Orphenadrine poisoning in a child: clinical and analytical data

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Abstract Orphenadrine is an anticholinergic drug used mainly in the treatment of Parkinson’s disease. It has a peripheral and central anticholinergic effect and a known cardiotoxic effect when taken in large doses. We report the successful outcome of the treatment of a 2 1/2-year-old girl who accidentally ingested 400 mg of orphenadrine hydrochloride (Disipal). One hour after ingestion she presented neurological symptoms: confusion, ataxic walking, and periods of severe agitation. Generalized tonic-clonic seizures appeared resistant to the administration of multiple antiepileptics. They ceased after a supplementary dose of intravenous diazepam, endotracheal intubation, and mechanical ventilation. An episode of ventricular tachycardia responded well to i.v. lidocaine. Physostigmine was administered in three successive doses. The initial orphenadrine plasma level (3.55 μg/ml) was in the toxic range, associated with high mortality. The calculated elimination half-life was 10.2 h and the molecule and/or its metabolites were found up to 90 h after ingestion.

Key words Orphenadrine intoxication · Physostigmine · Intoxication

Introduction

Orphenadrine is an anticholinergic drug mainly used to decrease the symptoms of Parkinson’s disease. It has a peripheral and a central anticholinergic effect. Overdose can result in confusion, athetoid movements, convulsions, cyanosis, coma, arrhythmias, shock, and cardiac arrest [1]. Accidental intoxication with orphenadrine in infants is infrequent [2]. This paper reports a case of orphenadrine intoxication in a 2 1/2-year-old girl. Physostigmine is a specific antagonist of peripheral and central anticholinergic effects [3]. Its use remains controversial.

Case report

A 2 1/2-year-old girl (estimated weight: 12 kg) was admitted to the pediatric intensive care unit (ICU) 3 h after ingestion of eight tablets of Disipal (orphenadrine hydrochloride 50 mg), which was her grandmother’s anti-Parkinson’s medication. This corresponds to 400 mg orphenadrine hydrochloride or 35 mg/kg body weight. Within 1 h of ingestion she presented ataxic walking, confusion, and episodes of severe agitation. About 1 h later she was admitted to a local hospital for tonic-clonic seizures with left eye deviation. At admission she received 1 intrarectal dose of diazepam (0.5 mg/kg), 1 mg (0.08 mg/kg) of clonazepam intramuscularly, and 100 mg of i.v. phenytoin, but the seizures persisted. Gastric lavage was performed and a first dose of activated charcoal was given.

After transfer and admission to the pediatric ICU she was still having convulsions. The seizures ceased after endotracheal intubation, mechanical ventilation, and i.v. administration of 10 mg diazepam. Prior to intubation, no paralyzing agents were used. There were abnormal movements of the upper limbs, fever up to 39.9 °C and episodes of agitation. The blood cell count, electrolytes, and coagulation [partial thromboplastin time (PTT) 79 %, normal range 70–100 %] were within normal limits. There was an increase in creatine kinase (212 IU/l) and lactate dehydrogenase (pH 7.25 and base excess –6.8) probably due to the seizures. An alteration of coagulation (PTT 56 %) appeared 24 h after ingestion and returned to normal within 48 h.

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Four hours after ingestion there was an episode of ventricular tachycardia responding well to a first loading dose of lidocaine (1 mg/kg), followed by a continuous i.v. infusion for the next 24 h (25 μg/kg per min). Five grams of activated charcoal were administered through a nasogastric tube every 4 h for 24 h. Cefuroxime was started (100 mg/kg per day) for suspected aspiration pneumonia.

A third episode of tonic-clonic seizures resolved after a second dose of i.v. diazepam (0.5 mg/kg). The first dose of physostigmine (0.02 mg/kg) was administered [3]. Her temperature decreased (38.0°C) and the agitation and athetoid movements diminished. After two successive doses of physostigmine (at 8 h and 15 h after ingestion) the child was successfully weaned from ventilation. The further evolution was satisfactory, and 24 h after admission the child was extubated. There was still an alteration in her mental status with episodes of agitation and confusion up to 84 h after ingestion. Six days after admission she left the pediatric ICU. Physical examination at discharge showed ataxic walking with enlarged base and turning in of the left foot. The right Babinski reflex was positive. These signs disappeared in the weeks following the hospitalization. She recovered completely.

The plasma levels of orphenadrine were monitored by high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection at 200 and 254 nm. After the addition of trimipramine (300 ng) as internal standard, 1 ml of alkalized plasma was extracted with 5 ml hexane isooamylalcohol (98/2). The chromatographic separation was performed on a C18 column, with a mobile phase of 30% acetonitrile in phosphate buffer (pH 3), the flow being 1.8 ml/min. The oven temperature was 50°C. The retention times for orphenadrine and the internal standard were 4.2 and 7.0 min, respectively. The linearity of the method was satisfactory within the concentration range studied (0.25–4.00 μg/ml).

Initial orphenadrine blood levels were high (3.55 μg/ml) and the drug and/or its metabolites were detected up to 90 h after ingestion (Fig. 1). The calculated elimination half-life was about 10 h.

**Discussion**

Only a small number of orphenadrine poisonings in children have been reported. In children, toxicity seems to begin at blood concentrations of 2 μg/ml and concentrations of 4 to 8 μg/ml may be fatal [1, 4, 5]. In this case the orphenadrine level was 3.55 μg/ml 3 h after ingestion, decreasing exponentially thereafter. Orphenadrine was detected up to 65 h after ingestion, its metabolites (not quantified) up to 90 h. The calculated half-life was 10.2 h, which is somewhat lower than that mentioned in previous papers (14–20 h) [1, 4, 5]. A possible explanation for this phenomenon could be the induction of the cytochrome P450 system caused by the coadministration of phenytoin [6].

Symptoms of orphenadrine intoxication are due to the central and peripheral anticholinergic effects of this medication. The major peripheral manifestations are mydriasis, tachycardia, vasodilatation, urinary retention, hyperpyrexia, and decreased sweating. Confusion, agitation, hallucinations, seizures, and coma reflect the central effect [1]. Direct cardiotoxic effects such as alteration in impulse formation and conduction, dysrhythmia, and heartblock are observed in animal models as well as in human intoxication cases [7, 8]. The cardiotoxic effect could be due to the sodium channel blockade in the myocardial tissue [9]. Research in rats shows that the primary cause of death is respiratory arrest. However, when artificial ventilation is established, death is mainly due to cardiac failure [8].

Orphenadrine absorption is rapid in rats and slow in humans: plasma peak levels are reached only 4 h after ingestion of a therapeutic dose. In cases of overdose, gastric emptying and the absorption are even slower since the anticholinergic effect slows gastric emptying down [2]. Therefore evacuation of the gastric contents should be started as soon as possible and even up to 6 h after ingestion. After gastric lavage, active charcoal can be given through the nasogastric tube.

The use of physostigmine in the treatment of anticholinergic overdose has been well documented but remains controversial [3, 10, 11]. Physostigmine is a reversible anticholinesterase agent and crosses the blood-brain barrier, thereby reversing both peripheral and central anticholinergic effects. Physostigmine has no influence on either the direct cardiotoxic effects or on the respiratory depression. On the contrary, it can suppress respiratory activity and further decrease the heart rate [7, 8].

In this case we counterbalanced the risk of physostigmine administration with its expected benefit. As the neurological signs and the suppression of spontaneous respiration were important, a trial dose of 0.02 mg/kg physostigmine was given [3]. The response was effective, the temperature decreased, and the athetoid movements diminished; there were no more episodes of convulsions. Convulsions are often observed as the first symptom and can already appear at low-dose intoxication [2, 12]. Intravenous or intrarectal administration of diazepam rapidly stops the convulsions [2, 4]. In our patient we noted an effect only after i.v. administration.