Research Results in Pharmacology

Research Results in Pharmacology 7(3): 93–100
UDC: 615.009·036.11·053.3·092
DOI 10.3897/rrpharmacology.7.70242

Research Article

Pathogenetic features of acute naphazoline poisoning in children

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Academic editor: Tatyana Pokrovskaia ♦ **Received** 17 June 2021 ♦ **Accepted** 12 September 2021 ♦ **Published** 29 September 2021

Citation: Karpushkina ES, Zhdanova OA, Batishcheva GA, Petukhova YuA (2021) Pathogenetic features of acute naphazoline poisoning in children. Research Results in Pharmacology 7(3): 93–100. https://doi.org/10.3897/rrpharmacology.7.70242

Abstract

Introduction: Acute poisoning by nasal decongestants is an important issue in pediatrics due to physiological and anatomical characteristics of the child's body and pharmacokinetics of drugs in early childhood.

Epidemiology: The number of poisonings by this group of drugs ranged from 4% to 39% during the period from 2000 to 2018. All the studies reported that the most severe degree of intoxication was observed in children aged 1–3 years.

Mechanism of action of nasal decongestants: The peculiarity of selective alpha2-adrenergic agonists is that when taken orally, misused or overdosed, they lose their selectivity for the target receptor. As a result, the drug causes acute poisoning and most often this effect occurs in children and adolescents.

Clinical features and diagnostic criteria: Clinical signs of acute poisoning can appear both as a result of an overdose of the nasal decongestants and due to a therapeutic use of the drug according to the instruction. The symptoms are manifested by hypothermia, skin pallor, bradycardia, arterial hypotension, profuse sweating, and acrocyanosis.

Imidazoline receptors and new opportunities: It is assumed that toxic effect of topical decongestants occurs not only by activation of alpha2-adrenergic receptors, but also through their influence on the selective imidazoline receptors. Based on the structure of these drugs, it is assumed that imidazoline receptors are the primary binding site for these drugs.

Conclusion: Understanding the described mechanisms of alpha2-adrenergic agonist action and peculiarities of the child's symptoms in acute poisoning is necessary for the timely diagnosis and selection of the correct treatment strategy.

Keywords

acute poisoning, children, alpha2-adrenergic agonists, naphazoline, mechanism of action, imidazoline receptors.

Introduction

Acute respiratory viral infection is the most frequent disease warranting a visit to a pediatrician and accounts for more than 90% of all outpatient visits among the children (Pshenichnaya et al. 2018). A viral infection is the most common cause of rhinosinusitis, triggers a number of inflammatory reactions and disrupts the autonomic innervation of the nasal mucosa increasing production of goblet cells (Kaliner et al. 1997). A large number of studies confirm the fact that a viral infection triggers an inflammatory process in the respiratory tract, which remains even after the virus is removed and leads to prolonged symptoms of rhinosinusitis (Gwaltney 2002). This mechanism

is based on various inflammatory mediators (leukotrienes, tumor necrosis factors, interleukins, histamine, etc.). Therefore, drugs acting on various receptors are used to reduce nasal edema. Local vasoconstrictor drugs, or nasal decongestants, which are targeted at alpha-adrenergic receptors, are widely used with a decongestant purpose in nasopharyngitis therapy in children (Naclerio et al. 2010; Baranov et al. 2015).

Unfortunately, acute poisoning by nasal decongestants often occurs in pediatric practice. These cases are most frequently associated with the use of imidazoline derivatives, primarily naphazoline (Wenzel et al. 2004).

On the one hand, growth of acute poisoning by nasal decongestants is due to the uncontrolled use of this group of drugs by parents. On the other hand, local pediatricians often ignore use of drugs of this group, neither explain the dosage regimen, frequency of administration of decongestants, nor focus on the age-related peculiarities of the nasal mucosa in children which has a high resorptive capacity (Karpova et al. 2018).

The specific feature of acute poisoning by this group of drugs is that the first signs of intoxication, such as drowsiness, hypothermia and skin pallor, remain unnoticed by the parents. As a result, more than 93% of the children were admitted to the intensive care unit or the toxicology department late (more than 4 hours) after the onset of the poisoning (Piskareva et al. 2008).

The aim of the research is to assess the current state of the problem of acute poisoning by nasal decongestants among the child population based on the analysis of the Russian and foreign studies. PubMed, e-Library, RSCI and other databases were used to study characteristics of alpha-adrenergic agonists and clinical features of acute poisoning by imidazoline derivatives in children. 43 publications for the period of 2000–2020 were analyzed.

Epidemiology

An increase in acute poisoning by nasal decongestants deserves special attention both in Russia and all over the world. According to some data, the share of poisonings by this group of drugs ranged from 4% to 25.9% during the period from 2000 to 2018 (Petukhova et al. 2019; Shilov et al. 2019; Zhamlikhanov and Fedorov 2019). Most often the poisoning occurred when drugs with naphazoline as the main active ingredient were used (up to 86.8% of all the poisonings by drugs of this group) (Tulupov et al. 2018; Petukhova et al. 2019; Shilov et al. 2019). According to the foreign studies in several countries, such as Croatia, Belgium and France, cases of acute poisoning by naphazoline were noted both after its normal therapeutic usage and due to overdose (Taylor and Maslov 2013; Lowry and Brown 2014; Díaz et al. 2018; Euwema and Swanson 2020). Depression of the central nervous system (alteration of consciousness progressing to coma) occurred in case of an accidental ingestion of the drug (swallowing) or a one-time instillation of a large dose of naphazoline (Taylor and Maslov 2013; Lowry and Brown 2014). As reported by most studies, this effect is especially prominent in early childhood (Senin and Morozov 2012; Kalashnikova and Chelpachenko 2013; Taylor and Maslov 2013; Lowry and Brown 2014; Díaz et al. 2018; Pshenichnaya et al. 2018; Petukhova et al. 2019; Shilov et al. 2019; Tulupov et al. 2018; Euwema and Swanson 2020).

A drug form and its resorption capacity determine a degree of toxicity. The resorption capacity of alpha2-adrenergic agonists is different. Systemic bioavailability of naphazoline is more than 50%, of xylometazoline – about 1%. In this respect, the percentage of children hospitalized with acute naphazoline poisoning remains at a high level (Wenzel et al. 2003; Pshenichnaya et al. 2018).

A central nervous system disorder, which manifested itself in drowsiness, was noted in 98% of the children in the nosological structure of acute naphazaline poisoning (Petukhova et al. 2019). Skin pallor and bradypnea were observed in 85% of the children, hypothermia – in 80%, and hyperhidrosis – in 80%. The number of patients with bradycardia varied from 60% to 83% in various studies (Petukhova et al. 2019; Shilov et al. 2019). The severity of these symptoms depended on the severity of the patient's state. According to the publications, 29% of the patients hospitalized had symptoms of medium severity and 71% were with severe symptoms (Senin and Morozov 2012).

Based on the analysis of the publications for 2019, 45% of the children were admitted to hospital in a serious state and 5% of the patients – in an extremely serious state (Petukhova et al. 2019; Shilov et al. 2019).

Some cases of severe naphazoline poisoning after its intranasal administration were also reported. Thus, a 18-month-old baby rapidly developed profound CNS depression accompanied by bradycardia, hypothermia, and hypoventilation after use of naphazoline in rhinopharyngitis treatment (Díaz et al. 2018). A one-month-old girl was admitted to hospital in coma with skin pallor, hypothermia, hypotension, bradycardia, and apnea after naphazoline instillation (Euwema and Swanson 2020).

All the studies reported that the most severe degree of intoxication was observed in pre-school children aged 1–3 years.

Mechanism of action of nasal decongestants

Specific features of the structure, location and pharmacological activity of adrenergic receptors

Alpha-adrenergic agonists are represented by a large group of biologically active agents, also called alpha-agonists or stimulators of alpha-adrenergic receptors (Norman and Nappe 2021). Adrenergic receptors differ by their mediated effects and localization, as well as drugs differ in their affinity for the receptors (Fig. 1).

Adrenergic agonists are divided into non-selective, stimulating alpha and beta-adrenergic receptors

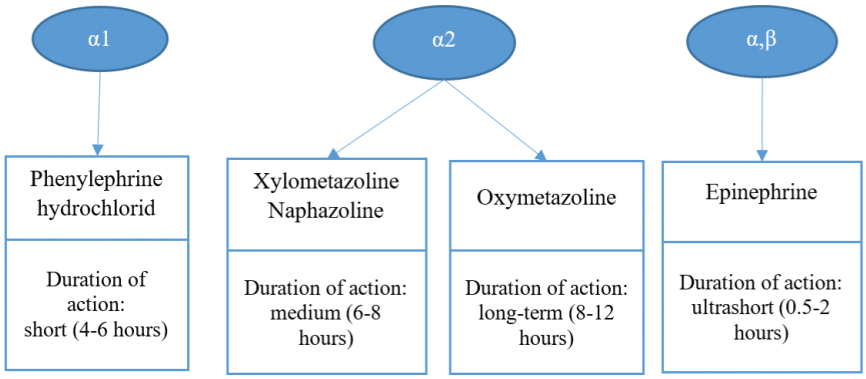

Figure 1. Affinity for the receptors and duration of action of adrenergic agonists.

(epinephrine), as well as activating alpha$_1$- and alpha$_2$-adrenergic receptors (noradrenaline). Phenylephrine hydrochloride belongs to selective drugs that activate alpha$_1$-adrenergic receptors, whereas naphazoline, xylometazoline, oxymetazoline – to selective alpha$_2$-adrenergic receptor agonists. All adrenergic agonists differ in duration of action (Fig. 1) (Norman and Nappe 2021).

Alpha$_1$-adrenergic receptors are localized on postsynaptic membranes and respond to the action of noradrenaline. They are located mainly in arterioles, and when they are stimulated, vascular permeability decreases, followed by spasm of arterioles and an increase in blood pressure (Fig. 2).

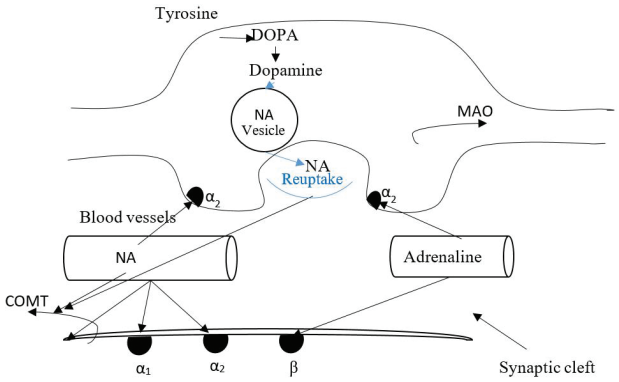

Figure 2. Adrenergic synapse. **Note:** DOPA – dihydroxyphenylalanine; A – adrenaline; NA – noradrenaline; MAO – monoaminoxidase; COMT – catechol-O-methyltransferase.

Alpha2-adrenergic receptors in cholinergic and adrenergic nerve endings are located presynaptically, in blood vessels – extrasynaptically and postsynaptically, and in the central system – postsynaptically (Norman and Nappe 2021).

Presynaptic alpha$_2$-adrenergic receptors have an effect on release of noradrenaline based on the negative feedback principle, which results in a blood pressure decrease (Fig. 2). According to the same "loop" principle, when the central alpha$_2$-receptors are stimulated, secretion of catecholamines reduces.

The peculiarity of selective alpha2-adrenergic agonists is that when taken orally, misused or overdosed, they lose their selectivity for the target receptor. As a result, the drug causes acute poisoning and most often this effect occurs in children and adolescents (Norman and Nappe 2021).

Naphazoline is an alpha2-adrenergic agonist, an imidazoline derivative that stimulates alpha2-adrenergic receptors (Johnson and Hricik 2003). Clonidine is also an imidazoline derivative, an alpha2-adrenergic agonist, but with a higher degree of selectivity. Besides, its mechanism of action is based on vasodilation, not on vasoconstriction. Clonidine activates the postsynaptic alpha2-adrenergic receptors of the vasomotor centers, reduces conduction of sympathetic impulses to the heart and blood vessels, which leads to a decrease in cardiac output, heart rate and peripheral vascular resistance. Clonidine penetrates the blood brain barrier and affects the reticular formation, which is manifested by the sedative effect of the drug (Bousquet et al. 1992). Serious or mild overdose of naphazoline induces a similar mechanism of action, stimulating the same receptors as clonidine, and causes a similar effect.

Anatomical and physiological specific features of the nose structure in children

The final clinical effect of a drug will vary depending on the types of alpha-adrenergic receptors involved. It is believed that alpha$_1$-adrenergic receptors in the nasal cavity are mainly located in the walls of the arterioles of the mucous membrane and stimulate their contraction. Stimulation of alpha$_2$-adrenergic receptors leads to contraction of 5 cavernous veins located under the mucous membrane of the middle and inferior nasal turbinates (Corboz et al. 2003). It has been proven that the main role in the innervation of the nasal mucosa in an adult is played by alpha$_2$-adrenergic receptors, which prevail over alpha$_1$-adrenergic receptors (Zaplatnikov et al. 2014). The cavernous tissue in the inferior and middle nasal turbinates only starts to develop in infants and is finally formed by the age of three. Therefore, nasal edema and inflammation in infants are mainly due to the filling of superficial arterioles with blood (Tulupov et al. 2018). For this reason, alpha2-adrenergic agonists cannot act upon alpha2-adrenergic receptors, instead the alpha$_1$-adrenergic receptors are stimulated.

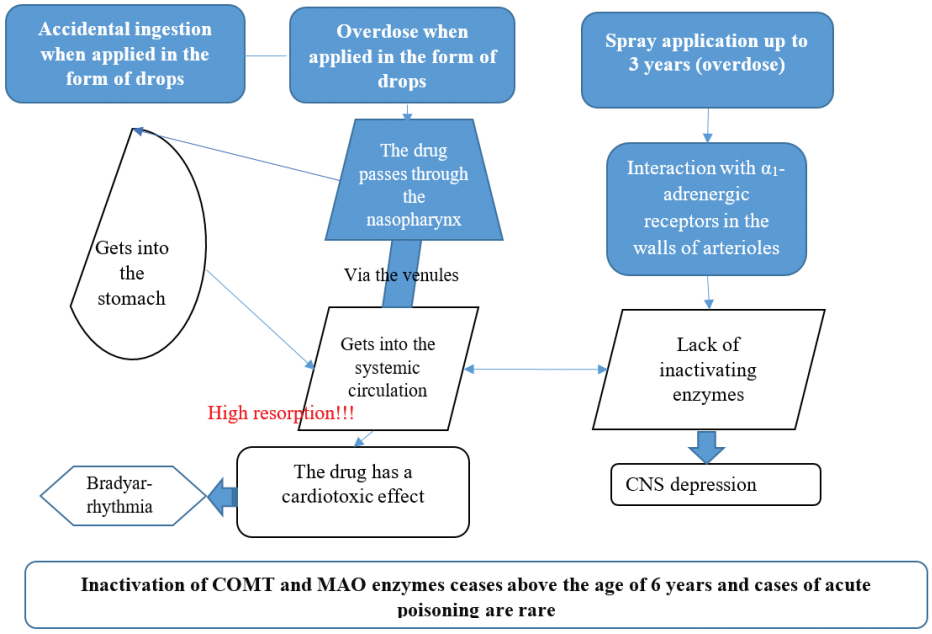

Figure 3. Scheme of the route of entry, absorption and distribution of naphazoline in a child's body depending on the drug entry route and age of a child. **Note:** MAO – monoaminoxidase; COMT – catechol-O-methyltransferase.

In children aged over three years, nasal mucosa edema causes an increase in the size of the inferior turbinates due to the filling of their cavernous tissue with blood. Use of naphazoline in young children leads to the situation that the local alpha-adrenergic agonist cannot detect the treatment sites, instead it enters the systemic circulation through the venules and causes symptoms of intoxication. This mechanism is presented below in the scheme of naphazoline absorption and distribution in children depending on their age (Fig. 3).

Cases of overdose are rare after the age of six since by that age, the mechanisms of adrenergic agonists inactivation are completely formed.

One of the causes of acute poisoning by nasal decongestants in children is use of a drug in the form of drops. When administered as drops, the drug gets from the nasal cavity, and nasopharynx into the gastrointestinal tract and the alpha2-adrenergic agonist is further absorbed into the systemic circulation. The cardiotoxic effect is the main symptom of systemic intoxication associated with the use of naphazoline (Fig. 3).

Once the drug gets into the systemic circulation, alpha-adrenergic receptors of the heart vessels are activated, the preload and, hence, contractility of the myocardium increase. Subsequently, the carotid sinus is involved and the activity of the vagus nerve increases, which results in bradyarrhythmia development in young children and in a paradoxical effect in the form of tachyarrhythmia in older children. It is believed that activation of central alpha-adrenergic receptors leads to the nervous system depression of various intensity, from drowsiness to coma, hypotension, respiratory failure, and pulmonary edema. Systemic side effects of naphazoline also include hypothermia, mydriasis, hyperhidrosis, transient arousal overreaction. and transient hypertension (Table 1).

Table 1. Side effects when alpha2-adrenergic agonists get into the systemic circulation

Side and toxic effects in case alpha2-adrenergic agonists get into the systemic circulation	
Cardiotoxic effect on alpha-adrenergic receptors of the heart vessels	Bradycardia Transient arousal overreaction Transient hypertension Recurrent bradycardia
High permeability of the blood-brain barrier, stimulation of adrenergic receptors of the vasomotor center of the brain, a decrease in the flow of sympathetic impulses	Depression of the nervous system causing drowsiness to coma Mydriasis Hypotension Pulmonary edema Respiratory failure Hypothermia Hyperhidrosis

Some authors believe that as a result of naphazoline passage across the blood-brain barrier, the adrenergic receptors of the vasomotor center are activated in children of early age. This leads to a significant reduction of sympathetic impulse flow and further to lack of energy and enthusiasm, drowsiness, development of bradycardia, and hypotension. With an increase in intoxication, the symptoms intensify up to coma (Mahieu et al. 1993; Vitezić et al. 1994; Malakhov et al. 2015; Kochetkov and Fatyanova 2017).

Main causes of acute poisoning in young children

Naphazoline causes systemic side effects (toxicity) primarily in children. Drug overdose of just a few extra drops can lead to severe intoxication (Tulupov et al. 2018). Clinical manifestations of the adrenomimetic effect (neurological status impairment, changes in the cardiovascular system, hypothermia, excessive constriction of the pupils) may occur even as a result of a therapeutic

use of the drug (Claudet and Fries 1997; Varvyanskaya and Lopatin 2015).

Currently, there is no clear explanation for this situation; however it is possible that a larger size of the nasal mucosa surface in children compared to adults significantly increases the resorption area of alpha2-adrenergic agonists. If a dose of topical decongestants is calculated per 1 kg of body weight, the size of the dose received by a child under 1 year old is 30 times higher than the dose of an adult. In addition, symptoms of acute poisoning appear with an increase in concentration of the local alpha-adrenergic agonists in blood due to the immaturity of the mechanism of reuptake of alpha-agonists of neuronal adrenergic receptors in the presynaptic terminals and low activity of enzymes – COMT (catechol-O-methyltransferase) and MAO (monoaminoxidase) (Kuzminov et al. 2018). Immaturity of the cavernous tissue in the nasal turbinates can also be the cause of intoxication. The inferior nasal meatus becomes the main conductor of the air flow only after the age of 7 (Garashchenko et al. 2016). Another cause of acute poisoning in children is the narrow therapeutic window of the drug, a small interval between the average therapeutic and the toxic doses (Radtsig et al. 2012; Garashchenko et al. 2016; Kunelskaya et al. 2017; Kuzminov et al. 2018).

It is noted that 0.025% naphazoline solution should be used for children from 2 to 6 years old (Taverner and Latte 2009; Chow et al. 2012; Fokkens et al. 2012). Unfortunately, the official solutions of the drug are produced with a minimum 0.05% concentration; hence, implementation of the recommendations in practice is a real problem (Tatochenko 1999). It should be emphasized that oral forms of naphazoline incur the major risk of systemic intoxication, and they are prohibited for use in pediatric practice in Russia until the age of 12. (Derbeneva and Guseva 2017; Radzig 2017; Bogomilsky et al. 2019).

Clinical features and diagnostic criteria

Clinical signs of acute poisoning can appear both as a result of an overdose of the nasal decongestants and due to a therapeutic use of the drug according to the instructions (Wenzel et al. 2003).

An analysis of the clinical symptoms revealed a two-phase intoxication with local alpha-adrenergic agonists.

The first phase is characterized by development of anxiety and sense of fear, weakness, headache, and tachycardia. Nausea and, very rarely, vomiting are also possible. The symptoms of the first phase are most often mild, usually disappear within 12 hours, and are therefore overlooked by parents.

The intoxication symptoms accrue in the second phase of poisoning and is manifested by obvious hypothermia, skin pallor, bradycardia, arterial hypotension (a decrease by more than 50% of the age norm), sometimes turning into hypertension, profuse sweating and acrocyanosis, as well as a change in the respiratory rate. Severe depression of the central nervous system (coma), a collaptoid state, and acute cardiovascular failure occur in extremely serious cases.

In case of an overdose or ingestion of local alpha2-adrenergic agonists, a general depletion of catecholamines and noradrenaline takes place, which leads to depression of the sympathetic nervous system.

The severity of clinical symptoms does not necessarily depend on a dose. The first signs of body damage are usually observed within 30–60 minutes, and distinct symptoms can appear 6–12 hours after taking the drug. On average, the onset of clinical manifestations can be expected in the period from 12 to 36 hours after the drug use (Norman and Nappe 2021).

Naphazoline influence on the kidney vessels should be taken into account. Blood flow decreases in the peritubular capillaries with an overdose of alpha2-adrenergic agonists. Nephrons in the cortical segment of the kidneys undergo ischemia, which leads to hypoxia of the tubular cells. In case of an acute naphazoline poisoning, activity of urine enzymes located in the plasma membranes or cytosol of the nephrons increases, which makes it possible to detect changes in the tubular apparatus of the damaged organ at the earliest time possible. Thus, in case of poisoning by nasal decongestants, changes in the biological fluids of the body are reflected in the laboratory parameters as well.

The following changes were observed in the blood laboratory tests of the children with local alpha2-adrenergic agonists poisoning: hemoglobinemia, erythrocytosis, leukocytosis, which correlated with high hematokrit. Dehydration of the body resulted in high urine density. Leukocytosis and thrombocytosis were regarded as an acute-phase body response in the analyses of this group of the children with poisoning. In addition, an increase in the number of thrombocytes can be a risk factor for development of thrombotic complications. Electrocardiograms of the patients with poisoning showed heart rhythm disturbance and cardiac conduction failure (Kalashnikova and Chelpachenko 2013; Díaz et al. 2018).

Thus, the identified laboratory changes in children with naphazoline poisoning confirm its toxic effect on the body manifested by acute-phase changes.

Imidazoline receptors and new opportunities

The current undersnading of the localization and action of adrenergic receptors show that they are involved in the functions of almost all organs and systems of the body. So the effect of alpha2-adrenergic agonists is a heterogeneous response to stimulation of adrenergic receptors. At the moment, there is no clear definition of how exactly the receptors affect physiologically and where precisely they are located (Kuzminov et al. 2018).

This issue obtained more interest when imidazoline receptors were discovered, although this fact further complicated the understanding of the systemic side effects of naphazoline.

It is assumed that the toxic effect of topical decongestants occurs not only by means of activation of alpha2-adrenergic receptors, but also through affecting the selective imidazoline receptors.

Three types of imidazoline receptors were defined, among which imidazoline-1(I-1) located above the alpha2-adrenergic receptor, and together they have influence on blood pressure. There is a supposition that imidazoline receptors and adrenergic receptors enhance each other's action in implementation of their functional reactions. Their functional relationship is determined by their similar features. It is possible that involvement of imidazoline receptors in their joint action occurs when the calcium channels are activated by alpha-adrenergic agonists. Studies have shown that I-1 receptors can also be involved in other physiological responses besides the cardiac function. Imidazoline receptors are localized in the heart, brain, beta cells of the pancreas and kidneys, and they can modulate various functions of the body accordingly (Bousquet et al. 1998; Wenzel et al. 2003).

The hypotensive effect of imidazoline compounds was first identified in the reticularis lateralis of the rostroventrolateral part of the medulla oblongata. It was demonstrated that imidazolines and the related substances lower blood pressure when used in this area, whereas no catecholamine was able to do this (Kuzminov et al. 2018).

The toxic effects of nasal decongestants, manifested by such symptoms as CNS depression, bradycardia, miosis, hypotension, respiratory depression, and hypertension (early and temporary), are similar to imidazoline effects. Based on the structure of these drugs and various studies, it is assumed that imidazoline receptors are the primary binding site for these drugs. This also explains the cases of rapid onset of the drug action with serious side effects after administration of relatively small amounts of the substance (Regunathan et al. 1995; Bucaretchi et al. 2003; Wenzel et al. 2003; Taylor and Maslov 2013; Lowry and Brown 2014).

Thus, despite the fact that many pathogenetic mechanisms of the naphazoline toxic effect have been determined, the values of laboratory predictors for prognosis and early assessment of complications of acute naphazoline poisoning have not been defined yet, which sets the direction for further study of this issue.

Conclusion

Alpha2-adrenergic agonists poisoning is leading in the structure of acute drug poisoning requiring emergency medical intervention. This is determined by the pathomorphological specifics of children and rapid evolution of the clinical symptoms of poisoning. Each stage of emergency medical care for children with nasal decongestant poisoning requires knowledge of the mechanism of action of a drug and an early diagnosis.

Conflict of interests

The authors of the article confirmed the absence of a conflict of interests to be reported.

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