Methadone poisoning due to accidental contamination of prescribed medication

Elke H. Roland,* MD
Gillian Lockitch,† MD, FRCP[C]
Henry G. Dunn,* MB, FRCP,
FRCP[C]
Donlim Peacock,‡ MD
Gordon E. Pirie,‡ MD, FRCP[C]

Two infants presented with fever and signs of brainstem dysfunction, including impaired consciousness, miosis, absence of oculocephalic responses, respiratory depression and a very peculiar tremor of the tongue and floor of the mouth. They were found to have methadone poisoning caused by accidental contamination of prescribed antibiotics in the same pharmacy, which was a dispensing centre for a methadone maintenance program. They recovered with supportive treatment only.

Deux jeunes enfants présentent de la fièvre et des signes d'atteinte du tronc cérébral: obnubilation, miosis, perte des réflexes oculocéphaliques, dépression respiratoire et un tremblement inusité de la langue et du plancher buccal. L'enquête découvre une intoxication par la méthadone consécutive à la contamination accidentelle d'un produit antibiotique prescrit. Dans les deux cas celui-ci avait été livré par une même pharmacie qui participe à un programme de traitement d'entretien par la méthadone. Les deux enfants guérisent à la faveur d'un traitement de soutien seulement.

Accidental methadone poisoning in children was reported principally in urban centres in the United States after the establishment of methadone maintenance programs for heroin addicts in the late 1960s. In most cases the child had gained access to carelessly stored drugs. Usually diagnosis relied heavily on history-taking.

We report two related cases of methadone poisoning in children in which the source of the poison was not readily ascertained by history-taking. The poisoning proved to be due to accidental contamination of prescribed antibiotics in a pharmacy.

Case reports

Patient 1

A 9-month-old infant had been irritable with an upper respiratory tract infection for 5 days. The day before the infant's admission to hospital the family physician diagnosed otitis media and prescribed amoxicillin. The first dose was given at bedtime. The next morning the baby slept later than usual. He was too drowsy to breast-feed but was given a second dose of medication. An hour later he was gasping, limp and diaphoretic. He was rushed to the local hospital, where he received respiratory support with an Ambu bag and oxygen. Thirty minutes later he had a generalized seizure. Respiratory arrest necessitated intubation and mechanical ventilation. A lumbar puncture showed normal cerebrospinal fluid (CSF). His parents denied exposure to toxic substances.

The infant was transferred to our hospital. At the time of arrival he was comatose, and his breathing was inconsistent, which necessitated continuation of the mechanical ventilation. He was flushed and diaphoretic. His rectal temperature was 38.6°C, and the right tympanic membrane was hyperemic. His bladder was distended. His muscle tone was flaccid, and there was no response to painful stimuli. His pupils were 2 mm in diameter and responded to light, but the retinal vessels were congested. His eyes were divergent, and oculocephalic ("doll's-eye") responses were absent. His corneal and gag reflexes were intact. There was a marked, continuous tremor of the tongue and the floor of the mouth. His muscle stretch reflexes were brisk and his plantar responses upgoing.

His blood leukocyte count was 15.9 × 10⁹/L (44% neutrophils, 46% lymphocytes and 10% monocytes). The serum electrolyte, calcium, magnesium, ammonia, glucose and amino acid levels were all normal. Liver function studies, blood gas analysis and culture of blood samples revealed no abnormalities. The Monospot test and viral studies gave negative results. A computerized tomography (CT) scan of the head was normal, but an electroencephalogram (EEG) showed poorly organized slow background activity of high amplitude, which suggested diffuse encephalopathy. A gastric aspirate and a urine sample were sent to be screened for toxic substances.

Over the next 12 hours the infant became more responsive, and the mechanical ventilation was stopped. He remained febrile for 3 days but was discharged after 5 days of hospitalization, resolving mild ataxia being the only apparent sequela.

Patient 2

Within 2 days after the arrival of the first infant at our hospital, when the diagnosis in that case was not yet clear, a 15-month-old infant with remarkably similar symptoms
was transferred to our hospital from the same local hospital. Two weeks previously she had been in hospital for 1 week with croup. Three days before her second admission the family physician had prescribed ampicillin. However, it was not given until the morning of admission, when her respiratory symptoms had worsened. She received the first dose of ampicillin at 9 am and then fell asleep. An hour later she was apneic and unresponsive, and she was rushed to the local hospital. Recurrent apnea necessitated intubation and mechanical ventilation. Her CSF was normal. Her parents also denied exposure to toxic substances.

At the time of arrival at our hospital the infant was stuporous, and her breathing was intermittent, which necessitated continuation of the mechanical ventilation. Her temperature was 39°C, but no source of infection could be found. Her neurologic features were similar to those of the first patient, and she had evidence of prominent brainstem dysfunction.

Her blood leukocyte count was 11.4 × 10⁹/L (56% neutrophils, 37% lymphocytes and 7% monocytes). Biochemical analyses (the same as those done for patient 1) yielded normal results. A chest x-ray film showed atelectasis in the upper lobe of the right lung. Cultures of blood revealed no bacteria or viruses. A CT scan of the head was normal. However, an EEG showed slow-wave activity suggestive of diffuse encephalopathy. A gastric aspirate and a urine sample were sent to be screened for toxic substances.

The infant improved with supportive treatment, and after 24 hours the mechanical ventilation was stopped. She was still ataxic at the time of discharge, 4 days later.

Analysis

We were impressed by the similarity of the clinical presentations of the two infants, who came from the same rural community. On the day of arrival of the second patient, methadone had been tentatively identified in the gastric aspirate and the urine sample of the first infant.

The antibiotics the infants had been receiving had come from the same pharmacy. Their analysis revealed methadone, 2.3 mg/mL in the amoxicillin suspension and 3.7 mg/mL in the ampicillin suspension. Samples of the same lots of the antibiotics (in powder form), obtained from the pharmacy, were found to contain no methadone.

The local office of the Health Protection Branch of the Department of National Health and Welfare confirmed that the pharmacy was a dispensing centre for the local methadone maintenance program. It was concluded that clear methadone liquid had been inadvertently added to the antibiotics as a diluent to produce suspensions suitable for children. Investigations by the College of Pharmacists revealed that four older children had apparently also received methadone-tainted medication, but these children had experienced milder symptoms.

Discussion

Usually methadone is dispensed as a fruit-flavoured solution by authorized pharmacies for methadone maintenance programs. The pleasant flavour makes it more likely to appeal to children. Early reports indicated that the lack of uniformity in the safety of the packaging of methadone, specifically the lack of child-resistant containers, represented a significant hazard for accidental poisoning. In addition, methadone addicts are often unaware of the danger to children presented by careless storage of the drug. The cases we have reported are unusual in that the accidental contamination of the antibiotics occurred in a pharmacy that dispensed methadone.

In the absence of suspicion of a specific toxin, thin-layer chromatography of the gastric aspirate and urine sample were performed in the first case; the results suggested the presence of methadone. Confirmation and quantitation were later provided by gas chromatography. These procedures are not generally available on a 24-hour basis in most clinical laboratories. Thin-layer chromatography requires particular expertise in interpretation. When methadone intoxication is suspected on clinical grounds, qualitative immunochemical analysis of a urine sample can provide rapid confirmation.

Although miosis and respiratory depression are seen in cases of opiate poisoning, they are also associated with a wide variety of other toxic conditions. Barbiturates, caffeine, parasympathomimetic and sympatholytic drugs, phenothiazines, ethanol, nicotine, organophosphorus pesticides, ergot preparations, propoxyphene and other agents may cause constriction of the pupils. Furthermore, although miosis suggests opiate poisoning, the pupils may become dilated with progressive hypoxic encephalopathy. Convulsions may occur in infants with methadone intoxication. Our patients showed striking clinical evidence of diffuse brainstem dysfunction, including miosis, absence of oculocephalic responses, respiratory depression and a peculiar tremor of the tongue and floor of the mouth. This unusual tremor was described by McCurley and Tunnessen.

The cases of methadone poisoning we have described presented a most unusual diagnostic challenge, since the lack of a history of exposure to narcotics and the associated fever obscured the picture, initially making viral encephalitis a more likely diagnosis than toxic encephalopathy.

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References