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. We present the first report in the English literature of pediatric cinnarizine poisoning and toxicokinetics. A 30-month-old toddler ingested 225 mg cinnarizine, 18 times the recommended dose for older children. Four hours later she became jittery with a wide based gait and later became drowsy. She was then examined by her family physician who reported stupor and twitching in both hands. Upon admission, six hours after the ingestion, she was stuporous and had three short generalized tonic-clonic convulsions. Full clinical recovery was seen 10 hours post ingestion. Serum cinnarizine level six hours after the ingestion was 7,407 ng/ml, much higher than the therapeutic levels in adults. Elimination half-life calculated by linear regression was 3.65 hours. It is hypothesized that cinnarizine-induced convulsions are related to antihistaminic mediated cholinergic and antidopaminergic effects of the drug. Pediatric patients with cinnarizine overdose need to be observed in a healthcare facility for potential neurological complications and be treated symptomatically. The delay to onset of clinical effect should be considered in the observation period.

Key words: cinnarizine, toddler, intoxication, toxicokinetics, poisoning, overdose

Introduction:

Cinnarizine, a piperazine derivative, is a widely prescribed medication for the treatment of vestibular disorders and motion sickness (1). It has also been used as an antiallergic (2) and antiepileptic agent (3), although this has never been proven nor accepted. Cinnarazine has antihistaminic, antiserotoninergic, antidopaminergic and calcium channel blocking properties (1, 2, 4, 5, 6). These various mechanisms of action allow for a wide range of therapeutic effects. However, side effects are limited and include mainly transient drowsiness, dizziness, headache and gastrointestinal disorders (7, 8). Among the rare side effects are cholestasis (6, 9) and extrapyramidal signs (6) including worsening of Parkinson Disease (1). Although Cinnarazine is not available in the USA, it is approved in many countries for usage in children older than five years of age but very little is known about its pharmacokinetics and side effects in toddlers. To date, no case of cinnarizine overdose in children has been reported in the English literature.

Case study:

A two and a half year old, 13 kg, healthy female was brought to the Emergency Department (ED) with a chief complaint of vomiting and stupor. One day prior to admission she had fever to 38.7ºC and a runny nose but was afebrile and well on the day of admission. Past medical history revealed a skull fracture at one year of age, without loss of consciousness or intracranial bleeding. Six hours prior to admission she was seen playing with cinnarizine package, which was missing nine 25 mg tablets (225 mg, 17.3 mg/kg). The parents denied all other medications at home except for acetaminophen. Four hours following the ingestion she became jittery and developed a wide based gait. One hour later she vomited three times and became lethargic. She was then examined by her family physician who reported stupor and twitching in both hands but no generalized convulsions. Upon arrival to the ED, her Glasgow Coma Score (GCS) was of 8/15. Vital signs were: heart rate 110 beats/minute regular, respiratory rate 25/min, blood pressure 126/65 mmHg (95^{th} percentile for age: 108/68 mmHg; blood pressure normalized an hour later), oxygen saturation 95% in room air. Capillary refill time was less than two 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 10.5 mg/dL, mean corpuscular volume (MCV) 73fL and platelet count 467,000/mm^3. Serum sodium was 141 meq/L, glucose 181 mg/dL, ionized calcium 1.17 mmol/L, potassium 3.4 meq/L and undetectable acetaminophen levels. Liver enzymes, kidney function tests, urinalysis and electrocardiogram were all within normal limits. Blood samples for cinnarizine levels were drawn on admission and 4 and 12 hours thereafter (6, 10 and 18 hours post ingestion).

Shortly after arrival to the ED (approximately six hours post ingestion) she had three 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 further anticonvulsant therapy was required. Ten hours post ingestion, she was fully awake with a GCS of 15/15 and normal findings in a comprehensive neurological examination. She was discharged after an uneventful 24-hour observation period. Electroencephalogram (EEG) performed eight 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, Texas, USA. The concentrations measured were 7,407, 2,629 and 711 ng/ml, on admission, 4 and 12 hours thereafter, respectively, (Figure). Elimination rate constant (k_{el}) calculated by linear regression of the ln concentrations of the three data points was 0.19 (r=0.992). T½, calculated from the equation T½ = $0.693/k_{el,}$ was 3.65 hours. Assuming that the onset of clinical manifestations (i.e. four hours post ingestion) occurred at the end of the distribution phase, back extrapolation will yield even higher concentrations that 7,407 ng/ml.

Discussion:

The recommended dose for cinnarizine in children older than five years of age is 6.25 mg - 12.5 mg three times daily and it is not approved for children younger than five years of age. In this case, a two and a half year-old child potentially ingested at least 18 times the recommended dose for older children. The two most striking signs were stupor and convulsions.

The peak serum cinnarizine concentration measured in our patient (7,407 ng/ml) is 26.9 times higher than the mean Cmax found in six young healthy adults receiving a single dose of 75 mg cinnarizine (275 ± 36 ng/ml) (11). This increase in Cmax is in the same order of magnitude as the ratio between the dose she ingested and the recommended therapeutic dose in older children (26.9 and 18, respectively). The elimination half life we found (3.65 hours) is in accordance with one report, 3.24 hours (12), and much shorter then that found in another report, 23.6 ± 3.2 hours (11). It is difficult to explain the different half-life found in the two adult studies and to the best of our knowledge, there are no data on cinnarizine therapeutic or toxic blood levels and on elimination T½ 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 of the convulsions, the excessive plasma cinnarizine levels, the biological plausibility, and the normal follow-up EEG. Our patient regained full consciousness ten 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, 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 overdoses ranged from 90 to 2,250 mg. Clinically, these cases reflect mainly symptoms of alterations in consciousness ranging from somnolence to stupor and coma, vomiting, extrapyramidal signs and hypotonia. In a small number of young children, convulsions developed; recovery was uneventful in four cases and not reported in one.

Central nervous system (CNS) depression, as in this patient, may be explained by the antihistaminic effect of the drug. CNS depression and convulsions are known complications of antihistaminic overdose (13, 14, 15). Histaminic pathways are widespread in the CNS and probably involved in sleep/wakefulness balance. CNS adverse effects of antihistamines are probably related to their interaction with the cholinergic, α-adrenergic and serotonin systems (16).

Cinnarizine also exerts calcium channel blocking activity that may consequently reduce dopamine neurotransmission (17). Patients treated with cinnarizine had reduced D2 receptor binding capacity on SPECT examination compared with an untreated control group (18). Similarly, overdose of other drugs with anti-dopaminergic activity, such as phenothiazines, can also induce convulsions (19). 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 side effects related to calcium channel blocking properties, such as bradycardia or hemodynamic instability, were observed.

For summary, 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 healthcare facility for potential neurological complications and be treated symptomatically**.** The delay to onset of clinical effect should be considered in the observation interval.

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Figure legend:

Cinnarizine concentration (ng/ml) versus time (hours) curve in a toddler intoxicated with cinnarizine. The times are per history and therefore are probably correct but not definite.