CASE REPORT

Caffeine to prevent respiratory failure and improve outcome in infant pertussis

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SUMMARY
Pertussis remains a dangerous disease for children around the world, especially for infants less than 6 months old. In this age group, high mortality and morbidity have been linked to the effects of the pertussis toxin, including lymphocytosis, pulmonary hyperviscosity and pulmonary hypertension. This paper reports on an infant with pertussis who received therapeutic caffeine. Caffeine might improve outcomes in pertussis by preventing apnoea, improving respiratory drive and decreasing pulmonary complications.

BACKGROUND
Whooping cough, caused by Bordetella pertussis, is a global health issue and is especially threatening for infants less than 6 months old. Available treatment is mainly supportive, and even with intensive care, mortality and morbidity remain high. Advanced care interventions—including high-frequency (HF) ventilation, inhaled nitric oxide (INO), leucocyte reduction therapy (LRT) and extracorporeal membrane oxygenation (ECMO)—have not been associated with improved outcomes in severely ill infants. This paper describes what we believe is the first reported use of caffeine in pertussis, associated with a positive outcome for our patient. Caffeine is an inexpensive, safe and widely available medication with a strong evidence base supporting its safety and efficacy in neonatal intensive care. This case report may support a pilot trial to study caffeine to prevent respiratory failure and improve outcome in infant pertussis.

CASE PRESENTATION
A 4-month-old male infant developed cough and rhinorrhoea. His parents denied fever, vomiting or diarrhoea. His father and brother had cough and congestion for 2 weeks and had been diagnosed with viral infections. A paediatrician diagnosed a viral infection in the infant. In the 48 hours before admission, the baby began breathing harder and coughing with paroxysms followed by apnoea, with episodes lasting from 10 to 30 s and requiring stimulation. His parents brought him to the emergency department, and he was then admitted to the neonatal intensive care unit (NICU).

Medical history
The baby was born at 27 weeks to a mother who went into preterm labour and developed chorioamnionitis. At delivery, he needed positive pressure ventilation, then nasal continuous positive airway pressure (CPAP) for respiratory distress syndrome. His Apgar scores were 1, 3, 5 and 7 at 1, 5, 10 and 15 min of life. His birth weight was 1005 g.

In the NICU, he was managed with CPAP and high-flow nasal cannula, but never required surfactant or mechanical ventilation. He did not develop intraventricular haemorrhage, retinopathy of prematurity or other complications, and he was discharged home on room air at 38 weeks' corrected gestational age. Prior to discharge, the NICU immunised the baby against Haemophilus influenzae type b, pneumococcus, diphtheria, tetanus, pertussis, hepatitis B and polio virus.

INVESTIGATIONS

Examination
The baby was afebrile at admission with a normal heart rate, blood pressure and respiratory rate. His oxygen saturation on nasal cannula oxygen was 95%. On examination, the baby was vigorous. He had nasal congestion and an intermittent paroxysmal cough. His lung sounds were clear and equal and his work of breathing was normal. He was having apnoeic events every 2–3 min requiring stimulation to resolve, but remained alert and responsive between spells.

Chest radiograph
Chest radiograph showed mildly hyperinflated lungs, faint bilateral peribronchial cuffing and no air leaks or lobar consolidation.

Laboratory studies
Laboratory studies showed white cell count of $17.9 \times 10^9/L$, with 33% neutrophils, 61% lymphocytes and 3% atypical lymphocytes and haemoglobin level of 12.4 g/dL. Blood culture was reported as no growth at 5 days. A venous blood gas was normal with a pH of 7.41 and a PCO$_2$ of 40 mm Hg. A rapid antigen test for respiratory syncytial virus was negative.

DIFFERENTIAL DIAGNOSIS
On NICU admission, the initial diagnosis was bronchiolitis, consistent with the family history of apparent viral illness and with the baby’s cough, rhinorrhoea and apnoea. We considered pneumonia and sepsis, though we felt these were less likely in an afebrile baby with minimal findings on chest X-ray.
We considered pertussis but felt this was less likely because the baby and all family members were immunised.

**TREATMENT**

The baby was given intravenous ceftriaxone and started on nasal CPAP of 5 cm H2O. Because of persistent apnoea despite CPAP, we considered intubation and mechanical ventilation. To try to avoid this, and based on evidence for the benefit of caffeine in bronchiolitis-associated apnoea, we gave 20 mg/kg of intravenous caffeine citrate. Within 1 hour, the baby had no further apnoea. He was given one more dose of 10 mg/kg caffeine citrate 24 hours after the initial dose.

**OUTCOME AND FOLLOW-UP**

Within 24 hours, the baby weaned off CPAP. Within 72 hours, he was off all respiratory support and had resumed breastfeeding. At 48 hours, a nasal swab PCR test was reported positive for *B. pertussis*. The patient and all family members were given a 5-day course of azithromycin. We monitored the baby for 48 more hours and discharged him home. He remains in normal health with no subsequent hospitalisations.

**DISCUSSION**

We believe this is the first report of therapeutic caffeine given (although serendipitously) to an infant with *B. pertussis*. The baby’s apnoea resolved within an hour after the first caffeine dose, and he did not go into respiratory failure.

Pertussis can be a dangerous and even fatal illness in the first few months of life. Risk factors for severe illness and mortality include age <4 months, low birth weight, prematurity, and absence or incomplete immunisation. Immunisation against pertussis is effective but does not completely protect infants. In addition, the waning of vaccine-derived immunity over time in older siblings and parents may increase risks to infants, even vaccinated infants—especially because pertussis is often underestimated in older patients, who might expose their infant siblings. It is important to note that our patient had some high-risk features for critical pertussis, including prematurity and low birth weight, but lacked others: he had received one dose of a vaccine against pertussis; he was over 4 months chronological age at the time of illness; and his white cell count was not extremely high.

In the past 20 years, multiple studies of pertussis have identified risk factors and outcomes for infants around the world. Recent studies include Haberling et al, Berger et al and Winter et al for the USA, Straney et al for Australia and New Zealand, Solano et al for Spain and the Dominican Republic and Heininger et al for Switzerland. In these studies, deaths in children less than 1 year—most of them unimmunised—account for almost all mortality associated with pertussis. Between 1999 and 2004, all US pertussis-related deaths (a total of 91) occurred in children 7 months and younger; 96% of the deaths occurred in infants less than 4 months old. In the data from the USA and Australia/New Zealand, most severely ill infants were less than 3 months old. Between 37% and 54% of the infants had apnoea, and between 27% and 43% were intubated and mechanically ventilated. Infants who were mechanically ventilated had higher white cell counts and were less likely to survive. Infants who died (4.8%–9.4%) were more likely to have been treated with conventional or HF ventilation, ECMO, INO, vasoactive medications or LRT.

The work of Cherry and colleagues, among others, suggests that these poor outcomes are linked to the pertussis toxin (PT). Among its actions, PT acts at G-protein-coupled receptors (GPCRs) to trigger an abnormal immune response, including extreme lymphocytosis. Leucocyte clusters found in pulmonary vasculature and lymphatics cause hyperviscosity, leading to severe pulmonary hypertension and hypoxic organ failure. Loss of G-protein activity related to PT has also been linked to cardiac myocyte injury. Based on this picture, in critically ill infants, Winter et al argue, ‘our data suggest that virtually all deaths are associated with the effects of PT and not the result of apnoea associated with cough illness.’

Apnoea may not be a direct cause of death in whooping cough, yet remains a cause of hypoxia and a risk factor for post-pertussis epilepsy and cognitive impairment. Apnoea has also been documented as a primary reason to intubate and ventilate infants with pertussis. For critically ill neonates and children with other respiratory diseases—including surfactant deficiency and asthma—mechanical ventilation is a risk factor for lung injury. A drug that decreases the risk of apnoea in pertussis could help some infants to avoid mechanical ventilation and its complications; a drug that might also decrease other respiratory complications of pertussis could have even greater benefit.

Caffeine is a methylxanthine used widely in NICUs to treat apnoea of prematurity. Methylxanthines competitively inhibit adenosine receptors at all receptor subtypes (A1, A2A, A2B and A3) in both the central nervous system and in respiratory muscles. Caffeine also antagonises adenosine receptors in respiratory and cardiovascular control centres in the medulla, increasing respiratory drive, strengthening diaphragm contraction and reducing apnoea. Caffeine also improves cerebral response to CO2 chemoreceptors.

Caffeine also acts as a non-selective phosphodiesterase (PDE) inhibitor, increasing cyclic AMP and cyclic guanosine monophosphate levels, thus relaxing smooth muscle, dilating airways and lowering pulmonary arterial pressure. Early caffeine treatment of neonatal rat pups has been shown to increase endothelial nitric oxide synthase levels as well as cyclic AMP levels. At standard doses for infants, caffeine has no known major risks. Neonatal use is associated with improved neurological development and cortical maturation.

Using caffeine early in infant pertussis might therefore improve outcome in at least two main ways. First, caffeine may prevent apnoea and increase respiratory drive, and so give patients with pertussis some of the benefits seen in trials of caffeine for apnoea of prematurity: increased success of non-invasive ventilation, decreased ventilator-induced lung injury, earlier discontinuation of positive airway pressure, shorter oxygen need and improved neurological outcome. For years, caffeine has also been used to treat bronchiolitis-related apnoea in infants and several studies have suggested benefit. A recent placebo-controlled trial of caffeine found that apnoea episodes were shorter in the caffeine group, though it failed to find other clinically important changes. Apnoea rates in infants with pertussis, however, are higher compared with infants with bronchiolitis. The benefit of reducing apnoea in pertussis could therefore be of greater clinical significance.

Second, caffeine may decrease mechanical disease in pertussis. It might do this through two mechanisms. First, as a PDE inhibitor, it could directly relax infant pulmonary vascular muscle and improve oxygenation. A recent study of 556 premature infants found that early caffeine therapy may strongly decrease the risk of late pulmonary hypertension linked to chronic lung disease of prematurity. In addition, caffeine might counter the immunological effects of PT, including pulmonary vascular hyperviscosity from leucocyte aggregation. As far as we know, there are no in vivo studies directly assessing the actions of caffeine against PT. Since caffeine and PT both act at GPCRs, including...
the A<sub>1</sub> adenosine receptor, could caffeine competitively antagonise PT at those sites, neutralising PT as a trigger of deranged immune signalling and severe lymphocytosis? Caffeine has already been shown to decrease serum concentrations of CD4 and CD8 lymphocytes in humans following exercise, and lymphocyte cytotoxicity against myocytes and the rate of mitosis of human lymphocytes in vitro.

Learning points

► Caffeine was given to a high-risk 4-month-old infant with whooping cough. The infant’s apnoea resolved and he did not progress to respiratory failure.

► Caffeine has several possible mechanisms of action in pertussis: it could decrease apnoea and improve respiratory drive, and it may treat pulmonary complications caused by the pertussis toxins.

► Caffeine is inexpensive, widely available, has a long half-life and has a strong evidence base to support its safety in infants.

► Caffeine could be given urgently to infants less than 6 months of age suspected of having pertussis. If a pilot trial of that practice showed initial safety and efficacy, it could support a multicentre, randomised, double-blinded, placebo-controlled trial.

Contributors JOE researched, drafted and edited the case history, discussion and conclusions. EP drafted the section on caffeine pharmacology and edited and contributed to all sections of the report. MG edited the paper and contributed to all sections of the report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer-reviewed.

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REFERENCES

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