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CASE REPORT

A fatal complication of doxylamine in a 1-year-old girl

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Introduction

Doxylamine is the active ingredient of several over-the-counter sleeping medications available in Germany. Most doxylamine-containing drugs are not approved for use in children and adolescents. However, the over-the-counter sedative Sedaplus® Saft is approved for prescription in children from the age of 6 months. Several fatal cases of doxylamine overdose have been published since the 1970s [1–7]. However, none of these relate to therapeutic blood concentrations of doxylamine. We report a fatal complication of a therapeutic dose of doxylamine in a 1-year-old girl and suggest that, as is the case in most European countries, doxylamine should not be used in very young children.

Case report

The 13-month-old girl with no previous history of disease presented to a GP with a history of waking up repeatedly at night due to teething problems. The doctor diagnosed a "sleeping disorder" and prescribed 2.5 to 5 ml Sedaplus® Saft, an over-the-counter antihistaminic drug containing 250 mg doxylamine succinate/100 ml. A medical history and a physical examination of the child were not documented in the doctor's notes.

The child received 3.5 ml of Sedaplus® Saft as well as a lidocaine-containing gel with a meal from her mother at 2100 hours that night. Whether the girl had another meal later that night or the following day could not be elucidated. A few hours after being taken to bed, she felt nauseous and vomited once. She then fell asleep again and slept through the night and well into the next day. According to her mother, she was still breathing at 1400 hours in the afternoon. At 1700 hours, her father found her lifeless in her bed and called an ambulance. The ambulance team removed large amounts of stomach contents from the airways by suction and resuscitated the child for 40 min; yet, they could not resuscitate the child.

At the medico-legal autopsy, the child was 80 cm high and weighed 9.2 kg. At the external examination, some petechial haemorrhages were present to the conjunctivae. Severe acute over-inflation and focal atelectasis were present to the lungs. Some stomach contents were present in the larger and smaller airways. There was no pre-existing internal disease present which had caused or contributed to the death.

The toxicological examination revealed the presence of doxylamine at a blood level of 0.16 mg/l and lidocaine at a blood level of 0.1 mg/l. Doxylamine metabolites were present in the urine and stomach contents. All other tested substances were negative.

Microbiological and virological examinations revealed no evidence of an infection. At the histological examination with routine hematoxylin–eosin, PTAH, PAS and connective tissue staining including extensive sampling of the heart to exclude myocarditis, some stomach contents were seen in the airways. The severe over-inflation of the lungs was confirmed, alongside some mild focal oedema, but no heavy oedema as is seen in many cases of intoxication. The other organs were normal. There were no signs of drug-induced cholestasis or hepatitis present, nor was there any indication of rhabdomyolysis.

Viewing the results of the post-mortem investigations and the clinical history together, having excluded other

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causes of death including infectious disease, the cause of death was stated as "aspiration of stomach contents". The doxylamine ingestion was considered a factor contributing to the death, probably having caused heavy sedation and thus predisposed for stomach content aspiration.

Discussion

Doxylamine is an antihistaminic drug with sedative properties which is used in the short-term treatment of sleeping disorders and which can be obtained from pharmacies across Germany without prescription. Cases of fatal doxylamine poisoning, especially in children, have already been described as early as the 1970s [1–3]. Fatalities may also be associated with doxylamine-induced rhabdomyolysis [4–6]. In adults, fatal doxylamine overdose has been observed in suicides [6, 7]. However, the cases described in the literature mostly relate to toxic doxylamine blood levels. We present the case of a fatal doxylamine complication associated with a blood level which is considered therapeutic in adult individuals.

Sedaplus® Saft is the only doxylamine-containing drug approved for the treatment of children of 6 months or older in Germany. The manufacturer recommends a dose of 2.5 ml for children aged 6 to 12 months and 2.5–5 ml for children of 1 to 5 years of age. The fact sheet warns that in children less than 1 year of age, the substance should only be applied after careful consideration of the potential risks and benefits, as there is an increased risk of sleep apnoea in this age group.

We report the case of a previously healthy 1-year-old girl who died of an aspiration of stomach contents after having received 3.5 ml of Sedaplus® Saft, which is within the dose range recommended by the manufacturer for this age group. The doxylamine blood level of 0.16 mg/l found at the toxicological examination is within the upper therapeutic range given for adults. However, a therapeutic range for children has not been defined. Large individual differences in the susceptibility to doxylamine toxicity have been suggested before [8], and children are known to be at higher risk for cardiorespiratory arrest than adults, suggesting that the therapeutic range of doxylamine might be narrower in children than it is in adults.

In the present case, doxylamine is very likely to have caused heavy sedation, thus predisposing for significant aspiration of the stomach contents. Other doxylamine side effects which may have contributed to the fatal outcome include nausea and vomiting, sleep apnoea and cardiac arrhythmia. From a medical point of view, the diagnosis of a sleeping disorder in an otherwise healthy, teething child aged 1 year appears problematic, and prescribing a sedative for such a condition must be considered questionable.

The pharmacokinetic properties of doxylamine in children are poorly understood. In adults, the maximum plasma level after oral application is reached 2.4 h after ingestion [9]. The half-life of doxylamine is given at 10 h on the data sheet. Provided the information given by the mother is correct in our case (one-time application of 3.5 ml doxylamine at 2100 hours, child still breathing at 1400 hours the day after), these data suggest that either the doxylamine level has been considerably higher several hours before death than the 0.16 mg/l found at toxicology, or that in children, the pharmacokinetic properties of doxylamine differ substantially from those in adults. Consequently, dosage recommendations for children extrapolated from adult data are not always sufficiently safe unless verified in studies with child participants. However, such a study may be deemed unethical due to the severe risks which may arise for the participants. It has to be noted that in the present case, we cannot be entirely sure of the time of death. Signs of death have not been reported by the ambulance crew, suggesting a time of death close to their arrival. However, an earlier time of death cannot be excluded with certainty.

Based on the reported case with fatal outcome of therapeutic doxylamine ingestion, we suggest that extreme caution should be exercised when applying over-the-counter sedatives in young children. Doctors, pharmacists and parents must be made aware of the risk of a potentially fatal outcome of such medication [10]. Moreover, it should be considered to disallow the use of doxylamine-containing drugs in very young children in general. In many countries, this has already been put into practice [11]. We have reported the case to the manufacturer of Sedaplus® Saft, to make them aware of the dangers of doxylamine use in young children. A reaction to our report is still pending.

Conclusion

The application of over-the-counter sedatives in young children can be dangerous and potentially fatal. Our case suggests that doctors and pharmacologists be made aware of the risk of fatalities and that the use of doxylamine-containing drugs in young children should be disallowed.

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