ORIGINAL ARTICLE

Clinical epidemiology and treatment outcome of Hexaconazole poisoning – A prospective six year study

ACHARYA ANAND[1] and PANDA ABINASH[2]

[1]Department of Pharmacology, Konaseema Institute of Medical Sciences & Research Foundation, Amalapuram, Andhra Pradesh, India
[2]Department of Pharmacology, M.K.C.G. Medical College, Berhampur, Odisha, India.

Abstract

Background: Hexaconazole is a category 3/4 of poison as per the W.H.O Expert Group on Pesticide Residues. Hexaconazole is used to control infection by fungi in paddy and other crops. Apart from destroying the target species, it can also cause damage to humans. There have been discrete reports of instances of human poisoning due to hexaconazole.
Methodology: A patient record-based cross-sectional study was carried out in Konaseema Institute of Medical Science & Research Foundation, Amalapuram, Andhra Pradesh, India during a period from March 2014 to April 2020 on 26 confirmed cases of hexaconazole poisoning. The clinic-demographic data, hematological, and biochemical parameters at the time of admission and at 72 hrs as well as the outcome were recorded and analyzed using descriptive statistics and paired t test.
Result: The prevalence of hexaconazole poisoning was 4.79% of all poisoning cases. The major clinical presentation was gastrointestinal symptoms with vomiting being commonest. There was no significant change in the biochemical and hematological parameters. The mean duration of hospitalization was 4.93±1.39 days. The recovery rate was 100% without any major sequel.
Conclusion: Poisoning due to hexaconazole is uncommon in comparison to poisoning by other pesticides in the agricultural community. The clinical manifestations of hexaconazole poisoning indicated that it is of non-serious nature and its recovery was without any sequel.

Keywords: Hexaconazole, clinical-epidemiology, treatment outcome

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INTRODUCTION

Hexaconazole is a fungicide used to control infection caused mainly by Ascomycetes and Basidiomycetes. It is effective against sheath blight of paddy, leaf spots, and blights on all types of crops (1).It is a member of the class triazole having chemical name 2-(2, 4-dichlorophenyl)-1-(1H-1, 2, 4-triazol-1-yl) hexan-2-ol. Green revolution resulted in doubling of the global food production in the last 50 years. Worldwide, an average of 35% of potential crop yield is lost to pre-harvest pests worldwide. So, to prevent the loss of the crop, pesticide use has recently increased in agriculture (2,3). Apart from killing the target species, pesticides also affect humans either intentionally or unintentionally. It has been reported that nearly 3 million cases of pesticide poisoning occur worldwide every year, resulting in more than 2,50,000 deaths annually. This intentional and unintentional pesticide poisoning is a serious problem in India like any other country where agriculture is the primary source of income (4).

Konaseema region of Andhra Pradesh is in the delta of Godavari River and there is an abundance of fertile lands and robust irrigation systems and agriculture is the major source of livelihood. Hexaconazole is used as a fungicide for the treatment of sheath blight of paddy and fungal infection of banana which is mainly cultivated in this area.

There is a paucity of research on clinical epidemiology and outcome of toxicity due to hexaconazole in humans except for few discrete case repots. For example, *Davi d et al* reported in a case report that a patient ingested 500 ml of Hexastar 5.5% EC™, a hexaconazole-containing product and toxicity manifested primarily as central nervous system symptoms like depression and generalized tremors. The patient recovered without sequel with supportive therapy (5). Likewise, *Humbi et al* reported one case of hexaconazole poisoning where the patient had an episode of vomiting and drowsiness that recovered completely without complications (6). Also, *Dawson et al* reported four cases of hexaconazole poisoning but there was no description about their clinical presentation and outcome (7).Going even further, *Pennings et al*, in their study, investigated the concentration-dependent effects of three known neuro-developmental toxicants, two triazoles, cyproconazole and hexaconazole, and the anti-convulsant, valproic acid. All compounds were found to influence epilepsy generating mechanism (8). With this background, the present study was carried out to find the

*Correspondence to: Dr Abinash Panda, MD, Associate Professor, Department of Pharmacology, M.K.C.G. Medical College, Berhampur, Odisha, India – 760004
Tell: 9861238578, E-mail address: drabinashpanda@rediffmail.com

clinical epidemiology and treatment outcome of hexaconazole poisoning.

METHODS

A patient record-based, descriptive cross-sectional study was conducted by the Department of General Medicine and Department of Clinical Pharmacology, Konaseema Institute of Medical Science & Research Foundation, Amalapuram, Andhra Pradesh, India during a period from March 2014 to April 2020. It is worth noting that all patients who confirmed a history of consumption of hexaconazole as evidenced by the availability of the empty or used container were enrolled for this study irrespective of age groups and gender. The study was approved by the Institutional Ethics Committee of Konaseema Institute of Medical Science & Research Foundation. Since it was a patient record-based study, waiver of consent was obtained from the ethics committee. The data was collected by the investigators themselves in a pre-designed case record form. Clinico-demographic data like age, gender, occupation, marital status, socioeconomic status as per modified Kuppuswamy scale (9), region, amount of poison consumed, circumstances of poisoning, and time elapsed before reaching the hospital were recorded. The findings of the biochemical and hematological parameters were also recorded. All the patients received supportive treatment based on the clinical presentation as per the institutional protocol. Psychiatric consultation was also done as required. Psychiatric assessment was based on the history, symptoms, and behavior of the patients. Patients with a history of sudden onset of self-harm without any psychiatric co-morbidity or any abnormality in cognitive functions like level of alertness, orientation to person, place or time were classified as impulsive. Those having any history of psychiatric illness, family history of suicidal attempts, stress, anxiety, and panic were classified as non-impulsive. The collected data was analyzed using Graphpad Prism Trial Version 7.0.Mean and standard deviation were used to present continuous variables. Additionally, frequency and percentage were used to present the categorical data. Paired sample *t* test was used to find out the statistical significance between the differences in the measurements of the continuous variables. A p value of ≤ 0.05 was considered as statistically significant.

RESULTS

During the study period, 542 patients were admitted due to various poisonings. 26(4.79 %) cases were attributed to hexaconazole. Mean age of the patients in hexaconazole poisoning was 28.18±10.94 years with a female predominance. There was a temporal distribution of the poisoning. Maximum (53.84%) number of cases was found during Jan-March followed by Oct-Dec (53.84%) months. Intentional poisoning occurred between evening and early morning (6 P.M to 6 A.M) in 46.15% of cases. The majority of the patients were from rural region and 18(69.23%) were married. Poisoning was common in lower social economic background and with suicidal intention. Mean amount of poison consumed was 85.62±60.59 ml. The mean of time required to reach hospital after consumption of poison was about two hours 118.5±63.56 minutes.[Table 1]The commonest clinical presentation was gastrointestinal symptoms like, vomiting, followed by diarrhea (62.5%) and increased salivation 12(46.15%). Pain abdomen was present in 37.5% patients. Dyspnea, palpitation and tremor were present in one patient each. Tachycardia (15.38 %) was more frequent than bradycardia (7.69%). Pulmonary signs like crepitation was present in two patients.[Table 2] There was no significant change in the hematological parameters like hemoglobin concentration, TWBC, TRBC, platelet count and ESR till after 72 hours of admission. The difference in the Serum ALT levels and serum chloride at admission and 72 hrs after was statistically significant ($p \leq 0.05$). [Table 3]The mean duration of hospital stay was 4.93±1.39 days and all patients recovered without any complications.[Table 4]Psychiatric assessment was done for all the patients in the current study. The commonest psychiatric manifestation was that the 18 (75%) patients were impulsive. Depression was found in 12.5% patients and 12.5% patients had stress. No

Table 1. Clinico-demographic profile of patients in hexaconazole poisoning

Clinico-demographic parameter		Number of patients (%)
Gender	Male	12 (46.15%)
	Female	14 (53.84%)
Month of poisoning	January to March	14(53.84%)
	April to June	4(15.38%)
	July to September	0
	Oct to December	8(30.76%)
Time of poisoning	6 a.m to 12 p.m	6(23.06%)
	12 p.m to 6 p.m	8(30.76%)
	6 p.m to 6 a.m	12(46.15%)
Place of residence	Rural	24(92.3%)
	Urban	2(7.6%)
Occupation	Student	5(19.23%)
	Housewife	13(50 %)
	Farmer	6(23.06%)
	Others	2(7.69%)
Marital status	Unmarried	8(30.76%)
	Married	18(69.23%)
Socioeconomic status (Modified Kuppuswamy scale updated for February 2019) [9]	Upper	0
	Upper middle	0
	Lower middle	2(7.69%)
	Upper lower	16(61.5%)
	Lower	8(30.76%)
Intent of poisoning	Suicidal	26(100%)
	Accidental	0
	Homicidal	0
Amount of poison consumed (Mean ± SD)		85.625 ±60.59 ml
Time elapsed between *pesticide* ingestion and hospitalization		118.5 +63.56 minutes

other psychiatric illness could be detected during the hospitalization.[Table 5]

DISCUSSION

Based on the obtained findings in this study, 4.79 % of all poisoning was due to hexaconazole. However, all the cases of poisoning due to hexaconazole were intentional cases. Most of the patients in the present study were of younger age group which corroborates with other studies on pesticide poisoning by *Kumaret al*, and *Banerjee et al* (10, 11). In present study there was female predominance. *Banerjee et al* and *Vijayakumari et al* have also observed a similar predisposition in their study on poisoning in general (11,12). In this study, most of the cases were housewives in rural areas who consumed poison in the evening hours. This observation is in tune with the findings of *Indu et al* (13). Season of poisoning was dependent on the availability of hexaconazole in household. This reflects the results claimed by *Singh et al* who maintained that hexaconazole was used during the crop

Table 2. Clinical presentation of patients at the time of admission in hexaconazole poisoning

Clinical presentation		Number of patients (%)
Vomiting		26(100%)
Diarrhea		18(62.5%)
Increased salivation		12(46.15%)
Pain abdomen		10(37.5%)
Dyspnea		2(7.69%)
Palpitation		2(7.69%)
Tremor		2(7.69%)
Heart Rate	Bradycardia	4(15.38 %)
	Tachycardia	2(7.69%)
Loss of consciousness		0
Seizure		0
Stupor		0
ECG changes		0
Crept in chest		2(7.69%)
Muscle weakness		0

Table 4. Treatment outcome of patients in hexaconazole poisoning

Outcome	
Duration of hospitalization in days (Mean + SD)	4.93+1.39
Number of patients recovered (%)	26 (100%)
Death	0
Disability	0

Table 5. Psychiatric manifestation of patients in hexaconazole poisoning

Type of manifestation		Number of patients (%)
Impulsive		18(75%)
Non impulsive	Depression	4(12.5%)
	Anxiety	0
	Stress	4(12.5%)
	Other psychiatric illness	0

Table 3. Biochemical and hematological parameters in hexaconazole poisoning

Parameter		At the time of admission	After 72 hours	p value
Hb % (g/dl)		12.76 ±1.29	12.87 ±1.21	.18
TWBC ($x10^9$/L)		12.75 ±3.63	9.79 ±1.21	.5
TRBC (million cells/mcL)		4.605±0.45	4.697±0.69	0.37195
Platelet count (lakhs/mcL)		2.495±0.67	2.625±0.56	0.33
ESR (mm/hr)		19.9±6.00	17.2± 6.06	.177
Serum bilirubin (mg/dL)		0.89±0.14	0.95±0.18	.22
Serum AST (IU/L)		28.4±8.46	31.7±10.80	.24
Serum ALT (IU/L)		22±5.79	31.74±11.76	0.019*
Serum alkaline phosphatase (IU/L)		89.6±21.40	90.22±15.75	0.47
Serum creatinine (mg/dL)		0.96±0.111	0.99±0.07	0.25
Serum urea (mg/dL)		33.1±7.21	30.3±4.84	0.20
Plasma Electrolyte (mEq/L)	Sodium	142.31±2.05	142.2±2.03	.455
	Potassium	4.17±0.19	4.08±0.28	.222
	Chloride	107.01±5.68	101.19±5.48	0.02*

AST = Aspartate aminotransferase, ALT = Alanine aminotransferase
*statistically significant

season when humidity was high during May to August and sheath blight of paddy (14). *David et al* in a case report observed that the amount of poison consumed was 500ml, but *Humbi et al* did not mention the amount of poison consumed in their study (5, 6). In the present research, the mean amount of poison consumed was 85.625±60.59 ml. After surveying various shops of fertilizer, it was observed that locally hexaconazole is available in 250 ml pack and 500 ml pack as such due to its limited use it was not stored in house in large volume.

In their study, Rao et al reported that median time from ingestion of poison to hospitalization was 1.5 hour in general, whereas *Thomas et al* found this to be 4 to 5 hours (15,16). Nevertheless, in this study the mean duration from ingestion of poison to admission was about 4 hours. The variability in duration may be due to differences in the availability of referral services and health infrastructure. Gastrointestinal followed by cardio respiratory changes were the commonest manifestation. Biochemical and haematological parameters were within normal range after 72 hours of ingestion of pesticide. Serum ALT was significantly elevated after 72 hours but remained within the normal range. Electrolyte concentration was also within the normal range after 72 hours of ingestion of poison. There was statistically significant decrease in serum chloride level within normal range. It has been documented that hexaconazole is metabolized in liver and excreted in bile and urine. Animal studies indicated an inconsistent change in biochemical and haematological parameters (17).The WHO Expert Group on Pesticide Residues have classified hexaconazole to be category 3/4 of poison and have mentioned its acute toxicity to be of lower order and could be caused by oral, inhalational, and cutaneous route (17). *Kumar et al* in their study done in south India observed that in hexaconazole poisoning, the mean duration of stay in hospital was 4.93±1.39 days whereas in case of organophosphorus poisoning it was 7.5±4.7 days (range 1–26) days (18). Impulsiveness and depression of less serious nature were the commonest central nervous system manifestation of hexaconazole poisoning. *David et al* and *Humbi et al* have made similar observations in their case report (5, 6). All patients recovered without any sequels. Depression and stress were also observed as the commonest effects in a study by *Weber et al* and *Salles et al* (19, 20). Azoles as a class exhibits broad spectrum antifungal activity, hexaconazole being one of them is largely used in agricultural practice. They were introduced into the therapy of fungal infections of humans in the early 1970s, parallel to the first agriculturally used azoles. They are the most extensively used broad spectrum antifungal drugs in clinical practice. The fungistatic action is due to the same mechanism as the compounds used as agricultural pesticides i.e. inhibition of cytochrome P-450-dependent lanosterol-14α-demethylase are necessary for the conversion of lanosterol to ergosterol in fungi leading to the depletion of ergosterol and the formation of a plasma membrane with altered structure and function (21). Clotrimazole was the first imidazole compound to be marketed in 1971 for topical use, whereas ketoconazole was the first to be used orally for the treatment of systemic fungal infections. Since early 1980s, it remained the drug of choice in nonlife-threatening endemic mycoses for almost a decade till the introduction of the first-generation triazoles like fluconazole and itraconazole that have displayed a broader spectrum of antifungal activity and a markedly improved safety profile. Despite their widespread use, these agents had clinically important limitations related to their suboptimal spectrum of activity, development of resistance, induction of hazardous drug-drug interactions, and their less than optimal pharmacokinetic profile and toxicity. The second-generation triazoles, including voriconazole, posaconazole, and ravuconazole have overcome some of these limitations and have a greater potency and possess increased activity against resistant and emerging pathogens, in particular against *Aspergillus spp.* (22). The primary toxicities associated with the azoles in clinical practice range from the common transient elevations in serum transaminases to the less common fulminant hepatoxicity and liver failure. Liver failure is rare but it may occur with any azole. Other toxicities like hypotension, peripheral/pulmonary edema, dizziness, headache, seizure, rash, and hypokalemia, myelosuppression are rare (23).Adverse effects described for azole compounds as medical agents are similar to those reported for the ones used agriculturally. Furthermore, the competitive inhibition of cytochrome enzymes by these compounds is not unique to fungal enzymes. It is noteworthy that the inhibition of non-target cytochrome enzymes leads to toxicologically relevant changes in the liver and endocrine system. Similarly, the inhibition of xenobiotic metabolising enzymes such as CYP3A4 by azoles can lead to potentially serious drug interactions (24).

CONCLUSION

The clinical manifestations of hexaconazole poisoning indicated that it is of non-serious nature and its recovery was without any sequel. However, the injudicious use of azoles in agricultural practice can lead to potential health risk during the production, application process, and as pesticide residues present in food in amounts exceeding the acceptable daily intake level.

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Conflicts of Interest: None to be declared

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