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Acute exposure to imidazoline derivatives in children

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Abstract

Objectives: To study acute exposure to imidazoline derivatives in 72 children younger than 15 years of age, followed-up from January 1994 to December 1999.

Method: This is a retrospective study of 72 patients with age between 2 months and 13 years (median 2 years; 25-75% = 1 to 3 years old) exposed to naphazoline (N = 48), fenoxazoline (N = 18), oxymetazoline (N = 5) and tetrahydrozoline (N = 1), through oral (N = 46), nasal (N = 24) or unknown (N = 2) routes.

Results: Fifty-seven children developed clinical manifestations such as somnolence (N= 34/57), sweating (N = 20/57), pallor (N = 17/57), hypothermia (N = 16/57), bradycardia (N=13/57), cool extremities (N = 9/57), restlessness (N = 7/57), tachycardia (N = 6/57), vomiting (N= 5/57), irregular respiratory pattern and apnea (N = 5/57), miosis/mydriasis (N = 4/57). Naphazoline was the active ingredient most frequently involved (N = 47), followed by fenoxazoline (N = 5) and oxymetazoline (N = 4). The onset of clinical manifestations was rapid, beginning within 2 hours after exposure in 32/57 children. Only supportive measures were employed, with one child requiring mechanical ventilation after accidental naphazoline ingestion. In most of the children resolution of symptoms occurred within 24 hours (N = 39/57). No deaths were observed. Patients exposed to naphazoline (N = 47/48) presented a higher frequency of clinical signs of poisoning in comparison with those exposed to fenoxazoline (N = 5/18) ($p < 0.001$). There were no significant differences in the frequency of patients who presented clinical manifestations considering the route of exposure [oral (N = 34/46), nasal (N = 21/24); $p = 0.31$].

Conclusion: Most children (especially those younger than 3 years) exposed to imidazoline derivatives (especially naphazoline) presented early signs of poisoning regardless of the exposure route (nasal or oral). The main signs observed were nervous system, cardiovascular and respiratory depression. Most children showed complete resolution of the symptoms within 24 hours.

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Introduction

Imidazoline derivatives are often employed as topical nasal and ocular decongestants, with rapid and prolonged action.[1-6] Its therapeutic action results from stimulation of the peripheral post-synaptic a2-adrenergic receptors of the mucosa, causing local vasoconstriction and, eventually

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systemic vasoconstriction and it may cause transitory arterial hypertension, pallor and diaphoresis.[1-5,7-10] Imidazoline derivatives can also stimulate post-synaptic α_2-adrenergic receptors at cardiovascular and central nervous system control centers, causing inhibition of cerebral sympathetic outflow.[5,7-9] In such situations patients, primarily children, may present bradycardia, arterial hypotension and neurological and respiratory depression resulting from toxic or "therapeutic" doses.[1,5,7,9-16]

According to data from the National Agency for Sanitary Vigilance (ANVISA- Agência Nacional de Vigilância Sanitária, May 2003), the main imidazoline derivatives found on the Brazilian market in the form of topical decongestants are naphazoline (59 products registered), oxymetazoline (15 products registered), fenoxazoline (nine products registered), tetrahydrozoline (eight products registered) and xylometazoline (four products registered). These products are indicated for symptomatic relief of acute conjunctivitis, rhinitis and/or adenoiditis, having little or no effect on chronic rhinitis and sinusitis or on vasomotor rhinitis.[1,3-7] The decongestant action begins after around 5 to 10 minutes, and the duration of the therapeutic effects of naphazoline and fenoxazoline varies from 3 to 6 hours, while for oxymetazoline it can be from 6 to 12 hours.[2,4,6] Continuous use of these medications for a few days can cause uncomfortable congestive rebound effects and rhinorrhea.[2,4,6] Despite the widespread use of these drugs and the potential risks of their use with children there is no consensus on their posology or the duration of treatment and they can be obtained without medical prescriptions.[1,5,7,9-11]

Based on these observations, the objective of this study was to perform a retrospective analysis of cases of acute exposure to imidazoline derivatives in children aged less than 15 years, followed by the Poison Control Center at the Medical Sciences Faculty of UNICAMP (CCI-FCM-UNICAMP), during the period between January 1994 and December 1999.

Methods

Medical records of patients followed by CCI-FCM-UNICAMP were selected by searching the center's database, using the following keywords: imidazoline derivatives, age less than 15 years and period between January 1994 and December 1999. The information contained in the medical records was checked by two observers and the following variables extracted to fill out the study protocol: age, sex, commercial name of the product involved, active ingredient and concentration, time interval between exposure and attendance at the CCI, exposure route, signs and symptoms observed, period of symptom remission, treatment employed and progress. In order to analyze the distribution of variable frequency a new database was created using Epi-Info 6.04 (CDC, Atlanta, GA, USA).

One hundred and four cases were analyzed, of which 72 were selected for the study. The criterion for inclusion was that all variables to be analyzed were present on the protocol, including monitoring of the patient until complete recovery from the clinical condition. The difference in frequency between given variables was compared using the chi-square test and Fisher's exact test. Values of $p < 0.05$ were considered to represent statistical significance. The project was approved by the Committee for Ethics in Research of FCM-UNICAMP, hearing 461/2001.

Results

The age of the 72 children treated varied from 2 months to 12 years, with a median of 21 months (25-75% = 12-36 months) and a mean of 26 + 23 months and 51.4% were female. In 46 cases exposure was via the oral route, via nasal in 24 and unknown in two cases. The median of time passed between exposure and first contact with the CCI was 2 hours (25-75% = 1 to 5 hours).

The brand names and active ingredients employed in the 72 cases are listed in Table 1, with products containing naphazoline as the active ingredient highlighted.

Of the 72 patients studied, 15 remained asymptomatic, the majority exposed to fenoxazoline (N = 13, Table 2). Comparing the frequency of symptomatic and asymptomatic patients according to the active ingredients naphazoline and fenoxazoline, it will be observed that patients exposed to naphazoline presented a greater risk of exhibiting clinical manifestations indicative of intoxication [Table 2; naphazoline (47/48) vs. fenoxazoline (5/18); Fisher's exact test, $p < 0.001$]. When considering the route of exposure in terms of the presence or absence of clinical manifestations [oral (N = 34/46) vs. nasal (N = 21/24)], the difference is not statistically significant (Table 3; chi-square test, $p = 0.31$).

Of the 57 patients that presented clinical manifestations, the great majority had been exposed to naphazoline (Table 2), with somnolence, diaphoresis, pallor, hypothermia and bradycardia the most common (Table 4). Only one patient, one year old, who had ingested a bottle of Sorine adulto® (naphazoline at 0.05%), required mechanical ventilation and was discharged from hospital in 3 days. The majority of the patients (68.4%) were asymptomatic 24 hours after exposure. There were no deaths.

Although the information on case development and outcome was incomplete for the excluded group (N = 32), this group was no different from the study group in terms of demographic characteristics and variables analyzed: age group (median = 20 months, 25-75% = 7 to 36 months); gender [female (N = 18), male (N = 13), not recorded (N = 1)]; interval, in hours, between exposure

Table 1 - Brand names, active ingredient and concentration of imidazoline derivates involved in 72 cases of acute exposure in children

Brand name	Active ingredient	Concentration (%)	n	%
Multigen-AL®	naphazoline	0.05	20	27.8
Aturgyl®	fenoxazoline	0.05* - 0.1	18	25.0
Sorine adulto®	naphazoline	0.05	13	18.1
Naridrin®	naphazoline	0.05* - 0.1	8	11.1
Afrin®	oxymetazoline	0.025* - 0.05	5	6.9
Privina®	naphazoline	0.05	2	2.8
Nazobio®	naphazoline	0.05	1	1.4
Lerin®	naphazoline	0.05	1	1.4
Visodin®	tetrahydrozoline	0.05	1	1.4
Non mentioned	naphazoline		3	4.2
Total			72	100.0

* Concentration of the active ingredient in preparations for pediatric use.

and attendance at the center (median = 2 hours, 25-75% = 1 to 5 hours); exposure route [nasal (N = 13), oral (N = 18), not recorded (N = 1)] and active ingredients involved [naphazoline (N = 26), fenoxazoline (N = 5) and oxymetazoline (1)].

Discussion

Imidazoline derivatives have been widely used since the 1940s, when naphazoline was launched on the pharmaceutical market.[2,4,11,14] Since then, sporadic works, the majority in the form of isolated case reports, have warned of the risks of the indiscriminate use of these drugs, primarily with children less than 2 years old.[5,7,9-14,16] Among papers published since 1970, only three studies described clinical series of patients exposed to imidazoline derivatives,[9-11] the results of which were similar to those described for the current series, highlighting neurological, cardiovascular and respiratory manifestations (Table 4). Of the 64 cases described by Bruni,[11] 74.9% occurred among children less than 2 years old. Mahieu et al.[9] analyzed 261 cases of exposure to imidazoline derivatives followed by

Table 2 - Comparison between the groups of asymptomatic and symptomatic patients among 72 children with acute exposure to imidazoline derivates according to the active ingredient

Active ingredient	Symptomatic	Asymptomatic	Total
Naphazoline	47	1	48
Fenoxazoline	5	13	18
Oxymetazoline	4	1	5
Tetrahydrozoline	1	0	1
Total	57	15	72

Table 3 - Main routes of exposure to imidazoline derivates among 57 children who presented clinical manifestations of toxicity according to the active ingredient

Active ingredient	Oral	Nasal	Unknown	Total
Naphazoline	28	18	1	47
Fenoxazoline	4	1	0	5
Oxymetazoline	2	2	0	4
Tetrahydrozoline	0	0	1	1
Total	34	21	2	57

Table 4 - Clinical manifestations of intoxication presented by 57 children after acute exposure to imidazoline derivatives

Clinical manifestations	n	%
Somnolence	34	57.9
Diaphoresis	20	35.1
Pallor	17	29.8
Hypothermia	16	28.1
Bradycardia	13	22.8
Cold extremities	9	15.8
Restlessness	7	12.3
Tachycardia	6	10.5
Nausea/vomiting	5	8.8
Bradypnea	3	5.3
Apnea	2	3.5
Mydriasis	2	3.5
Miosis	2	3.5

the Belgian Poison Control Centre, from 1986 to 1991, describing a more detailed analysis of 19 children. Of the 261 cases, 89.6% were children less than 4 years old, 75% due to accidental ingestion 25% after "therapeutic" use as nasal topicals (24%) or eye drops (1%).

The time passed between exposure and first contact with the CCI was less than 2 hours in 56.3% of the 72 patients. This is due to the rapid absorption of imidazoline derivatives, resulting in the early appearance of clinical manifestations.[2,4,6] Fifty of the 72 children exposed to imidazolines were less than 2 years old, representing 7% of all patients exposed to medications within this age group (N = 50/719), followed by the CCI during the period studied (1994-1999).

Of the 57 symptomatic patients, oral (N = 34) and nasal (N = 21) routes were the most common. Multigen-AL® was the main commercial product involved in naphazoline exposure (N = 20/48) and all of the children who had been exposed to this product developed clinical manifestations. Despite the nonexistence of any indications for imidazoline derivatives administered sub-lingually as systemic decongestants,[2,4,6] naphazoline (0.05%) is contained in this formulation associated with a pool of antigens, employed for "desensitization" of atopical patients via this route. The other patients exposed to imidazoline derivatives via oral route, and who presented clinical manifestations, must have been the result of accidental use. In respect of symptomatic patients exposed via nasal route, it is presumed that these manifestations were the result of toxic effects from indiscriminate use or from adverse effects. Commercial formulations for pediatric use contain, in general, half the concentration of those for adults[1,4,7] (Table 1). Taking the body surface area of RN and infants into account, these age groups may be being exposed to potentially toxic doses of these medications.

Pharmacology texts, from the British Pharmacopoeia and on treatment, during the 70s and 80s were already warning of the risks of using topical decongestants with children.[2,4,6] According to Schvartsman,[6] naphazoline should not be used with children less than six years old. This author recommends the use of oxymetazoline or xylometazoline as topical nasal decongestants for children between 2 and six years of age, and does not indicate any of these drugs for the under two years age group. In the data analyzed here, it was found that 47/48 of those exposed to naphazoline developed clinical manifestations, including cases where usage was topical and nasal (18 children, Table 3), while 13/18 of those exposed to fenoxazoline remained asymptomatic. This data indicates that topical fenoxazoline use for children may, perhaps, be safer than with naphazoline (Table 2).

Although there is no specific treatment, naloxone has been suggested as a possible antagonist[7,9,15] and is often employed in cases of intoxication by clonidine,[17-21] an α2-agonist drug derived from imidazoline used as a centrally acting anti-hypertension agent.[8,17-19] As it is opioid-like, clonidine has been indicated for the treatment of patients who are dependent on opioid drugs.[8,17-20] Intoxication by clonidine causes similar clinical manifestations to those produced by other imidazoline derivatives.[17-21] however there are no controlled trials proving the efficacy of naloxone in cases of intoxication

by topical decongestants. According to the literature consulted, naloxone was employed for just one fifteen-month old patient who had been exposed to oxymetazoline, without success.[9]

Once an hour has passed after ingestion, gastric lavage is no longer recommendable due to the rapid rate of absorption and the central neural depressive effect , increasing aspiration risks.[5,7,9,22] An isolated dose of activated charcoal may be of use up to one hour after ingestion, but the risk of aspiration is still present.[5,7,9,23] Despite these risks, a single dose of activated charcoal (N = 21) and gastric lavage (N = 14) were used with symptomatic children and there is no record of aspiration in any of the patients. Treatment of the clinical manifestations is basically symptomatic and supportive, including mechanical ventilation for patients with severe respiratory depression, while the use of atropine is questionable,[5,7,9] but was used with one patient in this series. Remission of the symptoms generally occurs in 24 to 36 hours.[1,5,7,9-14,16] In the current series, mechanical ventilation was employed in just one case and 68.4% of the patients were asymptomatic 24 hours after exposure.

Although 32 cases were excluded, the data from this group suggest that their removal will not have interfered with the results presented by the study group, indicating that there should not have been selection bias.

Within the methodological limits of a retrospective, it can be concluded that acute exposure to imidazoline derivatives, particularly to naphazoline and in children less than three years old, causes, in the majority of cases, irrespective of the exposure route (oral or nasal), the rapid appearance of clinical manifestations of intoxication, of which neurological, cardiovascular and respiratory depression stand out. These manifestations abate, in general within 24 hours of exposure. It can also be inferred that products containing these active ingredients should be indicated with great caution for this age group, calling particular attention to the risks of administering Multigen-AL®.

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