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Research Article

AN OBSERVATIONAL STUDY OF 11 CASES OF CARTAP POISONING - A RARE POISONING

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ABSTRACT

Objective: Cartap hydrochloride poisoning is an uncommon poisoning encountered in India. The aim of this study was to assess the characteristics, severity, management, and outcome of patients with Cartap poisoning, treated with N-acetylcysteine (NAC) in intensive care unit (ICU) of a tertiary referral hospital.

Methods: This is a retrospective study where 11 cases of Cartap poisoning admitted to hospital ICU between 2011 and 2016 were identified from the case records. The demographic data, mode of ingestion, time to treat, ingested dose and severity of poisoning, presenting features, duration of mechanical ventilation (MV), dose of NAC used, complications, and outcome were noted.

Results: Patients were scored as moderate or severe cases of poisoning. Severe cases consumed >10 g, underwent gastric lavage > 4 hrs, and took Cartap concomitantly with alcohol or in empty stomach. Duration of MV varied from 68-94 hrs in severe cases and 12-48 hrs in moderate cases. Average dose of NAC in severe case was 11.19 g and moderate case was 8.89 g. The most common presenting symptoms were vomiting, altered sensorium, and breathlessness. Severe cases had more complications, and the most common complication was hypotension followed by seizures. Survival was 100%.

Conclusion: 50% of Cartap poisoning cases had good survival outcome. Severity of poisoning depends on amount of Cartap ingested, time taken for gastric lavage, and concomitant administration of alcohol. Duration of MV and dose of NAC and complications encountered correlates with the severity of poisoning.

Keywords: Cartap hydrochloride poisoning, Intensive care unit, N-acetylcysteine.

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INTRODUCTION

Cartap hydrochloride, an analog of nereistoxin, a neurotoxic substance derived from marine annelid lumbriconereis heteropoda [1], is a low toxicity insecticide commonly used in paddy fields and vegetable farming in Eastern India. It produces its toxic effects by affecting neuromuscular function [2]. It is described as high effectiveness, low residue pesticide; however, when severe can result in respiratory failure and death [3]. In India, it is available in two forms 4% granular form and 50% water soluble powder form. Although a commonly used pesticide adequate literature regarding its treatment to toxic exposure or ingestion is lacking suggesting the rarity of such cases of poisoning. Cartap is a thiocarbamate and has a chemical formula $C_7H_{16}ClN_3O_2S_2$. Cartap inhibits the [3H]-ryanodine binding to the Ca^{2+} release channel in the sarcoplasmic reticulum in a dose-dependent manner, promotes extracellular Ca^{2+} influx, and induces release of internal Ca^{2+}. It was hypothesized that Cartap-induced contracture was, to a minor extent, a result of inhibition of the sarcoplasmic reticulum Ca^{2+} pump protein Ca^{2+} ATPase. Inhibition of the ATPase would result in the unloading of calcium from the sarcoplasmic reticulum [4]. The WHO classifies it as moderately hazardous (Class II) technical grade active pesticides, LD50 mg/kg being 325 mg [5] (in rats). The maximal acceptable daily intake (ADI) level is 0.05 mg/kg [6]. The USDA Foreign agricultural Service and Global Agricultural Information Network later stated that the ADI of Cartap is 0.1 mg/kg body weight [7], but unattended, delayed treatment, or in severe poisoning, death can occur. Mortality though low, early diagnosis, decontamination, appropriate life-saving supportive measures, and antidote treatment can ensure better survival. Keeping this in view, this study was undertaken with the primary aim to assess the factors that determined the severity of poisoning, and the secondary aim was to correlate the severity with the duration of mechanical ventilation (MV) and the dose of N-acetylcysteine (NAC) used and outcome of patients.

METHODS

This is a retrospective study conducted in a referral hospital that receives around 150 cases of poisoning annually. Although rare in incidence with occasional published cases reports, a study was undertaken between 2011 and 2016 revealed 11 patients admitted to hospital with Cartap poisoning. The behavioral characteristics, management, and response to treatment in patients who had consumed Cartap were studied.

After obtaining institutional permission, all the poisoning cases in the medicolegal section of the medical record division of the hospital were searched for Cartap poisoning. Confidentiality was maintained by not disclosing the identity of the patients. Ethical approval was not taken as it was a retrospective study. Diagnosis was based on history, production of bottle; as our hospital had no provision of measuring blood level of Cartap. All cases of suspected or diagnosed pesticide poisoning were documented as per the protocol that included detailed history, name of poison, amount ingested, taken with food or empty stomach or with alcohol; any local or previous treatment received; reporting time to hospital (for gastric lavage); clinical presentation - nausea, vomiting, hiccups, tremulousness, salivation, dyspnea, seizures, mydriasis, unconsciousness, and respiratory failure; antidote name and dose used, intensive care unit (ICU) management, and duration of MV and outcome.

As per the treatment protocol of agricultural poisons, patients were given gastric lavage, clothes were removed, and a soap water bath

was given. Initial assessment consisted of triaging the patient as mild, moderate, or severe cases of poisoning as per poison severity scoring (Table 1).

Initial resuscitation of all patients was done in the emergency unit. Patients presenting with GCS <8, convulsions, respiratory distress or low saturation, unstable hemodynamic, full stomach, and altered sensorium were intubated and mechanically ventilated. The antidote for Cartap poisoning used in our setup was NAC in a loading dose of 7.5 g intravenous (IV) followed by 350 mg every 8 hourly till patients were conscious, oriented with improved respiratory functions. Blood pressure was maintained with IV fluids and if required noradrenaline was administered. Patients were sedated with nalbuphine and lorazepam as per the ICU protocol with daily awakening trials.

Initial laboratory investigations comprising complete blood count, electrolytes, blood gas, chest X-ray, liver, and renal profile were done and later followed up as warranted. Serum pseudocholinesterase was estimated to rule out mixed poisoning. All patients were closely monitored and followed up throughout their ICU stay. Assist volume control was initially used to mechanically ventilate the patients and weaned off later using pressure support and continuous positive airway pressure; when patients fulfilled satisfactory spontaneous awakening trials and spontaneous breathing trials they were extubated. Patients who had excessive endotracheal and oral secretions were infused with glycopyrrolate in dose that adequately dried up secretions. The findings were recorded in standard case pro forma and were presented as numbers, percentages, and mean ± standard deviation. The data were finally analyzed using SPSS software version 20. The $p<0.05$ was considered statistically significant.

RESULTS

Between 2011 and 2016, 11 cases of Cartap poisoning reported to the hospital. Patients were scored as moderate or severe cases of poisoning. Out of these (8/11), 72.72% were males (3/11) and 27.27% were females. The age of patients ranged from 23 to 56 year with the mean age being 43.70 year. All had consumed 50% Cartap with suicidal intention only. Patients were triaged as moderate or severe cases of poisoning as per Persson's poison severity score. Six cases were assessed as severe cases out of which, 3 had consumed 15-20 g and 10-15 g of Cartap. Three moderate cases and all severe cases underwent gastric lavage >4 hrs. All severe cases took Cartap concomitantly with alcohol or in empty stomach. Duration of MV varied from 68 to 94 hrs in severe cases and 12-48 hrs in moderate cases. Average dose of NAC in severe case was 11.19 g and moderate case was 8.89 g. Survival was 100% (Table 2).

Table 1: Persson *et al*. poisoning severity scores [8]

Severity grades score	Symptoms
None (0)	No symptoms or signs related to poisoning
Minor (1)	Mild, transient, and spontaneously resolving symptoms
Moderate (2)	Pronounced or prolonged symptoms
Severe (3)	Severe or life-threatening symptoms
Fatal (4)	Death

Most common and consistent presenting symptoms were vomiting, altered sensorium, and breathlessness. Hypotension in two case responded to fluids and in rest had to be topped up with inotropes. Allergic manifestation mostly in the form of rashes was self-limiting. Seizures in two patients persisted for 2-3 days requiring dual anticonvulsants (Table 3).

Severe cases had more complications and the most common complication was hypotension followed by seizures. Out of 6 cases of hypotension, 4 were in shock and 2 had prolonged hypotension. All responded to fluid challenge and inotrope support. Seizure was infrequent and generalized or focal in 3 cases and frequent generalized convulsion was witnessed in 2 cases. One patients in shock developed adult respiratory distress syndrome (ARDS), and one both ARDS and acute renal failure (ARF) (Table 4).

DISCUSSION

Cartap poisoning can mimic organophosphate (OP) or organochlorine poisoning and in many situation has been provisionally diagnosed as OP poison [9]. However, the situation in our case was different. We were handling with all cases of known Cartap poisoning which made our management easier. However, to rule out cases of mixed poisoning, we did a serum pseudocholinesterase in all cases which was found to be normal. All our patients had consumed 50% powder form. Most of the published reports in India mentions ingestion of 50% Cartap for suicidal poisoning. This form is used in India for control of diamondback moth in cabbage and cauliflower and is easily available. Although it is known to be of moderate toxicity, Gupta *et al*. says that it becomes toxic if consumed more than 75 ml of solution containing 50% Cartap along with alcohol [10]; that is, 3.75 g. All of our patients had consumed more than that. Although Lao in his initial studies says that Cartap is a safe compound with oral LD 50 in monkey being 100-200 mg/kg body wt [4], his later findings demonstrated diaphragmatic contracture and death of rabbit on ocular installation [3].

Most of studies on toxicology epidemiology is based on OP poisoning, the most common pesticide used for poisoning. It says that poisoning is more common among males being 60.46%; the mean age group is 30.51±10.78 year and the cause is a suicidal intention [11]. In our case, the poison being a rare poison, the figure is very small to comment on, but (8/11) 72.7% were males, mean age was 43.70 year (range - 23-56 year), and the purpose was suicidal showing similar demographic

Table 2: Correlation of demography, dose of Cartap, and time of reporting with PSS score, duration of MV and dose of NAC, outcome

Age	M/F	Cause	How ingested	Approximate amount ingested (g)	Time to gastric lavage (h)	Poisoning severity score	Duration of MV (h)	Dose of NAC (g)	Atropine used	Outcome
50	M	Suicidal	With food	10-15	<4	Moderate	30	8.90	No	Survived
45	F	Suicidal	With food	5-10	4-8	Moderate	24	8.50	No	Survived
40	M	Suicidal	With alcohol	15-20	4-8	Severe	90	11.40	Yes	Survived
32	F	Suicidal	Empty stomach	10-15	>8	Severe	90	11.70	Yes	Survived
55	M	Suicidal	With alcohol	10-15	4-8	Severe	68	10.30	Yes	Survived
56	M	Suicidal	With food	5-10	<4	Moderate	12	8.20	No	Survived
50	M	Suicidal	With food	10-15	4-8	Moderate	42	9.25	No	Survived
38	M	Suicidal	With alcohol	15-20	>8	Severe	94	12.06	Yes	Survived
40	M	Suicidal	Empty stomach	15-20	4-8	Severe	84	11.00	Yes	Survived
52	M	Suicidal	With alcohol	10-15	4-8	Severe	70	10.65	No	Survived
23	F	Suicidal	With food	10-15	4-8	Moderate	48	9.60	No	Survived

M/F: Male/female

Table 3: Presenting symptoms

Symptoms	Number of cases
Vomiting	11
Drowsiness/altered sensorium	11
Breathlessness/hypoxemia	10
Hypotension	8
Rashes/allergic manifestations	6
Seizures	5

Table 4: Complications

Complication	Number of cases
Seizures	5
Hypotension/shock	6
ARF	1
ARDS	3

ARDS: Adult respiratory distress syndrome, ARF: Acute renal failure

characteristics as of OP poisoning. Most of the cases were referred before 8 hrs which shows the awareness of the people of rural Odisha and the good referral system made easy by introduction emergency ambulance.

We received all moderate-to-severe cases of poisoning. We presume that mild cases of this moderately hazardous poison were managed in local or government hospital out of ICU. Of the 11 cases, 6 were severe cases and 5 were moderate cases of poisoning. The severe cases had consumed either 15-20 g or 10-15 g of Cartap, and all had reported 4 hrs after poison ingestion, and hence the treatment was started only after this. Before this only, a few underwent induced vomiting in the local hospitals. The concentration of Cartap is an important determining factor of the severity of poisoning and outcome [12]. This can be explained from the fact that the maximum quantity of poison ingested in our case was approximately 15-20 mg which is more than the dose reported in Kurisaki *et al*. case and in both cases of Kurisaki *et al*. and Kuwahara *et al*., gastric lavage was also done early, but their patients died of multiorgan failure [13,14]. Percentage of Cartap in these cases was 75%; in our case all patients had consumed 50% Cartap, probably the most common formulation available, thus justifying the concentration of poison as an important determining factor of mortality. Senthilkumaran observed that the food and alcohol enhanced the toxicity of Cartap [15]. Severe poisoning in our case was found in patients who had concomitantly consumed alcohol or ingested in empty stomach.

The shortest duration of MV was 12 hrs and longest 94 hrs. In most of the published reports, patients were extubated in 48 hrs [9]. In the only case report by Sodalagunta [16], patient was extubated on the 4th day and the volume ingested was around 50 g which was much more than ours. Maximun dose of NAC given to our patient was 12 g. Praveen Kumar and Sodalagunta in their cases have used 15 g of the same antidote which is quite comparable [16,17]. Monica *et al*. has used BAL in her patient. Sodium dimercaptopropanesulfonate and sodium dimercaptosuccinate are effective sulfhydryl antidotes for acute insecticides poisoning such as SCD [sodium ammonium dimethyl-2-(propane-1, 3-dithiosulfate) monohydrate], nereistoxin, and Cartap in mouse models [18]. At present, the recommended antidotes for Cartap poisoning are 100-200 mg of L-cysteine IV or 20-60 mg of British Anti-Lewisite (dimercaprol; 2, 3-dimercapto propanol) intramuscular. It is possible that the effect of calcium binding of these antidotes is the mechanism of antagonizing the respiratory depression occurring in Cartap toxicity. Although there are yet no clear cut guidelines to the use of NAC, it has been used with good results [17,19]. Similar doses were used by Kalyaniwala *et al*. and their patient was weaned off from ventilator in 36 hrs [20]. We preferred to use this dose and repeat it over the next 3-4 days depending on the severity of the case. We have not encountered any side effects in the dose used and all our patients recovered. Atropine was used in most patients where excessive secretion was encountered to prevent secondary infection.

Of the complications we encountered, the most common was hypotension. Six cases required inotrope support and one in shock developed both ARDS and ARF. He became oliguric but urination improved on day 3 and he was extubated on the 4th day. Frequent generalized seizures responded to lorazepam followed by phenytoin sodium and if required levetiracetam. Both Kurisaki *et al*. and Kurisaki reported death of a 36-year-old male and a 50-year-old female, respectively, on the 5th and 6th day of ingestion of 75% Cartap [13,14]. In both cases, patient developed MOD (multiorgan failure). Both had received early gastric lavage but not any antidote. Although L-Cysteine and not NAC is the recommended antidote, we used NAC in our case due to easy availability, its successful administration in few published case reports and our familiarity of its use. All our patients with multiorgan failure recovered. In case of death due to MOD reported by Kurisaki *et al*. and Bunai *et al*., the blood concentration of Cartap was found to be 10.6 mcg/ml [13] and 11.5 mcg/m [21], respectively, whereas in Kiyota *et al*. case, where the patient survived after ingesting 50% Cartap the blood level was estimated to be 1.14 mcg/ml [22]. Singh *et al*. in a case study of paraquat poisoning, opined that different treatment modalities, namely, pulse therapy with cyclophosphamide and methylprednisolone, and hemoperfusion may be used to manage patient's condition. However, the patients may develop severe neutropenia and thrombocytopenia, but we had not found neutropenia or thrombocytopenia in our case series [23]. Khan *et al*. in their study revealed that females outnumbered males. Maximum numbers of cases were reported in the rainy season. Organophosphorus poisoning was observed to be the most common method. 21-30 year olds were most prone to suicidal poisoning, ascribed to their perturbation concerning the future issues [24]. Similarly studies on heavy metal poisoning have been done, but such studies with cartap is lacking [25].

We had no access to the measurement of blood level of Cartap which was the limitation of our study.

CONCLUSION

Unlike OP poisoning, Cartap poisoning is a rarer poisoning, probably due to its lesser availability. The reason is mostly suicidal. The age of ingestion is found to be varied but fall in the domain of productivity life. 50% of Cartap poisoning treated results in good survival outcome. NAC is associated with improved outcome of patients with Cartap poisoning. The severity of poisoning increases with the amount of Cartap ingested, time taken for gastric lavage, and when taken without food or with alcohol. Duration of MV, dose of NAC, and complications encountered correlates with the severity of poisoning. All patients recovered from complications. Atropine can be used to reduce increased secretions observed in severe cases of Cartap poisoning.

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