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Case report

# Naphazoline intoxication in a child—a clinical and forensic toxicological case

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**Abstract**

The imidazoline derivative naphazoline, an $\alpha_2$-adrenergic agonist, is used as non-prescription eye and nasal preparation because of its vasoconstrictive and decongestive properties. Especially in children, overdose and/or systemic side effects due to absorption can quickly cause severe central nervous system depression and cardiovascular adverse effects. In a 7-year-old boy was diagnosed a naphazoline intoxication by toxicological analysis. The case was also of forensic interest, because the naphazoline mixture was prepared in a pharmacy in a concentration 80 times above the adequate dosage for children. In general, physicians, pharmacists and the public should be educated about the toxicity of over-the-counter preparations.



*Keywords:* Imidazoline; Naphazoline; Intoxication; Children; Pediatric; Forensic

## 1. Introduction

The imidazoline derivative naphazoline belongs to the $\alpha_2$-adrenergic agonists which are used in over-the-counter eye and nasal preparations because of its vasoconstrictive and decongestive properties (Fig. 1). Other derivatives include tetrahydrozoline, oxymetazoline, and xylometazoline. Inappropriate use or unintentional ingestion of these agents especially in children can quickly cause severe central nervous system depression and cardiovascular adverse effects [1–5]. We report about a 7-year-old boy, who has been treated for 2 days in a hospital with the diagnosis of convulsions in connection with intoxication of naphazoline. The case is also of forensic interest because the naphazoline mixture was prepared in a pharmacy in a concentration 80 times above the adequate dosage for children.

## 2. Case report

A 7-year-old boy was inconspicuous until the evening. Suddenly he began to vomit repeatedly, rolled his eyes, and has been unconscious for 2 min. After that he had a headache. Before this attack he was treated once with Vomex A Supp (40 mg) and nose drops. At hospitalisation in reduced general condition the patient was described as somnolent with paleness of the skin and rolling eyes. Reaction only was found in case of strong pain stimulus. Additionally eupnea, a reddened throat, bradycardia, diminished bowel sounds, reduced tonus of the musculature, and miosis were diagnosed. In the hospital initially a CCT was made to exclude an intracranial bleeding. Laboratory parameters as well as blood gas analysis showed no abnormalities, so that the boy was hospitalised into the intensive care unit and treated with infusion therapy. A persistence of bradycardia near 50 bpm for the first 6 h was observed with a blood pressure initially at 145/95 mm Hg. The patient was still somnolent. Awakening and adequate reactions were only found after 6 h of time with retrograde amnesia for the events of the

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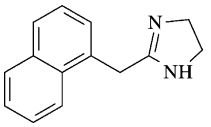
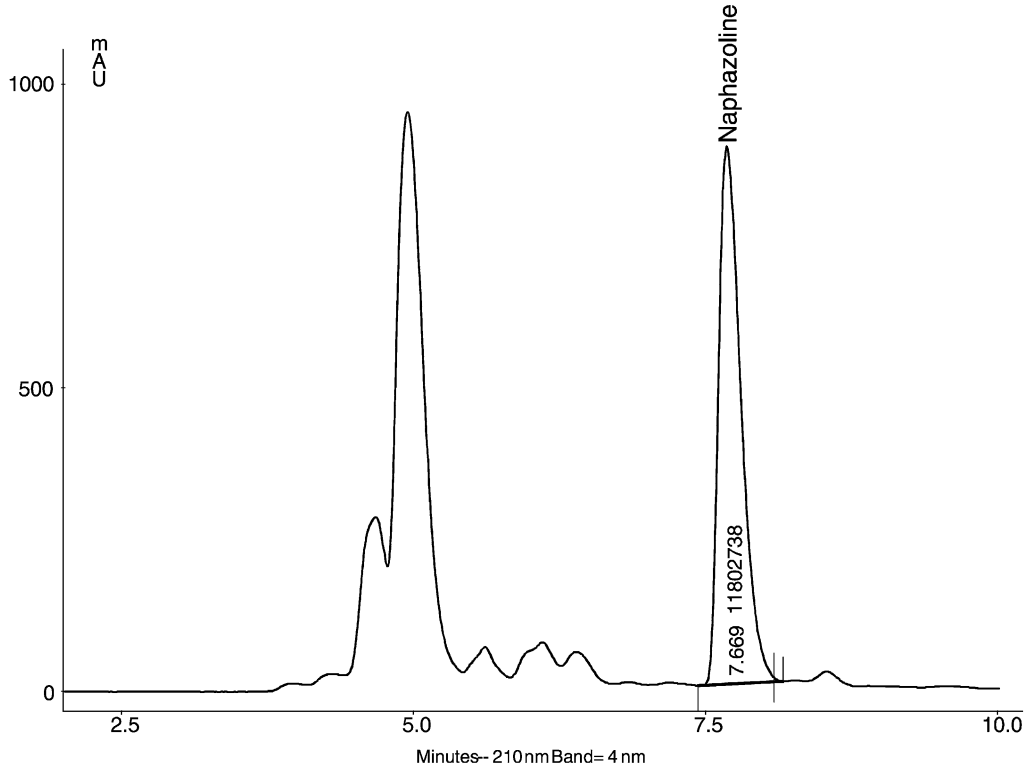



Fig. 1. Naphazoline.

preceeding hours. After quick normalisation of the vital parameters a transfer to the regular ward was possible. Under close-meshed monitoring there were no pathological parameters observed.



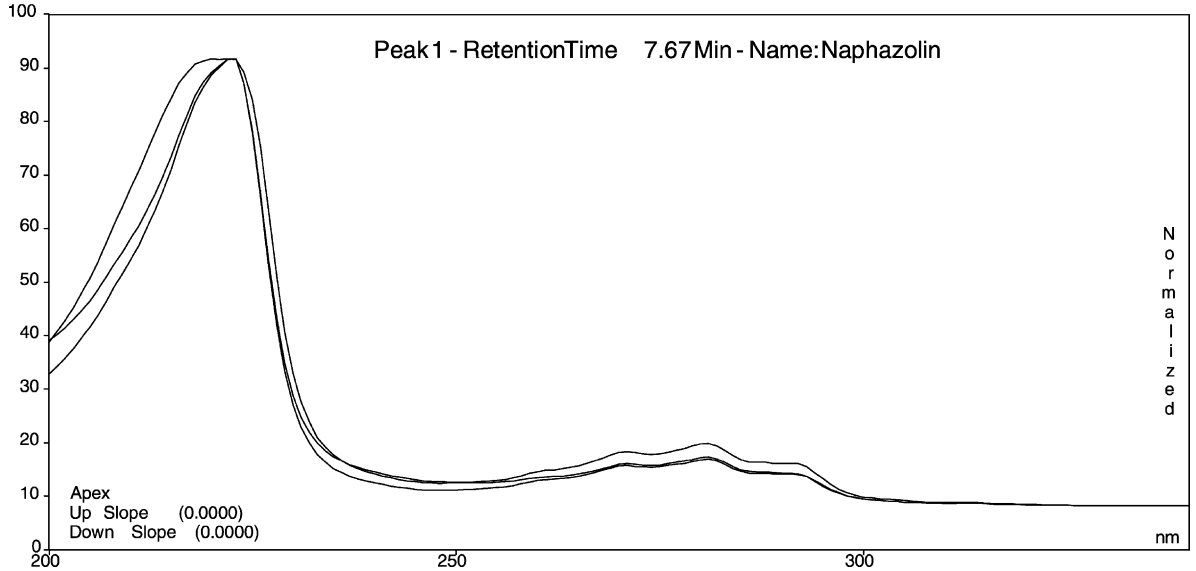




Fig. 2. Urine analysis (1 ml) using HPLC/DAD after LLE with dichloromethane at pH 9. Additionally vomitted gastric content as well as the nose drop solution were analysed.

## 3. Toxicologic analysis

A urine sample and vomitted gastric content were assayed for acidic, neutral, and basic drugs using the established routine procedures. These are immunochemical methods (CEDIA DAU using a Hitachi 911, Microgenics, Passau, Germany) and liquid–liquid extraction (LLE) as well as solid-phase extraction (SPE) procedures with further analysis by gas chromatography-mass spectrometry (GC-MS), and high performance liquid chromatography with diode array detection (HPLC/DAD) [6,7]. Additionally the REMEDi HS drug profiling system, an automated HPLC-based instrument, was used to identify basic and neutral drugs according the guidelines of the manufacturer (BIORAD, Munich, Germany). The latter gave first evidence of the presence of naphazoline in the urine sample and vomit. These results were confirmed by HPLC/DAD after LLE at pH 9 using dichloromethane (Fig. 2). Additionally the nose drop solution was quantitatively analysed by HPLC/DAD. Naphazoline was found in following concentrations:

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|---|---|
| Urine (mg/l) | 1.32 |
| Vomitted gastric content (mg/l) | 0.64 |
| Nose drop solution (mg/l) | 40 |

## 4. Discussion

The chemical–toxicological analysis furnished the proof for the presence of naphazoline in the given nose drops as well as in the vomitted gastric content and in the urine sample of the boy. Pharmacologic actions of such imidazoline derivatives are peripheral and central $\alpha_2$-adrenergic receptor stimulation. The topical vasoconstrictor activity of these $\alpha$-sympathomimetica prompts their use in nasal mucosal congestion and conjunctival hyperemia. Because of the danger of systemic side effects due to absorption a careful dosage is particularly recommended with infants, children and sensitive patients. Clinically, patients may exhibit miosis, mydriasis, palpitations, hypertension or hypotension, bradycardia, pallor, cyanosis, diaphoresis, anxiety, insomnia, tremor, agitation, hallucinations, seizures, lethargy, obtundation, and coma [8]. A specific antidote does not exist, treatment is symptomatic and supportive. It has been hypothesised that naloxone might be beneficial in imidazoline toxicity. Crucially for the prognosis of the intoxication is an excorporation of the drug as fast as possible if necessary by means of nose gastrolavage. Under safety device of the vital functions a clinical treatment is possibly indicated. Most cases of serious toxicity in children followed unintentional oral ingestion [1]. The ingestion of only 2.5 ml of 0.05% tetrahydrozoline (1.25 mg) has resulted in respiratory depression [9]. Otherwise appropriate intranasal administration of as little as one or two drops of a 0.1% imidazoline solution has produced central nervous system depression in infants [10,11]. Intoxication occurs regularly at doses of naphazoline 0.05 mg/kg body weight after nasal application, 0.1 mg/kg after oral ingestion in babies and 0.3 mg/kg after oral ingestion in children older than 2 years. Because of rapid absorption, symptoms develop within the first hour, peak after 6–8 h, and disappear after approximately 12–36 h [2]. Otherwise according to our knowledge no fatalities were described in literature. Babies and infants may receive naphazoline only in strongly diluted solutions. With a concentration of 0.5 mg/ml (0.05%) naphazoline is available as nose spray for children prescription-free in trade. The nose drop solution given by the parents in the described case had been manufactured in a pharmacy. An analysis resulted in a concentration of 40 mg/ml (4%), which was 80 times above the adequate dosage for children. Considering the content in the solution and the proof of naphazoline in the vomit the symptomatology could be explained easily by systemic naphazoline effects. Due to the positive treatment process the parents of the boy did not prosecute the responsible person of the pharmacy. In the context of an apology after examination of the toxicologic results a dilution error was granted from her side.

In summary, also an usually harmles valid medication—here nose drops had been indicated—can lead possibly to a substantial intoxication. An appropriate first suspicion should be pursued in the context of a clinical–toxicological investigation in any case with useful analytical methods, in order to give the clinician a certainty and a security regarding therapies which can be introduced as fast as possible. In a lot of cases a clinical–toxicological analysis can later possibly be seen under forensic aspects as demonstrated in our case report. In the opinion of some pediatrics, imidazoline containing medications should be discouraged for children under 7 years of age and kept out of their reach [5]. In general, physicians, pharmacists and the public should be educated about the toxicity of over-the-counter preparations.

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