67.64%) were exposed to the adverse drug reaction. These values are significantly showed that males are more prone to get substance induced psychosis. In this study, 28.12% of the patients were alcoholic and 71. 87% were non-alcoholic. Out of the patient with atropine induced psychosis, 5 of the male patients were alcoholic and 2 of them were non-alcoholic .None of the female patient was taking alcohol at least for once. The alcohol intake showed additive effect on the substance induced psychosis. In other studies also showed that, the data show that males present higher levels of consumption than women the case of alcohol abuse[2]. Moreover, alcohol intake is seems that substance abuse could be a risk factor for developing psychosis in males[3]. Pre-morbid psychiatric history or family history of schizophrenia put an individual at risk[4].

In study 31-50 years age group showed more number of incidences than other groups. S. Ochoa et al states that men usually develop the illness at age 18–25, while in women, the mean age of onset is 25–35.Women seem to have two peaks in the age of onset of disease: the first after menarche and the second once they are over 40[5]. However, in 1998, Castle et al. found that early-onset age distribution is similar between men and women[6].Number of studies found no gender difference in the age of onset[7].

In our study, higher incidence of the hyperactive symptoms were present in both males than females and depressive symptoms were too less in both males and females. But Morgan et al. identified a higher prevalence of depressive symptoms and lower prevalence of negative symptoms in women in a large sample of patients with psychosis[8]. Higher prevalence of depressive and anxiety symptoms in women had been found in previous studies[9, 10]. However, no gender differences were found in the study by Barajas et al. There is not a clear influence of gender in the symptoms presented in people with schizophrenia and first-episode psychosis[11]

Atropine intoxication is potentially lethal. In the most severe cases differential diagnosis with acute psychosis must be made. The diagnosis is based on clinical symptoms resulting from the inhibition of muscarinic cholinergic neurotransmission. The signs and symptoms can be stated according to the atropine equivalent dose[12] (see Table I). Usually 10mg of atropine causes psychotic symptoms than any other doses. In our study all of the patients admitted for organophosphorus poisoning got more than 10mg. 2 mg/0.7 ml is followed by 2 additional 2 mg/0.7 ml injections given in rapid succession are recommended 10 minutes after receiving the first injection if the victim develops any of the following severe symptoms: strange or confused behaviour, severe difficulty breathing or severe secretions from the lungs and airways, severe muscular twitching and general weakness, involuntary urination and defecation, convulsions or unconsciousness.3 injections of 2 mg/0.7 ml if is given the patient with severe symptoms of insecticide exposure. Severe symptoms are: strange or confused behaviour, severe difficulty breathing or severe secretions from the lungs and airways, severe muscular twitching and general weakness, involuntary urination and defecation, convulsions or unconsciousness[13].

Table 3: Signs and symptoms of anti-cholinergic poisoning according to the atropine equivalent dose[12].

Atropine dose	Signs and symptoms
0.5mg	Slight decrease of heart rate; certain mouth dryness; inhibition of sweating.
1.0mg	Definite mouth dryness; thirst; increased heart rate, occasionally preceded by decreased heart rate; mild pupillary dilation.
2.mg	Fast heart rate; palpitations; remarkable mouth dryness; dilated pupils; close vision somewhat blurry.
5.0mg	All the symptoms mentioned above but in remarkable degree; difficulty speaking and swallowing; restlessness and fatigue; cephalalgia; dry and hot skin; difficulty urinating; decreased intestinal peristaltism.
10.0mg	All the symptoms mentioned above but in even more remarkable degree; fast and weak pulse; nearly obliterated iris; very blurry vision; reddened, hot, and dry skin; ataxia; restlessness and excitation; hallucinations and delirium; coma.

The pathophysiology of the atropine induced psychosis was poorly understood. Psychosis is pharmacologically unrelated, so it is categorised as bizarre. While coming to the causality assessment, it is done by Naranjo scale and WHO UMC scale. As per the Naranjo criteria, the probability that an adverse event is related to drug therapy is classified based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships and previous patient experience with the medication. There are several previous conclusive reports for atropine induced psychosis in substance abused patients[14].The adverse reaction improved after de-challenge and worsened the condition after re-challenge. Cholinesterase level was increased during the atropine administration. In WHO UMC scale, Probable reaction is with laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge) and possible is with a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. The objective evidence was given by cholinesterase level which is found to be increased up to 6653 µg/ml.

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 b e used as treatment of atropine induced psychosis. The outcome of the reaction was found to be recovered.

CONCLUSION

The incidence of atropine induced psychosis amounts to be 31.3 % in medicine wards. Length of the hospital was increased due to ADR. Patient who is taking higher doses causes more incidences of psychotic symptoms than others. So physician should be vigilant while prescribing the doses.

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