

Accidental Modopar[®] Poisoning in a Two-Year-Old Child. A Case Report

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ABSTRACT

Levodopa is a dopamine precursor and a mainstay treatment in the management of Parkinson's disease. Its side effects induce dyskinesia, nausea, vomiting, and orthostatic hypotension. Acute levodopa poisoning is uncommon, with only a few reported cases in the medical literature. Treatment of poisoning by levodopa is mainly supportive. The case of a child admitted to a hospital for acute levodopa poisoning is presented in this report.

Keywords: Levodopa, Parkinson's disease, antiparkinsonian drugs, mechanical ventilation

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INTRODUCTION

Parkinson's disease is one of the most common neurodegenerative disorders, second only to Alzheimer disease. Approximately 1% of the British population over 65 years[1], and 1-2 per 1000 of the European population[2] are reported to suffer from this disease.

Classic motor symptoms include bradykinesia, rigidity, essential tremor and postural instability. These symptoms are due to the loss of dopaminergic neurons in the *substantia nigra* (SN). The clinician is tasked with differentiating between idiopathic Parkinson's disease and other diseases presenting with akinetorigid syndrome, as well such as multiple system atrophy, dementia with Lewy bodies, corticobasal degeneration, vascular Parkinsonism or drug-induced Parkinsonism [3]. Pharmacologic treatment includes levodopa, which is a dopamine precursor; dopamine agonists like pramipexole which stimulate dopaminergic receptors in the central nervous system; catechol-O-methyl transferase inhibitors such as entacapone and monoamine oxidase aldehyde dehydrogenase B (MAO-B) inhibitors such as rasagiline and selegiline, which inhibit the breakdown of levodopa and dopamine. When the condition becomes refractory to medical treatment, deep brain stimulation helps to alleviate the symptoms [4].

Levodopa, beside dopaminergic agonists, is a drug commonly prescribed in Parkinson's disease. Antiparkinsonian poisoning is very rare, even in the adult population with only a few reported cases. Accidental poi-

soning by drugs is more common in childhood, though no reports of levodopa poisoning in children have been sourced in the literature.

This report concerns a previously healthy two years old boy, weight: 15 kg and height: 110 cm. who was admitted to the Hassan II University Hospital (Fez, Morocco) upon accidental ingestion of an antiparkinsonian drug.

CASE DESCRIPTION

A two years old boy accidentally ingested four, 250 mg tablets of Modopar[®] (Roche, Casablanca, Morocco), each containing 200 mg of levodopa and 50 mg of benserazide. The tablets belonged to the child's grandfather currently under treatment for Parkinson's disease, and the bottle containing them was found beside the child. The patient was admitted to the hospital's emergency ward forty minutes following the ingestion.

Upon admission, the patient's vitals were recorded as, heart rate 141 bpm, blood pressure 90/60 mmHg, polypneic with a respiratory rate of 30 CPM, SpO₂: 95% in room air. A neurological examination showed a conscious child with a Glasgow Coma Scale (GCS) of 15.

The pupils were of equal size and reactive, with major contraction movement disorders of the neck (cervical dystonia) and repetitive and non-rhythmic movements

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of the upper and lower limbs (chorea). The remainder of the physical examination was otherwise unremarkable.

Following his admission, the child underwent gastric lavage with saline. Test including a complete blood count, a metabolic panel, (Table 1) and liver function tests, all of which were within normal ranges.

Toxicological screening did not identify levodopa or dopamine in blood, and urine samples as testing for these medications was unavailable in the hospital's laboratory.

Initially, 4 mg diazepam (DIAPHARM®, PHARMA5, Casablanca, Morocco) was given intravenously, but dystonia and chorea persisted despite giving another 4 mg (i.e. 0.25 mg/kg) dose intravenously dose. As the dystonia and chorea did not subside but increased in frequency within the next hour, and out of concern of aspiration should further benzodiazepines be necessary, a decision was taken to intubate the child.

After rapid sequence induction with intravenous propofol (Diprivan ©, Maphar, Casablanca, Morocco) 100 mg and 20 mg intravenous rocuronium (Esmeron ©, MSD Maroc, Casablanca, Morocco) and then 50 mcg intravenous fentanyl (Fentanyl Mylan ©, Synthemedic, Casablanca, Morocco). After securing the airway with a 4 cm cuffed endotracheal tube, the child was put on mechanical ventilation and sedated with midazolam (Midazolam Aguettant©, Hemolab Pharma, Casablanca, Morocco).

The patient was then transferred to the intensive care unit for further care.

The results of an *arterial blood gas (ABG)* test were unremarkable: pH: 7.42 PaCO₂: 33 mmHg PaO₂: 216 mmHg HCO₃⁻: 22 SaO₂: 99%.

As the patient still exhibited mild dystonia even under sedation, midazolam (Midazolam Aguettant©,

Hemolab pharma, Casablanca, Morocco) was titrated at 100 mcg/kg/hour. Movement disorders subsided progressively afterwards, and the patient was extubated 24 hours later. After extubation, the child was stable with a heart rate of 100 beats per minute, blood pressure was 100/70 mmHg, respiratory rate was 25 breaths per minute, and SpO₂ was 96% in room air. Movement disorders faded away completely the day following weaning from mechanical ventilation.

As laboratory values remained normal, the patient was discharged the day following his admission.

■ DISCUSSION

Levodopa, L-3,4-dihydroxyphenylalanine, is the metabolic precursor of all catecholamines and is typically produced from tyrosine by the action of tyrosine hydroxylase. It is decarboxylated to dopamine by dopa decarboxylase[5]. It is one of the most effective agents in the treatment of Parkinson's disease. Upon oral administration, the drug is quickly absorbed and reaches peak plasma levels with thirty minutes to two hours. The plasma half-life is usually between one to three hours. However, digestive absorption depends on gastric pH, rate of emptying of the stomach as well as food intake. Two-thirds of the dose is metabolized to dopamine before entering the blood-brain barrier. Various metabolites such as homovanillic acid and dihydroxyphenylacetic acid are encountered in the urine eight hours after ingestion. Thus, only one to three per cent of the given dose enters the brain and consequently to prevent extracerebral decarboxylation, levodopa is usually prescribed together with a decarboxylase inhibitor such as benserazide or carbidopa[6].

Although the adverse effects of levodopa therapy are well described[7], the literature is rather sparse regarding acute levodopa overdose.

Treatment of the acutely levodopa-poisoned patient remains supportive. Unlike other common drug poisonings such as acetaminophen, the treatment of levodopa poisoning is limited as there is no antidote nor a consensual management protocol

The small number of case reports published in the literature reported received only supportive treatment measures. There is no published evidence to support the efficacy or clinical benefit of gastric lavage. Hypertension has been described in the acute phase of levodopa overdose and generally has been transient [8, 9].

Table 1 Metabolic panel upon admission

| Metabolic panel | Values |
|-------------------|--------|
| Sodium (mEq/l) | 137 |
| Potassium (mEq/l) | 4.5 |
| ALAT (UI/l) | 23 |
| ASAT (UI/l) | 17 |
| CPK (µg/l) | 70 |
| Calcium (mg/l) | 95 |
| Magnesium (mg/l) | 60 |

Walsh et al. (2016) stated that should severe hypertension persist short-acting vasodilators are recommended. Nitroprusside is the first-choice drug rather than β -blockers to avoid an enhanced bradycardia risk theoretically. Hypotension should be treated first with fluid resuscitation before resorting to vasopressors such as norepinephrine. "Agitation and dyskinesia may be managed initially with intravenous benzodiazepines such as lorazepam or diazepam, titrated to mild sedation" with <0.5 mg/kg for diazepam and <2 mg/dose for lorazepam). If necessary, neuromuscular blockade may be implemented for control of "extreme movement disorder or severe combativeness" [10].

There are no published data that indicate the value of dialysis in acute levodopa intoxication.

Delmas et al. (2008) described a case of a patient who ingested a controlled-release form of levodopa with carbidopa. Serial catecholamines measures showed no correlation to the intensity of the symptoms, which were, in that case, mainly agitation and hemodynamic instability [11]. Hoehn and Rutledge (1975) described a 61-year-old patient with Parkinson's disease who ingested approximately 100 g of levodopa and presented with marked confusion, agitation, "jerking movements," restlessness, and initial hypertension followed by orthostatic hypotension [8].

The patients in both these cases responded well to supportive care.

In a case report of a woman with no previous history of Parkinson's disease, who ingested approximately 15–17 tablets of carbidopa-levodopa (Sinemet © 10/100 mg tablets, Merck, Sharp & Dohme, West Point, Pennsylvania) and an unknown amount of ibuprofen, carisoprodol, and hydrocodone/acetaminophen, was described as lethargic with choreiform movements. These movements were unaffected by the administration of morphine sulphate and diazepam was administered intermittently for almost sixty hours until the patient's dyskinesia resolved. She was treated supportively and recovered without apparent sequelae [9].

A case of acute colitis, as a levodopa side effect, has recently been reported in a 86 year old patient. This case is a reminder of the side effects that clinicians should be aware of in cases relating to drug overdose or long-term prescribing[12]. Our case is to our knowledge, the first one reporting acute levodopa poisoning in a child. Accidental ingestion of another antiparkinsonian agent, bromocriptine mesylate (Parlodel© 2.5 mg tablets, Sandoz Pharmaceuticals, East Hanover, New Jersey), a dopamine receptor agonist, has already been described by Vermund et al.[13]

Vermund et al. reported a case which was the first concerning an antiparkinsonian agent poisoning in a child. The drug ingested was bromocriptine and a dopamine receptor agonist [13]. Paediatric levodopa poisoning in developed countries remains rare and most medical investigations are aimed toward reducing the already mentioned side effects[14].

In the current case, the patient had reportedly ingested a total amount of 800 mg of levodopa (53 mg/kg) compared to the recommended therapeutic doses of 1 mg/kg to a maximum of 10 mg/kg.

The facilities for testing blood levels of dopamine and its metabolites were unavailable at the time when this patient was being treated. The patient was very agitated with movement disorders, including dystonia and chorea, which warranted the use of sedation and mechanical ventilation.

The approach used may seem a bit aggressive as there are other options to treat levodopa-induced dyskinesia. There is a whole array of compounds that may be used as antidyskinetic therapy ranging from antidopaminergics like neuroleptics such as clozapine to anticholinergic drugs like biperiden [15]. The use of such drugs has not as far as is known, been reported in cases of acute levodopa poisoning. As the patient had already received a significant amount of diazepam, it was decided to secure the airway to prevent complications from aspiration. A symptom-free extubation was carried out the following day. No other biological abnormalities, other than a mild elevation of creatine phosphokinase (CPK) were recorded. The patient was discharged home upon full recovery after 48 hours.

CONCLUSION

Levodopa poisoning is very rare and induces neurological symptoms, especially movement disorders, as well as haemodynamic instability. As no antidote is available, treatment is mainly supportive.

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CONFLICT OF INTEREST

The authors declare having no conflict of interest.

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