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Pediatric Cinnarizine Overdose and Toxicokinetics

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ABSTRACT

Cinnarizine, a piperazine derivative, is a widely prescribed medication for the treatment of vestibular disorders and motion sickness. Cinnarizine has antihistaminic, antiserotoninergic, antidopaminergic, and calcium channel–blocking properties. We present the first report in the English literature of cinnarizine poisoning and toxicokinetics. A 30-month-old toddler ingested 225 mg of cinnarizine, 18 times the recommended dose for older children. Four hours later, she became jittery with a wide-based gait and vomited 3 times. She was examined by her family physician, who reported stupor and twitching in both hands. On admission to the hospital, 6 hours after the ingestion, she was stuporous and had 3 short, generalized tonic-clonic convulsions that were controlled with a single dose of midazolam. Full clinical recovery was seen 10 hours after ingestion. Serum cinnarizine levels were 7407, 2629, and 711 ng/mL on admission and at 4 and 12 hours thereafter, respectively, 26.9 times higher than the therapeutic levels in adults. Elimination rate constant, calculated by linear regression of the ln concentrations of the 3 data points, was 0.19. Half-life, calculated from the equation $t_{1/2} = 0.693/k_{el}$, where k_{el} is the elimination rate constant, was 3.65 hours. The manufacturing company revealed that their database contains 23 reports of cinnarizine overdose (adult and children), received between 1972 and 2004. Clinically, these cases reflect mainly symptoms of alterations in consciousness ranging from somnolence to stupor and coma, vomiting, extrapyramidal symptoms, and hypotonia. In a small number of young children, convulsions developed; recovery was uneventful in 4 cases and not reported in 1. The neurologic complication may be explained by the antihistaminic effect of cinnarizine because central nervous system depression and convulsions are known complications of antihistaminic overdose. It is hypothesized that cinnarizine-induced convulsions also are related to the antidopaminergic effect of the drug. Apart from the convulsions, no other adverse effects related to calcium channel–blocking properties, such as bradycardia or hemodynamic instability, were observed. Pediatric patients with cinnarizine overdose need to be observed in a health care facility for potential neurologic complications and be treated symptomatically. The delay to onset of clinical effect should be considered in the observation period.

CINNARIZINE, A PIPERAZINE derivative, is a widely prescribed medication for the treatment of vestibular disorders and motion sickness.[1] It also has been used as an antiallergic[2] and antiepileptic agent,[3] although this has never been proved or accepted. Cinnarizine has antihistaminic, antiserotoninergic, antidopaminergic, and calcium channel–blocking properties.[1,2,4–6] These various mechanisms of action allow for a wide range of therapeutic effects. However, adverse effects are limited and include mainly transient drowsiness, dizziness, headache, and gastrointestinal disorders.[7,8] Among the rare adverse effects are cholestasis[6,9] and extrapyramidal signs,[6] including worsening of Parkinson's disease.[1] Although cinnarizine is not available in the United States, it is approved in many countries for usage in children who are older than 5 years, but very little is known about its pharmacokinetics and adverse effects in toddlers. To date, no case of cinnarizine overdose has been reported in the English literature.

Key Words: cinnarizine, toddler, intoxication, toxicokinetics, poisoning, overdose
Abbreviations: ED, emergency department; GCS, Glasgow Coma Score; $t_{1/2}$, half-life; CNS, central nervous system

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CASE STUDY

A 2.5-year-old, 13-kg, healthy girl was brought to the emergency department (ED) with a chief complaint of vomiting and stupor. One day before admission, she had fever to 38.7°C and a runny nose but was afebrile and well on the day of admission. Medical history revealed a skull fracture at 1 year of age, without loss of consciousness or intracranial bleeding. Six hours before admission, she was seen playing with a cinnarizine package, which was missing nine 25-mg tablets (17.3 mg/kg). The parents denied all other medications at home except for acetaminophen. Four hours after the ingestion, she became jittery and developed a wide-based gait. One hour later, she vomited 3 times and became lethargic. She was examined by her family physician, who reported stupor and twitching in both hands but no generalized convulsions. On arrival to the ED, her Glasgow Coma Score (GCS) was 8 of 15. Vital signs were as follows: heart rate, 110 beats per minute regular; respiratory rate, 25/minute; blood pressure, 126/65 mm Hg (95th percentile for age: 108/68 mm Hg; blood pressure normalized 1 hour later); and oxygen saturation, 95% in room air. Capillary refill time was <2 seconds, and body temperature was normal. Her pupils were equal, reactive to light, and not dilated, and ocular fundi were normal with no evidence of papilledema. Deep tendon reflexes were absent throughout. The rest of her physical examination was unremarkable. White blood cell count was 15 000/mm^3, hemoglobin was 10.5 mg/dL, mean corpuscular volume was 73 fL, and platelet count was 467 000/mm^3. Serum sodium was 141 mEq/L, glucose was 181 mg/dL, ionized calcium was 1.17 mmol/L, potassium was 3.4 mEq/L, and serum acetaminophen level was undetectable. Liver enzymes, kidney-function tests, urinalysis, and electrocardiogram all were within normal limits. Blood samples for cinnarizine levels were drawn on admission and at 4 and 12 hours thereafter (6, 10, and 18 hours after ingestion).

Shortly after arrival to the ED (~6 hours after ingestion), she had 3 short episodes of generalized tonic-clonic convulsions that were controlled with a single dose of intravenous midazolam (0.1 mg/kg). Convulsions did not recur, and no additional anticonvulsant therapy was required. Ten hours after ingestion, she was fully awake with a GCS of 15 of 15 and normal findings in a comprehensive neurologic examination. She was discharged after an uneventful 24-hour observation period. Electroencephalogram that was performed 8 months after discharge was normal.

Pharmacokinetic Evaluation

Serum cinnarizine concentrations were analyzed by an ion trap mass spectrometer (Finnigan PolarisQ) interfaced to a gas chromatograph (Trace GC 2000; ThermoQuest, Austin, TX). The concentrations measured were 7407 ng/mL, 2629 ng/mL, and 711 ng/mL, on admission and at 4 and 12 hours thereafter, respectively (Fig 1). Elimination rate constant, calculated by linear regression of the ln concentrations of the 3 data points, was 0.19 (r = 0.992). Half-life ($t_{1/2}$), calculated from the equation $t_{1/2} = 0.693/k_{el}$, where k_{el} is elimination rate constant, was 3.65 hours. Assuming that the onset of clinical manifestations (ie, 4 hours after ingestion) occurred at the end of the distribution phase, back extrapolation will yield even higher concentrations than 7407 ng/mL.

DISCUSSION

The recommended dose for cinnarizine in children who are older than 5 years is 6.25 mg to 12.5 mg 3 times daily, and it is not approved for children who are younger than 5 years. In this case, a 2.5-year-old child potentially ingested at least 18 times the recommended dose for older children. The 2 most striking signs were stupor and convulsions.

The peak serum cinnarizine concentration measured in our patient (7407 ng/mL) is 26.9 times higher than the mean maximum concentration (Cmax) that was found in 6 young, healthy adults who received a single dose of 75 mg of cinnarizine (275 ± 36 ng/mL).[10] This increase in Cmax is in the same order of magnitude as the ratio between the dose that our patient ingested and the recommended therapeutic dose in older children (26.9 and 18, respectively). The elimination $t_{1/2}$ that we found (3.65 hours) is in accordance with 1 report, 3.24 hours,[11] and much shorter than that found in another report, 23.6 ± 3.2 hours.[10] It is difficult to explain the different $t_{1/2}$ found in the 2 adult studies, and to the best of our knowledge, there are no data on cinnarizine therapeutic or toxic blood levels and on elimination $t_{1/2}$ in children.

The cause-and-effect relationship between the exposure to cinnarizine and the convulsions is strongly supported by the temporal relationship, the short duration

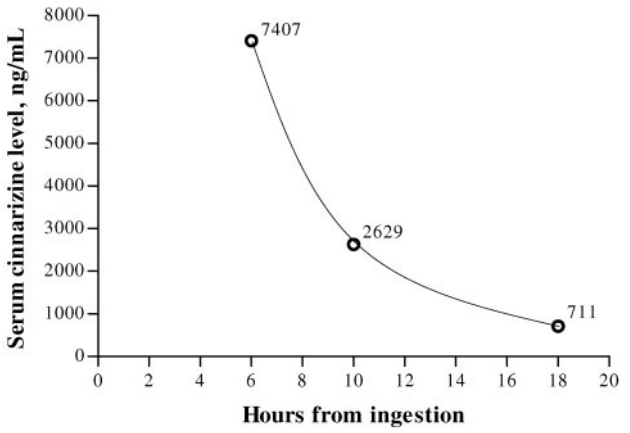

FIGURE 1
Serum cinnarizine concentration (ng/mL) versus time (hours) curve in a toddler who was intoxicated with cinnarizine. The times are per history and therefore probably are correct but not definite.

of the convulsions, the excessive serum cinnarizine levels, the biological plausibility, and the normal follow-up electroencephalogram. Our patient regained full consciousness 10 hours after ingestion. This time course suggests that the toxic effect faded within 2.73 half-lives, corresponding to elimination of 84% of cinnarizine body load.

We performed a Medline search for previous published cases of cinnarizine intoxication and contacted the manufacturing company of cinnarizine (Janssen-Cilag, Johannesburg, South Africa) for any unpublished data. No published cases were found in the English literature, but we received unpublished data from the company. Their Benefit Risk Management database contains 23 reports of overdose with cinnarizine (adult and children), received between 1972 and 2004. The acute cinnarizine intoxications ranged from 90 to 2250 mg. Clinically, these cases reflect mainly symptoms of alterations in consciousness ranging from somnolence to stupor and coma, vomiting, extrapyramidal symptoms, and hypotonia. In a small number of young children, convulsions developed; recovery was uneventful in 4 cases and not reported in 1. The most recent case in the database is of a 4-year-old boy who ingested 2100 mg of cinnarizine with an uneventful recovery. He presented with vomiting, drowsiness, coma, tremor, and hypotonia.

Central nervous system (CNS) depression, as in our patient, may be explained by the antihistaminic effect of the drug. CNS depression and convulsions are known complications of antihistaminic overdose.[12–14] Histaminic pathways are widespread in the CNS and probably involved in sleep–wakefulness balance. CNS adverse effects of antihistamines probably are related to their interaction with the cholinergic, α-adrenergic, and serotonin systems.[15]

Cinnarizine also exerts calcium channel–blocking activity that consequently may reduce dopamine neurotransmission.[16] Patients who were treated with cinnarizine had reduced D2 receptor–binding capacity on single-photon emission computed tomography examination compared with an untreated control group.[5] Similarly, overdose of other drugs with antidopaminergic activity, such as phenothiazines, also can induce convulsions.[16] We suggest that part or all of these mechanisms can contribute to the CNS depression and convulsions in cinnarizine overdose. Apart from the convulsions, no other adverse effects related to calcium channel–blocking properties, such as bradycardia or hemodynamic instability, were observed.

CONCLUSIONS

This is the first case of cinnarizine poisoning and toxicokinetics reported in the English literature. The main clinical signs were CNS depression, wide-based gait, and convulsions. The toddler recovered quickly without sequelae. Although uncommon, pediatric patients with cinnarizine overdose need to be observed in a health care facility for potential neurologic complications and be treated symptomatically. The delay to onset of clinical effect should be considered in the observation period.

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