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CASE REPORT

A case series of xylometazoline overdose in children

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Introduction. Serious intoxications associated with low doses of imidazolines have been reported. Therefore, the treatment advice for children with xylometazoline overdose is usually to observe the child in the hospital, even after exposure to very low doses. Our aim was to determine the frequency of severe symptoms after xylometazoline exposure, and the systemic dose of xylometazoline below which asymptomatic children do not need to be hospitalized for observation. *Methods*. From May 2002 until December 2004, we prospectively collected data on all consecutive cases of xylometazoline exposure in children <6 years old reported to our poisons centre. Follow-up information was collected. The systemic dose was calculated and the frequency of severe symptoms was observed. *Results*. During 32 months, we included 101 cases of xylometazoline exposure in children. For 63 out of these 101 cases, follow-up information could be collected. No severe symptoms were observed after exposure to xylometazoline doses reported to be below 0.4 mg/kg (95% confidence interval: 0–6%). *Conclusion*. We conclude that less than 6% of children exposed to xylometazoline, at doses reported to be less than 0.4 mg/kg body weight, may develop symptoms that require hospitalization.

Keywords Xylometazoline; Imidazoline; Intoxication; Paediatric poisoning

Introduction

Imidazoline-derivatives are registered world-wide for use as nasal decongestants. The imidazoline-derivatives available in the Netherlands are oxymetazoline, tramazoline, and xylometazoline. However, more than 90% of all enquiries about imidazoline overdose received at the Dutch National Poisons Information Centre concern exposure of young children (0 to 4 years old) to xylometazoline, with approximately 45 enquiries a year. Xylometazoline is a benzyl-imidazoline derivative, which acts as a vasoconstrictor and reduces swelling and congestion when applied to mucous membranes. It is indicated for the relief of nasal congestion associated with rhinitis, common cold, sinusitis, and hay fever or other allergies. World-wide, products containing xylometazoline are available under many different brand names. In the Netherlands, xylometazoline is available as an over-the-counter (OTC) product. Nose drops and nasal spray are available in three different concentrations: 0.1% (1 mg/ml), 0.05% (0.5 mg/ml), and 0.025% (0.25 mg/ml), usually in bottles of 10 ml.

Xylometazoline and other imidazoline-derivatives act as agonists for central and peripheral α_2-adrenergic receptors and they are possible agonists for central imidazoline-receptors. Systemic overdose of imidazoline-derivatives may result in alternating periods of central nervous system depression and stimulation, depending on whether central or peripheral α_2-adrenergic receptor stimulation predominates (1,2). Peripheral α_2-adrenergic effects are usually overshadowed by central α_2-adrenergic effects, so that in systemic overdose the central, sympatholytic effects often predominate (3,4). Symptoms usually develop within a few minutes to four hours (5–7). Previously reported symptoms of systemic imidazoline overdose include miosis, drowsiness, lethargy, hypotension, hypothermia, bradycardia, hypotonia, respiratory depression and coma, but also mydriasis, anxiety, agitation, hallucinations, convulsions, hypertension, tachycardia, pallor, cyanosis, and diaphoresis (1,3,4,7). These symptoms are mainly derived from case reports and case series of nasal and oral exposures of children to imidazolines other than xylometazoline (e.g., oxymetazoline, tetrahydrozoline, and naphazoline). Only a few individual case reports about the exposure of patients to xylometazoline have been published (8–10). One of these reports describes a case of a 15-day-old girl who received one drop of 0.1% xylometazoline in each nostril,

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resulting in a serious intoxication with hypotonia, irregular breathing, and even coma (10). This and other reports of serious intoxications with imidazolines in children have led to a tendency of clinical toxicologists and poisons information centres to be very cautious with xylometazoline overdoses in children. Usually, the treatment advice provided is to admit the child to the hospital for observation, even after intoxication with doses only just above the therapeutic daily dose (11,12).

It is not known how often severe symptoms occur in cases of xylometazoline overdose, since no case series have been published yet. In order to determine the frequency of severe symptoms after xylometazoline exposure, we prospectively conducted a case series study in children aged 0 to 6 years. Subsequently, we tried to establish an upper limit for the systemic dose of xylometazoline in mg/kg body weight, below which the risk of developing severe symptoms is so small that asymptomatic children may not need to be hospitalized for observation.

Methods

Patients and case definition

Data on all consecutive cases of xylometazoline exposure in children (0 to 6 years old) reported to our poisons centre from May 1, 2002 until December 31, 2004 were collected prospectively. A xylometazoline exposure was defined as any oral or nasal administration of xylometazoline, either by the patient him/herself or by others (e.g., the parents) that was reported to our poisons centre.

Data collection

Medical practitioners calling our poisons centre for advice about xylometazoline exposure in children were informed about the possible symptoms and treatment of the intoxication by our information specialists, in accordance with our standard operating procedures. During this first phone call, information about age and body weight of the patient, estimated dose, route of exposure, and symptoms were collected and recorded. Patients' records were safely stored in our database and not accessible to others. Since there were no interventions or risks for the patients associated with our study, review and approval of the study by a Dutch medical ethics committee was not required and informed consent from the patients was not needed for use of the data.

A few hours to several days after the first phone call, the medical practitioners of the children involved were contacted by mail or by telephone by our information specialists to collect follow-up information. Particularly, information about the clinical course of the intoxication (newly developed symptoms, resolution of symptoms) and, if possible, more precise information about the estimated administered dose was collected. The duration between the moment of exposure and the request for follow-up information was required to be at least four hours since, according to literature, symptoms of xylometazoline exposure start within minutes to four hours after exposure (5–7). Follow-up information was collected using a standardized enquiry form. The information specialists collecting the data were not blinded to the study aims.

Dose estimation

The systemic dose in mg/kg body weight was calculated using the estimated dose as mentioned by the medical practitioner on two separate occasions. A first estimation of the dose was requested from the caller in the first phone call. Later, during the collection of follow-up information, we again requested specific information about the dose, to be able to establish the dose as precisely as possible. The second dose estimation was considered to be more reliable than the first so that when the two dose estimations differed, the second dose estimation was used to calculate the systemic dose. In cases lost to follow-up, the systemic dose in mg/kg was based on the estimated dose mentioned in the first phone call only. For calculation of the systemic dose, one drop was assumed to be 0.05 ml, one spray 0.1 ml, and one sip 5 ml. The systemic dose was not confirmed by analysis of blood or urine samples, since hospitals in the Netherlands do not routinely have a test available to determine xylometazoline concentrations in biological samples.

Analyses

The frequency of severe symptoms (i.e., symptoms that require hospitalization) was observed and a 95% confidence interval was calculated for the probability of occurrence of severe symptoms. Since the probability was zero, Hanley's formula can be used for the upper limit of the 95% confidence interval (CI), so that the CI is (0, 3/N) (13). Nonparametric tests were used to test whether there were significant differences in the children's age, body weight, and systemic dose between the group with follow-up information available and the group lost to follow-up.

Results

During 32 months, we received enquiries about 101 cases of xylometazoline exposure in children. Twenty cases concerned nasal application of xylometazoline and 81 cases concerned ingestion of xylometazoline. In 78 cases, children exposed themselves (e.g., by taking sips from a bottle) but in 23 cases the parent himself/herself exposed the child to an overdose. The only symptoms that were present at the moment of the first phone call to our poisons centre were hypertension and mydriasis in one case, tachycardia in one case, an episode of swollen facial veins in one case, and vomiting and decreased appetite in another case. To evaluate the clinical course of the exposures and to be certain that no new symptoms developed after the first phone call,

follow-up information was requested for all cases of xylometazoline exposure. Follow-up information could be collected for 63 cases. Thirty-eight cases were lost to follow-up. This was largely due to the medical practitioners and not to the patients, since a number of medical practitioners either didn't have the time or motivation to cooperate, or they had lost contact with the patient and could not provide us with follow-up information.

Table 1 shows descriptive data for cases with follow-up information available and cases lost to follow-up. There were no statistically significant differences for age, body weight, and systemic dose between the two groups (Mann-Whitney test, $p>0.05$).

In the 63 cases with follow-up information available, no additional symptoms related to xylometazoline exposure were reported upon follow-up. Twenty five of these 63 children were admitted to a hospital and the other 38 were observed at home by their parents. Eight children received treatment: in two children vomiting was induced, in one child activated charcoal and a laxative were administered, and five children underwent gastric lavage. In three out of the five children that underwent gastric lavage, activated charcoal and a laxative were also administered. Vomiting and gastric lavage were not advised by our poisons centre, but performed on the physician's or parent's initiative.

In two of the 63 cases, a systemic dose could not be calculated, because the patients' parents were not able to give the medical practitioner an estimate of the administered dose. The median systemic dose, derived from parental estimation, in the remaining 61 cases was 0.20 mg/kg body weight (range: 0.02 – 0.91 mg/kg). From these 61 cases, the number of cases per dose range is shown in Figure 1.

No severe symptoms requiring hospitalization were observed in any of these 61 cases. In 80% of these cases, the systemic dose was less than 0.4 mg/kg body weight. Since the number of children with a systemic dose above 0.4 mg/kg body weight was quite low (5 cases or less per dose range, see figure 1), we chose to calculate a 95% confidence interval only among children with a reported systemic xylometazoline dose below 0.4 mg/kg body weight. In this group, the 95% confidence interval for the probability of occurrence of severe symptoms was 0–6%. We had too few children with a systemic dose of 0.4 mg/kg body weight or higher to give a reliable estimate of the probability of occurrence of severe symptoms with higher systemic doses.

Discussion

In this case series, no severe symptoms were reported after xylometazoline exposure in children. In 63 cases with follow-up information available, there were four cases in which symptoms were present at the moment of the first phone call to our poisons centre. However, for at least two of these cases a causal relation of the symptoms with xylometazoline overdose was questionable: in the first case a child developed hypertension and a "dubious" mydriasis (judged as being dubious by the treating physician of the patient) after exposure to a xylometazoline dose of 0.08 mg/kg body weight. According to the treating physician, anxiety may have been the cause of the symptoms, as the child was very frightened at the time. In the second case, with a xylometazoline dose of 0.2 mg/kg body weight, tachycardia was only noticed by the mother and not observed upon examination in hospital.

The remaining two cases in which symptoms were reported concerned an episode of swollen facial veins in one child after a xylometazoline dose of 0.24 mg/kg body weight and vomiting and decreased appetite in another child after a xylometazoline dose of 0.42 mg/kg. We do not know whether these symptoms were related to xylometazoline overdose. In any case, these symptoms can be classified as minor symptoms, for which no observation in the hospital is needed.

Table 1. Descriptive data for children in cases with follow-up information and cases lost to follow-up

	With follow-up information	Lost to follow-up	Total
Number of cases	63	38	101
Median age (range)	2 yrs (10 d – 5 yrs)	2 yrs (14 d – 5 yrs)	2 yrs (10 d – 5 yrs)
Median body weight (range)	12.3 kg (3 – 20 kg)	12.5 kg (3 – 22 kg)	12.5 kg (3 – 22 kg)
Median systemic dose[1] (range)	0.20 mg/kg[2] (0.02 – 0.91 mg/kg)	0.20 mg/kg[3] (0.01 – 1.3 mg/kg)	0.20 mg/kg[4] (0.01 – 1.3 mg/kg)
Route of exposure			
Oral	53 (84%)	28 (74%)	81
Nasal	10 (16%)	10 (26%)	20
Responsible for intoxication			
Patient	52 (83%)	26 (68%)	78
Other (e.g., parents)	11 (17%)	12 (32%)	23
Hospital admissions	25	unknown	unknown

[1]So far as dose estimations were available, [2]median of 61 cases, [3]median of 36 cases, [4]median of 97 cases; yrs = years, d = days, kg = kilogram, mg = milligram.

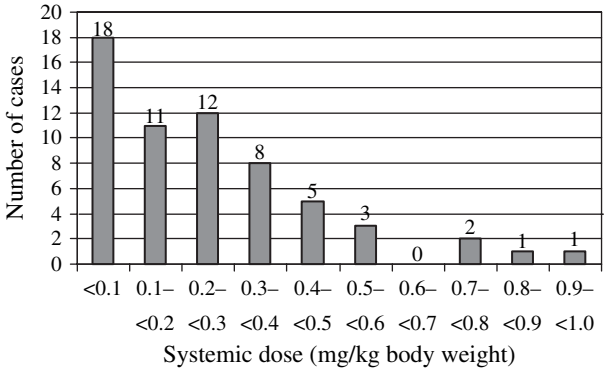

Fig. 1. Number of cases of xylometazoline exposure (with follow-up information available) per dose range.

It is possible that patients who were observed at home developed symptoms that were not recognized as such by the parents, resulting in these patients being classified as "asymptomatic" while they were not. In this way some minor symptoms may have remained unnoticed. We believe that severe symptoms that require hospitalization would not have gone unnoticed by the parents.

Thirty-eight cases out of 101 were lost to follow-up. Whether severe symptoms developed in these cases is not known. However, since it is customary (but not obligatory) for callers to contact our poisons centre again when the clinical outcome is worse than anticipated, it follows that with the appearance of severe symptoms some callers would have contacted our poisons centre again, especially since our centre is the only poisons centre in the Netherlands. Besides, the group of cases lost to follow-up was very similar to the group of cases with follow-up information available regarding age, body weight, and systemic dose of xylometazoline. Therefore, it is unlikely that bias was introduced into our study due to these cases being lost to follow-up.

There are two types of bias: information bias and selection bias. Information bias refers to error introduced into a study as a result of differences in the measurement of information on exposure or outcome data between groups. Information bias may have influenced the results of our study. In 30% (19 out of 63) of the cases with follow-up information available, the child was less than two years old. In these cases, the dose may have been more often overestimated and the symptoms underestimated since the children were too young to express themselves. This may especially occur with symptoms that are hard to observe by parents, such as changes in heart rate. However, we believe that severe symptoms would have been observable, even for parents.

Recall bias, a type of information bias, is possible when subjects are retrospectively asked about the dose of xylometazoline administered. Subjects may underestimate the dose when no symptoms occurred, while they may overestimate the dose when severe symptoms developed. However, since no severe symptoms were reported in our case series, the effect of this possible recall bias in our study would be an underestimation of the upper dose limit, which is less dangerous than to overestimate the upper dose limit and does not undermine our conclusion.

Selection bias is a common problem for poisons centres: severe cases of poisoning are more often reported to poisons centres than mild intoxications, or intoxications for which the appropriate treatment is well known to physicians (14). The effect of selection bias on our study would be to overestimate the effects of xylometazoline intoxications, which, for public health reasons, is less dangerous than to underestimate them.

The finding that in our case series children did not develop severe symptoms after exposure to xylometazoline doses below 0.4 mg/kg body weight, is in contrast with the case report by Dunn et al., which describes the case of a 15-day-old girl who received one drop of 0.1% xylometazoline in each nostril, resulting in a serious intoxication with hypotonia, irregular breathing and coma (10). The body weight of the girl is not mentioned in this report, so that in this case no exact dose in mg/kg body weight can be calculated. Assuming that one drop constitutes 0.05 ml and assuming the weight of the little girl was around 3–5 kg, the dose would have been around 0.02–0.03 mg/kg. However, as stated by the authors in this case report, the actual administered dose may have been higher than expected, since the position of the nose-drop bottle during administration can greatly influence the dose. In addition, the exposure was not confirmed by blood or urine analysis.

In our case series, it was not always clear how much xylometazoline was administered exactly, so that the actual systemic dose may have been higher or lower than the systemic dose we calculated. The exposures were not confirmed by blood or urine analysis, since hospitals in the Netherlands do not routinely have a validated test available to determine xylometazoline concentrations in biological samples. However, based on our findings, we conclude that at systemic doses reported to be below 0.4 mg/kg body weight it is reasonable practice to observe asymptomatic patients at home for 4–6 hours.

The usual treatment advice for children exposed to xylometazoline is to admit the child to hospital for observation (11,12). This is a costly undertaking and inconvenient and worrisome for the children and their parents. If our findings would be implemented in the management of xylometazoline intoxications, a lot of children would be spared unnecessary hospitalization and costs for health care could be reduced. Theoretically, in a maximum of six out of 100 children observed at home, relevant symptoms might develop after all. However, we believe that the health risk for these children would be minimal, since we indicate that the children need to be observed closely by their parents in the first 4–6 hours after exposure. If necessary, the parents can contact a health care provider as soon as any symptoms appear. More data are needed to assess the risk of developing severe symptoms after exposure to systemic doses of xylometazoline above 0.4 mg/kg body weight. Thus, in these cases hospitalization may be considered.

Conclusion

We conclude that at systemic doses of xylometazoline below 0.4 mg/kg body weight it is reasonable practice to observe asymptomatic patients at home for 4–6 hours. After exposure to xylometazoline doses above 0.4 mg/kg body weight hospitalization may be considered.

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