

Salicylate intoxication from teething gel in infancy

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Clinical records

Patient 1

A 7-month-old boy presented with a 24-hour history of restlessness, tachypnoea, poor feeding and vomiting. An abdominal ultrasound was thought to show possible intussusception. The infant's medical history, including the perinatal period, was unremarkable. His body weight was normal (9 kg). There was no family history of note, and the family denied giving him medications (including complementary or alternative treatment) apart from paracetamol.

He appeared lethargic, with minimal motor and verbal response, although this improved when a low blood sugar level (2.0 mmol/L; reference range [RR], 3.0–5.5 mmol/L) was corrected. Test results of arterial blood gas levels showed a well compensated anion-gap metabolic acidosis, with a lactate level elevated to 7.8 mmol/L (RR, <2.0 mmol/L); pH, 7.38 (RR, 7.35–7.43); partial pressure of carbon dioxide (PaCO₂), 14 mmHg (RR, 32–45 mmHg); partial pressure of oxygen (PaO₂), 129 mmHg (RR, 69–116 mmHg); plasma bicarbonate (HCO₃), 8 mmol/L (RR, 22–32 mmol/L); base equivalent (BE), -7 (RR, -2 to +2); sodium, 142 mmol/L (RR, 135–145 mmol/L); potassium, 4.9 mmol/L (RR, 3.6–5.1 mmol/L); and chloride (Cl), 113 mmol/L (RR, 95–105 mmol/L).

Initial urinalysis showed a specific gravity of 1.025 (RR, 1.015–1.025), pH of 6.0 (RR, 5.0–8.0) and elevated ketones (80 mg/L; RR, 5–30 mg/L), but was otherwise normal. Results of a repeat abdominal ultrasound were normal. Apart from persistent tachypnoea, hyperpnoea and periods of appearing lethargic and less interactive, the infant's vital signs and results of a physical examination were unremarkable. The unexplained anion-gap metabolic acidosis persisted. Metabolic investigations showed a mild transaminitis (serum aspartate aminotransferase [AST], 568 U/L and alanine aminotransferase [ALT], 946 U/L [RR for both, <45 U/L]) and hyperammonaemia (plasma ammonia, 183 µmol/L [RR, <50 µmol/L]). Accordingly, extra intravenous (IV) dextrose was administered (increased to 9.3 mg/kg/min); a urine specimen was sent for urgent mass spectroscopy; and oral administration of a cocktail of vitamins (biotin, B₁₂, riboflavin and carnitine) was commenced, as well as IV bolus doses and then continuing infusions of sodium benzoate and arginine. At this time, the working diagnosis was of an organic acidemia or urea cycle defect with decompensation, caused by intercurrent illness.

Over the following 8 hours, with these measures in place, the transaminitis and hyperammonaemia improved marginally, but the infant's conscious state deteriorated and he required endotracheal intubation. Once intubated, hyperventilation to a PaCO₂ blood level of about 20 mmol/L was continued and the patient was prepared for haemofiltration. The urine spectroscopy result showed salicylate metabolites, and blood testing showed a quantitated salicylate level of 1.44 mmol/L (therapeutic range, 1.1–2.2 mmol/L). A regimen of aggressive urinary alkalisation, as well as potassium supplementation, was commenced using IV sodium bicarbonate 2 mmol/kg/h and potassium chloride 5 mmol/h.

During the next 12 hours, the metabolic acidemia resolved: the elevated serum lactate and plasma ammonia levels normalised, and the patient became more interactive and responsive.

The following day, detailed examination of the contents of the family's home medicine cupboard revealed Bonjela teething gel (Reckitt Benckiser [8.7% choline salicylate]), which the family admitted to using on the infant's gums frequently over the preceding 2 months. Based on an average application of two to three tubes of Bonjela (15 g per tube) per week over 2 months, it was estimated that he received about 60 mg/kg/day of choline salicylate.

Urine alkalisation with IV sodium bicarbonate was continued for a total of about 36 hours, during which the serum salicylate level fell to <3 mg/dL (<0.22 mmol/L) and all other biochemical parameters were within normal limits. Seventy-two hours later, he was discharged from hospital, with normal neurological examination results.

Patient 2

A 13-month-old girl was referred to the hospital outpatients department with failure to thrive. She had a normal gestational and delivery history, and her initial growth parameters were on the third centiles for height and weight. When the infant was aged 9 months, her weight started to fall away from the third centile. She was said to have a good appetite and normal stools. Her parents denied she had a history of medication use.

A clinical examination revealed a happy, active, non-dysmorphic girl. Results of initial investigations of her failure to thrive were normal (including serum levels of electrolytes, calcium, magnesium, phosphate, thyroid-stimulating hormone and thyroxine; liver function tests; serological tests for coeliac disease; full blood count and film; stool microscopy and examination for cysts, ova and pathogens; and karyotype analysis). The exception was an arterial blood gas test result, which showed a mixed metabolic acidosis and respiratory alkalosis (pH, 7.46; PaCO₂, 25 mmHg; PaO₂, 147 mmHg; HCO₃, 13 mmol/L; BE, -7) and mild hyperchloraemia (Cl, 110 mmol/L). Ammonia was slightly elevated at 67 µmol/L. Urine spectroscopy surprisingly showed a high concentration of salicylate metabolites. On further questioning, the parents admitted to giving the child Bonjela gel for teething frequently over several months and, on occasion, to using up to a whole tube of Bonjela at night to settle her to sleep. The result of a quantitated blood salicylate test done 4 days after admission was 0.2 mmol/L.

Traces of phenol were also found on the urine spectroscopy and a search of the family's house revealed a phenol-based cleaning agent used daily in the house. The significance of this finding was uncertain. There were no other dermatological, gastrointestinal or central nervous system symptoms suggestive of chronic phenol exposure.

Bonjela use was stopped, results of a repeat urine spectroscopy were clear, and subsequent levels of blood gases normal. The patient made a good recovery and her normal growth pattern resumed. ♦

Choline salicylate is a non-acetyl salicylate medicament. Compared with aspirin (acetylsalicylic acid), it has effective anti-inflammatory properties but less analgesic and antiplatelet action.

The case of Patient 1 is a valuable reminder of the potential toxicity of chronic salicylate intake at dosages close to those recommended for over-the-counter teething gels (see following). Our accounts of

both patients show the value of taking detailed medication histories for people presenting with unexplained intoxication. Medication histories should include patients' exposure not only to prescribed or over-the-counter medications, but also topical, dermal or mucosal applications, and any complementary or alternative preparations. Checking contents of the home medicine cupboard may be necessary if further clarity is required. The account of Patient 2 graphically

shows the potential for chronic salicylate intoxication to be subtle and difficult to diagnose.

Since the late 1970s, chronic poisoning is the most frequently encountered form of salicylate intoxication.¹ During chronic aspirin intake, major hepatic elimination pathways become saturated, extending the half-life of salicylate.^{2,3} Orally ingested salicylate usually has a serum half-life of 2–4 hours at low doses, and this may increase to as high as 12 hours when used at higher anti-inflammatory doses.⁴ For Patient 1, an elimination half-life of about 28 hours was estimated from serial retrospective measurement of salicylate levels over 18 hours before urine alkalinisation.

Salicylates are metabolised more slowly in neonates than in those with mature liver function.⁵ The pathophysiology of chronic salicylate intoxication involves an uncoupling of oxidative phosphorylation and interference in carbohydrate, lipid and amino acid metabolism. The toxicities manifested by Patient 1 are attributable to these processes. He was initially hypoglycaemic, with documented elevation of serum lactate and pyruvate levels, as well as having evidence of secondary lipolysis and increased ketone body formation. Salicylates inhibit hepatic aminotransferases, which increases blood amino acid levels and can produce aminoaciduria.⁶ Salicylates also impair the urea cycle both indirectly, by inhibiting the respiratory chain, and directly, by suppressing production of ornithine transcarbamylase; these effects explain both patients' hyperammonaemia.⁷

The clinical manifestations of salicylate intoxication are protean, with acute intoxication more commonly causing gastrointestinal symptoms, and chronic intoxication presenting with central nervous system symptoms.⁸ In children, neurological impairment, metabolic acidosis, and hypoglycaemia are common findings of chronic salicylate poisoning. These symptoms were all observed in Patient 1, and the classic combination of metabolic acidosis and respiratory alkalosis was present in Patient 2. Central nervous system disturbances include hyperventilation, agitation, tremor, altered behaviour, memory deficits and altered conscious state.

Serum levels of salicylate between 1.1 and 2.2 mmol/L are considered therapeutic for treatment of inflammatory conditions; in acute intoxication, a level of more than 3.6 mmol/L is likely to indicate severe intoxication. Chronic salicylate intoxication occurs with lower serum concentrations because, over time, a larger amount of salicylate is distributed to tissues, such as those of the central nervous system. Therefore, in chronic intoxication, an initial serum salicylate concentration is of limited value.² Mortality is much higher in chronic intoxication than a single ingested overdose.⁸ Early diagnosis and aggressive supportive treatment such as induced alkaline diuresis and haemodialysis are paramount in the management of symptomatic salicylate poisoning. Acidaemia enhances salicylate transfer into brain tissue. Alkalinising the serum raises the blood pH above that of the brain pH and shifts salicylate from tissues to the plasma. In addition, alkalinising the urine enhances renal excretion of salicylate.⁴

It is noteworthy that there is little evidence supporting the use of choline salicylate-containing gels to relieve the discomfort of teething. There is stronger support for other measures: paracetamol or ibuprofen for pain or fever; teething gels that contain local anaesthetic; and non-pharmacological options such as cold teething rings.⁹ Ours is not the first report of significant salicylate intoxication secondary to the application of teething gel containing choline salicylate.^{10–12} In 2002, the United Kingdom's Commission on Human Medicines issued unequivocal advice that salicylate-containing products are contraindicated in children and young people under the age of 16 years except on specific medical advice.¹³ The Bonjela teething gel that is sold

Lessons from practice

- Chronic salicylate intoxication in infants may be subtle but potentially life-threatening.
- Significant inadvertent salicylate poisoning from over-the-counter preparations can occur.
- All salicylate-containing products should have an appropriate warning label.
- Warnings are not present on packaging of several salicylate-containing teething gels that are marketed for infants in Australia and New Zealand. ◆

within the UK no longer contains salicylate — the analgesic component is now lignocaine, although the manufacturer continues to market salicylate-containing products for adults. As of April 2009, the Medicines and Healthcare Products Regulatory Agency in England had received three reports of adverse reactions in children associated with the use of topical oral gel containing choline salicylate.¹⁴

It is important to appreciate that dosing of this gel directly from the tube is potentially inaccurate, increasing its risks of causing chronic toxicity. The package labelling instructs the carer “to cover the tip of the index finger” with the gel and then apply it to the affected area up to a maximum of six times daily. Commentators have suggested that “... according to manufacturers' recommendation of one application every 3 hours, one third of a tube could be utilised in 24 hours”.⁴ The mother of Patient 1 admitted using two to three 15 g tubes per week over a long period. This equates to twice the minimum daily dose reported to have caused toxicity following chronic ingestion.⁷

The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) states that salicylate intoxication by unintentional overdose of teething gel has been reported “on a number of occasions” to the NZ National Poisons Centre.¹⁵ In Australia, the Therapeutic Goods Administration regards teething gels as “therapeutic goods” and therefore, in our view, these gels should be subject to the requirement that labels of over-the-counter aspirin-containing products include a warning statement.¹⁶ Warnings are not present on packaging of several salicylate-containing teething gels that are marketed for infants in Australia and NZ. It is important that nurses, doctors, pharmacists and families are aware of the potential risk.

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Competing interests

None identified.

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