In seriously ill neonates, diagnosing the underlying illness is often difficult. Symptoms such as somnolence, hypothermia, apneas, respiratory insufficiency, micro-circulation disorders, or metabolic acidosis can occur in severe infections, congenital abnormalities, and several congenital metabolic deficiencies. The authors report the cases of three patients with life-threatening illness. They fear that in these cases, an association existed with the administration of decongestant nose drops at the recommended dosage.

Case reports

The most important clinical data and findings of the three patients are summarized in the table. The first patient, a baby girl, developed an infection of the upper respiratory tract at age 14 days, which was accompanied by rhinitis. From the 15th day she received nasal drops containing xylometazoline, at the recommended dosage, for three days. On the 18th day, she was admitted as an inpatient because her general condition had been deteriorating steadily; late-onset sepsis was suspected. A few hours after admission she went into respiratory arrest and had to be intubated and ventilated. An electroencephalogram performed at this point showed serious general changes (“burst suppression” pattern). The symptoms disappeared within a day. The second patient was treated from his 4th day with xylometazoline-containing nasal drops at the recommended dosage for a respiratory infection with obstructed nasal breathing. He too was admitted as an inpatient because his general condition deteriorated after five days; he suffered a respiratory arrest after two hours and had to be intubated. After 24 hours his breathing had returned to normal, but extubation was delayed for another 2 days because of ventilator-associated pneumonia.

The third patient was a girl who had been born prematurely with a gestational age of 28 plus 2 week’s pregnancy. Her postnatal development was uneventful; she had a moderate apnea-bradycardia syndrome and received caffeine citrate in decreasing dosage up to her 35th week. Regulation of her breathing at discharge was uneventful. Four weeks after discharge (corrected age: 1 week) she was readmitted. Three days earlier she had received nose drops containing oxymetazoline for a respiratory tract infection with obstructed nasal breathing, at the therapeutic dose. On admission, her extremities were twitching, her EEG was uneventful, and she had a series of striking central apneas, which ceased totally within 48 hours after administration of oxygen and caffeine citrate (10 mg/kg per day peroral).

None of the three patients showed any signs of intracranial processes, metabolic disorders,
or typical bacterial or viral infections (table). Without specific therapy the symptoms disappeared over a few days and did not recur in an observational period of several months.

**Discussion**

Vasoconstricting substances from the imidazoline group are widely used. Thanks to their primarily local α-adrenergic effect they are particularly suitable for topical use on the nasal mucous membranes and the eye. For use in children, the nasal drops or sprays are available in different strengths. Intoxication after oral administration in higher doses has been reported (1–3). The symptoms were mainly somnolence, bradycardias, and arterial hypotension. Neurological effects are, however, known in this group of substances with regular use at the prescribed dosage. In older children, these manifest primarily as states of anxiety or excitement and particularly as visual hallucinations (4–6). In neonates and very young babies the neurological effects manifest in a different manner. In individual published case reports, gasping for breath, hypothermia, impaired consciousness, and bradycardias and tachycardias have been described after imidazoline-containing nose drops at the prescribed dosage.

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**TABLE**

Clinical data and findings of the three patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Premature 28 + 2 week’s of pregnancy</td>
</tr>
<tr>
<td>Age at admission</td>
<td>2 weeks</td>
<td>2 weeks</td>
<td>Corrected: 1 week</td>
</tr>
<tr>
<td>Sex/weight</td>
<td>F/730 g</td>
<td>M/800 g</td>
<td>F/630 g</td>
</tr>
<tr>
<td>Administered substance</td>
<td>Xylometazoline 0.025%</td>
<td>Xylometazoline 0.025%</td>
<td>Oxymetazoline 0.01%</td>
</tr>
<tr>
<td>Dosage (recorded retro-spectively)</td>
<td>3 times daily, 1–2 drops into both nostrils, for 3 days</td>
<td>3 times daily, 1–2 drops into both nostrils, for 6 days</td>
<td>3 times daily, 1 drop into both nostrils, for 3 days</td>
</tr>
<tr>
<td>Body temperature</td>
<td>35 degrees C</td>
<td>35.5 degrees C</td>
<td>37 degrees C</td>
</tr>
<tr>
<td>Clinical presentation at admission</td>
<td>Reduced general condition, apathy, periodic shrill screaming, marbled pale skin</td>
<td>Reduced general condition, somnolent, periodic screams, twitching arms, tachycardia, pallor</td>
<td>Reduced general condition, apathy, twitching right arm and leg, gray skin tone, cyanotic lips</td>
</tr>
<tr>
<td>Further course</td>
<td>Respiratory arrest, intubation, 18 hours in a coma with loss of reaction to pain</td>
<td>Striking apneas, in a coma for 24 hours, extubation only after 72 hours because of pneumonia</td>
<td>Striking apneas, administration of oxygen and, repeatedly, caffeine; symptoms disappeared totally within 48 hours</td>
</tr>
<tr>
<td>C-reactive protein, (differential) blood count, blood culture</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
</tr>
<tr>
<td>Test for respiratory syncytial virus</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Pertussis serology</td>
<td>Not done</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Herpes simplex PCR</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>EEG &quot;Burst suppression&quot; pattern without identifiable focus. Repeat after 24 hours uneventful</td>
<td>&quot;Burst suppression&quot; pattern (under gamma hydroxybutyric acid 20 mg/kg per hour). Repeat after 96 hours uneventful</td>
<td>Uneventful</td>
<td></td>
</tr>
<tr>
<td>Metabolic diagnosis</td>
<td>Uneventful (ammonia, lactate, galactose, acylcarnitine profile, aminocids in urine and plasma, organic acids in urine, sulfur test, thyroid hormone)</td>
<td>Ammonia initially 155 µmol/l, lactate in serum initially 8.6 mmol/l, increased lactate excretion in urine. Sack to normal within 72 hours. Uneventful acylcarnitine profile, aminocids and organic acids</td>
<td>Uneventful (ammonia, lactate, galactose, acylcarnitine profile, aminocids in urine and plasma, organic acids in urine)</td>
</tr>
<tr>
<td>Sonography of the skull</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
</tr>
</tbody>
</table>

PCR, Polymerase chain reaction
(7–10). After topical administration of similar α-adrenergic substances to the eye, comatose states in small infants have been observed despite correct dosage (11).

In the meantime, an explanation has been found for the neurological side effects of imidazolines. Clonidine, another imidazoline derivative, is increasingly used as a sedative because of its neurological effects. Animal experiments have shown that the effects mediated by clonidine are based not only on the stimulation of central α2-adrenoceptors in the locus coeruleus but that additionally, groupspecific imidazoline receptors exist in the rostral ventrolateral medulla (12, 13). Apneas have been described often after therapeutic use of clonidine in spinal anesthesia of neonates and premature babies (14, 15). In the animal model, apneas can be triggered by injection of clonidine into the medulla, through inhibition of postinspiratory neurocytes (16). Hallucinations and states of excitement may also occur as possible side effects of clonidine (5). It is assumed that neonates, whose blood brain barrier is not fully developed (17), are possibly more sensitive to the central side effects of the imidazolines.

The three cases are consistent with the course as described for the few cases in the literature for children of this age group. In all three children, the symptoms receded after discontinuation of the nose drops within a few days, even without specific treatment (table). It has to be stressed that with the serological investigations that were conducted, a primary infectious cause for the pathologies observed cannot definitely be excluded. The infectious strains that are typical for age and symptoms (table) were, however, not found. The rapid disappearance of the initial symptoms without specific treatment and the uneventful infectious measurements argue, in the eyes of the authors, against an exclusive infectious pathogenesis.

The observed symptoms bradycardia, hypothermia, apnea, coma, and shocklike drop in blood pressure are known for xylometazoline and oxymetazoline overdose particularly in children and are listed in the information materials. The dosages recorded through medical history were all consistent with the individual recommendations. As the dosages were recorded retrospectively, however, and because currently there are no tests for detecting the presence of xylometazoline or oxymetazoline in plasma or cerebrospinal fluid, overdosage cannot be excluded with certainty.

A causal association between the pathologies observed and the drug doses administered cannot be stated with any certainty. The typical symptoms of overdosage, however, give credence to the assumption that in neonates, the sensitivity for the neurological side effects of imidazoline preparations may be increased. This assumption has also been expressed in earlier case studies (7–10) and is supported by the exclusion of common differential diagnoses in the cases presented here. In view of the threatening symptoms, which in the patients described here resulted in intensive care interventions, the authors think that further prospective studies are urgently needed.

Conflict of Interest Statement
The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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REFERENCES

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