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CASE REPORT

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Anti-cholinergic syndrome following accidental poisoning with cyproheptadine in a Nigerian toddler: A case report

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Abstract: Cyproheptadine is an antihistamine that is also used as appetite stimulant in children. We report a three-year old who developed anticholinergic syndrome following accidental ingestion of a large dose of cyproheptadine. The child was conservatively managed, and he recovered fully with no immediate sequelae. We report this case to create awareness on the harmful effects of cyproheptadine ingestion.

Keywords: Cyproheptadine, anticholinergic syndrome, poisoning.

Introduction

Poisoning is reported to be responsible for 7% of deaths among under-5 children and the cause of mortality in 2% and 5% in developed and developing countries respectively.[1] Common aetiologic agents of poisoning in our environment include kerosene, hypochlorite and pesticides. Cyproheptadine is a first-generation antihistamine. It is readily available over the counter, used for treating allergic symptoms, appetite stimulation and off label treatment of vascular headaches.

Cyproheptadine exerts its antihistamine and antiserotonin effects by competing with free histamine and serotonin for binding at their respective receptors. Antagonism of serotonin on the appetite centre of the hypothalamus may account for cyproheptadine's ability to stimulate the appetite, while the antihistamine effect accounts for its role in managing allergic conditions.

The drug is associated with side effects such as sedation, sleepiness, agitation, nervousness, excitability, insomnia, chest pain, arrhythmia, and urinary retention. Fatality was reported in a 42-year-old female who suffered poisoning with cyproheptadine.[2] Muhlendahl et al[3] reported 113 cases in German children in whom symptoms appeared 6-12 hours post-ingestion; these symptoms included somnolence, excitation, hallucinations, ataxia, tachycardia, and muscle twitching. No fatality was recorded at dose of 0.3-6.15mg/kg, and no report of such in children.

The objective of this report is to create awareness about the harmful effect of the drug when consumed in excess in children particularly when used as appetite stimulant, highlight the management protocol that was followed and review the literature as regards cyproheptadine toxicity. To the best knowledge of the authors there are no previous report of cyproheptadine toxicity in a Nigerian child as well as in the West African sub region.

Case report

O.G, a three-year old male was rushed into Children Emergency Room of the Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria on account of restlessness and high-grade fever, six hours post-ingestion of Cyprigold® syrup (an appetite stimulant containing cyproheptadine hydrochloride)

He was presumed well until six hours prior to presentation when his mother noticed an empty bottle of Cyprigold® with him while some quantity of the drug was noticed in his mouth. The drug was procured off the shelf few days earlier and was administered to him by his father on account of poor appetite. He was estimated to have consumed about 160ml of the syrup. Two hours post ingestion, he was noticed to have become restless and ataxic. Four hours post ingestion, he developed continuous, high-grade fever, which was neither associated with seizure, nor loss of consciousness. There was no difficulty in breathing, change in urinary output, urinary retention, dryness of mouth or increased thirst. No home remedy was administered prior to presentation. The child was initially taken to a primary healthcare centre where unnamed intramuscular medications were administered. He was subsequently referred to the teaching hospital when there was no improvement in his clinical condition. Pre-morbidly, he was a kindergarten pupil with above average academic performance.

At presentation he was conscious, pupils where dilated (4mm bilaterally) reactive to light, agitated, restless, with abnormal rhythmic, jerky movement of the upper

limbs and picking at imaginary objects. He was not pale, not in respiratory distress and a febrile (36.5^0C), there were no signs of meningeal irritation. His anthropometric parameters were within the normal range for his age. He was tachypnoeic (respiratory rate 40 cycles per minute), and tachycardic (pulse rate 134 beats per minute) but with no cardiac murmurs or abnormal heart rhythm on auscultation. His blood pressure (systolic 90mmHg and diastolic 60mmHg)was less than the 90^{th} percentile for age and sex. Other physical examination findings were not remarkable.

A provisional diagnosis of acute anticholinergic crisis secondary to accidental cyproheptadine poisoning was made. The child was admitted for observation in the Children's Emergency Room.
Intravenous Normal Saline 20mls/kg was infused over one hour (to aid elimination of the drug) and this was followed with 15mg of intravenous frusemide (forced diuresis). A *statum* dose of intravenous diazepam (5mg) was also administered. The laboratory results of full blood count, serum electrolytes, urea and creatinine and electrocardiography were essentially normal. There was no facility to assay serum levels of cyproheptadine or its metabolites. The child was hospitalized for 24 hours and was subsequently discharged home having made good recovery with the resolution of the earlier symptoms and signs. His mother was counselled on safe drug storage at home, and permission sorted from the parents to publish the case and use his health records for this report.

Discussion

Cyproheptadine is a first-generation, antihistamine medication, used to treat allergic symptoms such as watery eyes, runny nose and hay fever.[4] It has additional anticholinergic, anti-serotonergic and local anaesthetic properties. It is also used in the management of Cushing syndrome and migraine. Cyproheptadine is noted to have orexigenic effect which is not authorized for use in many countries.[5] Its safety, efficacy, and mechanism of action as an appetite stimulant in children has not been established. In this report, the drug was bought over the counter solely for its appetite-stimulating effect. Its positive appetite stimulating effect and ability to cause weight gain in children with non-organic failure to thrive at a dose of 0.3mg/kg/day for at least 14days is known.[6]

The index patient consumed 160mls (64mg) of the drug equivalent to 4.6mg/kg body weight which far exceeded the recommended dose of 0.3mg/kg/day and therefore, exhibited anticholinergic syndrome at presentation.[6]
Anticholinergic syndrome arising from poisoning or drugs such as tricyclic antidepressant, antipsychotic, carbamazepine and hysocine have been well reported in literature, there is paucity of data on cyproheptadine toxicity in children, with only a handful of case reports globally, and none from West African Sub region.

Lee and So[7] in Hong Kong reported two cases of accidental poisoning with drugs with anticholinergic effect, one was an anti-motility drug while the other was cyproheptadine. Both children presented with signs and symptoms compatible with acuteanticholinergic syndrome.[7]
Anticholinergic syndrome has both central and peripheral nervous system manifestations. The central nervous system manifestations include altered consciousness, irritability, confusion, and pupillary dilatation. The index patient at presentation was restless, agitated and confused with bilaterally dilated but reactive pupils.
The peripheral nervous system manifestations include hyperthermia, tachycardia, constipation, and urinary retention.[6,8] The index patient had fever and tachycardia while the other features were absent.

A combination of anticholinergic agents, or other compounds with similar activity, may lead to more severe toxicity and symptoms such as paralytic ileus, this was well elucidated in the report by Lee and So.[7]Children may be more susceptible to the adverse effects of anticholinergic agents even at seemingly 'therapeutic' doses.[9] The calculated ingested dose in the index patient was 15 times above the recommended therapeutic dose. McGovern et al[10] reported a case of anti-cholinergic syndrome following cyproheptadine overdose, with confirmatory cyproheptadine levels in the blood. The blood level in the reported case was within the therapeutic level, yet the child developed anticholinergic syndrome.[10]

The principle of management of a child with suspected anticholinergic syndrome, involves early presentation at the emergency room, gastric lavage, if child presents early and administration of activated charcoal to prevent further absorption.[11] The latter was not done in the index child because he presented at our facility six hours post-ingestion. It is important to note that induced emesis is not advised, especially when there is altered level of consciousness to prevent aspiration, also commonly used emetic medications have been noted to have both central nervous and respiratory depressive effect.[12]
Intravenous fluid replacement with added diuretic was presumably helpful in the index case, helping with the elimination of the drug. Close monitoring of the consciousness level, blood pressure, and heart rate are other important components of the management. The index patient did not require urinary catheterization as there was no urinary retention.
Most patients will make a complete recovery when the ingested medication has been eliminated by the body. The terminal half-life of the drug is eight hours[13] and the peak plasma level is 1-3 hours. The peak plasma level coincides with the onset of symptoms manifestation in the index patient. The child made remarkable recovery within 12 hours and was further observed for another 12 hours before he was discharged home. The hospital was not equipped to assay for the serum level of cyproheptadine like other toxicological procedures, though anticholinergic effect has been reported when drug was consumed in the therapeutic range.[10]

However, caution needs to be exercised in the interpretation of toxicological screening for cyproheptadine (a tricyclic benzocycloheptene) as false-positive results for tricyclic antidepressants have been observed in the presence of cyproheptadine intoxication.[14]

Physostigmine, a cholinesterase inhibitor could be used in treatment of life-threatening complication arising from cyproheptadine poisoning-induced anticholinergic syndrome.[13] Physostigmine penetrates the blood brain barrier easily and prolongs the activity of acetylcholine at the target tissues, thereby reversing the peripheral and central nervous anticholinergic effects though this was not required in this case.

Anticholinergic syndrome may be a potentially life-threatening complication of cyproheptadine hydrochloride poisoning. A high index of suspicion is required, to make the diagnosis in children. especially when they present with hypertension, tachycardia, hyperthermia, agitation, delirium, coma, seizures, dilated pupils, dry and hot skin, reduced or absent bowel sounds, paralytic Ileus, urinaryretention. Confirmatory serum cyproheptadine levels are not required to confirm diagnosis or initiate treatment.[9]

Mandatory use of child-resistant caps on drug containers and keeping drugs out of reach of children can significantly reduce the morbidity and mortality associated with accidental childhood poisoning.

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