CLUSTER OF NAPHAZOLINE AND PHENYLEPHRINE INTOXICATIONS IN CHILDREN DUE TO A COMPOUNDING PHARMACY ERROR

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Objective: We present 6 cases of intoxication after inadvertent use of a naphazoline and phenylephrine preparation for the reconstitution of oral antibiotic solutions.

Case report: A nasal decongestant solution was mistakenly used in a pharmacy as a diluent to reconstitute antibiotic suspensions. The solution contained 1 mg/ml naphazoline and 2.5 mg/ml phenylephrine (full composition in table 1). The pharmacist discovered the mistake and alerted the Poison Centre when a 1 year old boy presented with pallor after the intake of 4 doses of Augmentin®. Over the last 4-5 days, the same solution was used for the preparation of antibiotic suspensions delivered to 6 other children. We advised the pharmacist to inform the parents and to refer the children to the hospital for medical assessment. Within one day, 6 children presented at the emergency unit of the local hospital. The patients, aged from 16 months to 12 year old, had received between 2 to 12 doses of 4 to 5 ml. Patients characteristics are presented in table 2. We received limited information about a seventh child, the elder sister of case 5, and did not include her in the table.

Bradycardia, pallor and somnolence were the most frequent symptoms. Headache, vomiting and photophobia were additional symptoms reported in a 8 year old boy (case 5).

All children developed mild symptoms which resolved spontaneously after 24h. Case 5 remained 5 days in the hospital because of a confirmed influenza infection.

Table 1 Product composition

Substance	Quantity	%
Phenylephrine	12,5 g	0,25
Naphazoline	5 g	0,1
Glycerine	100 g	2
Propylene glycol	100 g	2
Chlorbutol	25 g	0,5
Eucalyptol	2,5 g	0,05
Menthol	1,5 g	0,03
Niaouli Oil	1,35 g	0,027
Na EDTA	0,75 g	0,015
Distilled water	ad 5 L	-

Table 2. Patient characteristics, number and volume of doses received, quantity of naphazoline (Naph) and phenylephrine (PE), symptoms and duration of medical observation (case n° 1: index case).

Case number	Gender	Age	Weight	Number of doses	Volume (ml)	Naph (total, mg)	Naph mg/kg/dose	PE (total, mg)	PE mg/kg/dose	Bradycardia	Pallor	Somnolence	Vomiting	Diaphoresis	Headache	Photophobia	Ataxia	Duration (days)
1	M	1 y	10	4	4	16	0,4	40	1,0	-	1	1	-	-	-	-	-	1
2	F	16m	11	8	5	40	0,5	100	1,1	1	1	1	1	-	-	-	1	1
3	M	19m	13	2	5	10	0,4	25	1,0	1	-	1	-	1	-	-	-	1
4	M	6 y	?	10	5	50	?	125	?	1	1	1	-	-	-	-	-	1
5	M	8 y	41	11	5	55	0,1	137,5	0,3	1	1	-	1	-	1	1	-	5
6	M	12 y	44	12	5	60	0,1	150	0,3	1	1	1	-	1	-	-	-	1
Total (by symptom)										5	5	5	2	2	1	1	1	

Discussion: Naphazoline, an imidazoline derivative, and phenylephrine are α-adrenergic agents commonly used in nose drops for their vasoconstrictive and decongestive properties.

Imidazoline derivatives have a narrow therapeutic index. [1,4,6] This is particularly true for naphazoline.[3,6] Even small doses can lead to systemic manifestations. [4] Nasal and oral absorption of naphazoline can induce central nervous system depression, cardiovascular adverse effects and/or respiratory depression more particularly in young children.[1,2,3]

The estimated toxic dose of naphazoline after oral intake is 0.1mg/kg under 2 years of age and 0.3 mg/kg for children over 2 years.[5] By the intranasal route, toxicity may occur at doses of 0.05 mg/kg.[2] Naphazoline is rapidly absorbed after oral administration. Clinical features may develop within the first hour(s) after intake, peaking after 8 hours.[1,2] Complete resolution of symptoms is usually observed within 24 hours.[3]

Phenylephrine has a low oral bioavailability owing to irregular absorption and first pass metabolism. By the oral route, the toxic threshold is considered to be 1 mg/kg. Its plasma half-life is 2 to 3 hours. In this series, the dose of epinephrine was below or close to the toxic threshold in all patients. The 3 younger children (highlighted in table 2) were repeatedly exposed to doses of naphazoline 4 fold above the estimated toxic dose (0.1 mg/kg). The observed effects are most probably. mainly due to naphazoline.

References

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Conclusions

This series confirms the observations from previous reports that sleepiness, pallor and bradycardia are frequent features of naphazoline intoxication.[1] Strikingly, the clinical picture in young children who received repetitive doses, each one well above the estimated toxic threshold, was not more severe than in the older children exposed to multiple "infra-toxic" doses.