



OPEN ACCESS

## CASE REPORT

## Caffeine to prevent respiratory failure and improve outcome in infant pertussis

John Evered,<sup>1</sup> Eric Pfeifer,<sup>2</sup> Matthew Gracianette<sup>3</sup>

<sup>1</sup>Department of Pediatrics, Oregon Health and Science University, Portland, Oregon, USA

<sup>2</sup>Neonatal Intensive Care Unit, PeaceHealth Southwest Medical Center, Vancouver, Washington, USA

<sup>3</sup>Randall Children's Hospital, Legacy Emanuel Medical Center, Portland, Oregon, USA

**Correspondence to**

Dr John Evered, jevered@icloud.com

Accepted 17 March 2018

**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 whether caffeine may improve outcome when given urgently to infants with suspected whooping cough.

**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.



**To cite:** Evered J, Pfeifer E, Gracianette M. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223102

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 H<sub>2</sub>O. 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 absent 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 unrecognised in older patients, who might expose their infant siblings.<sup>1,2</sup> 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.<sup>3–7</sup> 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.<sup>3</sup> In the data from the USA and Australia/New Zealand,<sup>4–7</sup> 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,<sup>8</sup> 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,<sup>5</sup> '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.<sup>7–10</sup> Apnoea has also been documented as a primary reason to intubate and ventilate infants with pertussis.<sup>11–13</sup> For critically ill neonates and children with other respiratory diseases—including surfactant deficiency and asthma—mechanical ventilation is a risk factor for lung injury.<sup>14,15</sup> 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 CO<sub>2</sub> chemoreceptors.<sup>16–18</sup>

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.<sup>19–23</sup> Early caffeine treatment of neonatal rat pups has been shown to increase endothelial nitric oxide synthase levels as well as cyclic AMP levels.<sup>24</sup> At standard doses for infants, caffeine has no known major risks. Neonatal use is associated with improved neurological development and cortical maturation.<sup>25,26</sup>

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.<sup>27–33</sup> For years, caffeine has also been used to treat bronchiolitis-related apnoea in infants and several studies have suggested benefit.<sup>34–36</sup> A recent placebo-controlled trial of caffeine found that apnoea episodes were shorter in the caffeine group,<sup>37</sup> though it failed to find other clinically important changes. Apnoea rates in infants with pertussis, however, are higher compared with infants with bronchiolitis.<sup>38,39</sup> The benefit of reducing apnoea in pertussis could therefore be of greater clinical significance.

Second, caffeine may decrease pulmonary 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.<sup>40</sup> 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>2A</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,<sup>41</sup> lymphocyte cytotoxicity against myocytes<sup>42</sup> and the rate of mitosis of human lymphocytes in vitro.<sup>43</sup>

### 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 toxin.
- ▶ 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.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

### REFERENCES

- 1 Poddighe D, Nedbal MG, Mastricci N, *et al*. Pertussis manifesting as recurrent cough and wheezing in an incompletely vaccinated 8-month-old infant. *BMJ Case Rep* 2017;2017:bcr-2017-221562.
- 2 Salim AM, Liang Y, Kilgore PE. Protecting newborns against pertussis: treatment and prevention strategies. *Paediatr Drugs* 2015;17:425–41.
- 3 Haberling DL, Holman RC, Paddock CD, *et al*. Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. *Pediatr Infect Dis J* 2009;28:194–8.
- 4 Berger JT, Carcillo JA, Shanley TP, *et al*. Critical pertussis illness in children: a multicenter prospective cohort study. *Pediatr Crit Care Med* 2013;14:356–65.
- 5 Winter K, Zipprich J, Harriman K, *et al*. Risk factors associated with infant deaths from pertussis: a case-control study. *Clin Infect Dis* 2015;61:1099–106.
- 6 Straney L, Schibler A, Ganeshalingam A, *et al*. Burden and outcomes of severe pertussis infection in critically ill infants. *Pediatr Crit Care Med* 2016;17:735–42.
- 7 Heinger U, Weibel D, Richard JL. Prospective nationwide surveillance of hospitalizations due to pertussis in children, 2006–2010. *Pediatr Infect Dis J* 2014;33:147–51.
- 8 Cherry JD. Pertussis in young infants throughout the world. *Clin Infect Dis* 2016;63(Suppl 4):S119–22.
- 9 Olsen M, Thygesen SK, Østergaard JR, *et al*. Hospital-Diagnosed Pertussis Infection in Children and Long-term Risk of Epilepsy. *JAMA* 2015;314:1844–9.

- 10 Study of intellectual performance of children in ordinary schools after certain serious complications of whooping cough. Swansea research unit of the royal college of general practitioners. *Br Med J* 1987;295:1044–7.
- 11 Lewis M, Bush GH. Ventilatory support for children with whooping cough. *Anaesthesia* 1980;35:979–83.
- 12 Gillis J, Grattan-Smith T, Kilham H. Artificial ventilation in severe pertussis. *Arch Dis Child* 1988;63:364–7.
- 13 Namachivayam P, Shimizu K, Butt W. Pertussis: severe clinical presentation in pediatric intensive care and its relation to outcome. *Pediatr Crit Care Med* 2007;8:207–11.
- 14 Cavari Y, Sofer S, Rozovski U, *et al*. Non invasive positive pressure ventilation in infants with respiratory failure. *Pediatr Pulmonol* 2012;47:1019–25.
- 15 Yañez LJ, Yunge M, Emilfork M, *et al*. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. *Pediatr Crit Care Med* 2008;9:484–9.
- 16 Oñatibia-Astibia A, Martínez-Pinilla E, Franco R. The potential of methylxanthine-based therapies in pediatric respiratory tract diseases. *Respir Med* 2016;112:1–9.
- 17 Dent G, Rabe KF. Effects of theophylline and non-selective xanthine derivatives on PDE isoenzymes and cellular function. In: Schudt C, Dent G, Rabe KF, eds. *Phosphodiesterase inhibitors*. London: Academic Press, 1996:41–64.
- 18 Welsh EJ, Bara A, Barley E, *et al*. Caffeine for asthma. *Cochrane Database Syst Rev* 2010;1:CD001112.
- 19 Simons FE, Becker AB, Simons KJ, *et al*. The bronchodilator effect and pharmacokinetics of theobromine in young patients with asthma. *J Allergy Clin Immunol* 1985;76:703–7.
- 20 Pauwels R. The effects of theophylline on airway inflammation. *Chest* 1987;92–325–7.
- 21 Usmani OS, Belvisi MG, Patel HJ, *et al*. Theobromine inhibits sensory nerve activation and cough. *FASEB J* 2005;19:231–3.
- 22 Schröder RL, Jensen BS, Strøbaek D, *et al*. Activation of the human, intermediate-conductance, Ca<sup>2+</sup>-activated K<sup>+</sup> channel by methylxanthines. *Pflugers Arch* 2000;440:809–18.
- 23 Fox AJ, Barnes PJ, Venkatesan P, *et al*. Activation of large conductance potassium channels inhibits the afferent and efferent function of airway sensory nerves in the guinea pig. *J Clin Invest* 1997;99:513–9.
- 24 Jing X, Huang YW, Jarzembowski J, *et al*. Caffeine ameliorates hyperoxia-induced lung injury by protecting GCH1 function in neonatal rat pups. *Pediatr Res* 2017;82:483–9.
- 25 Dobson NR, Patel RM, Smith PB, *et al*. Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. *J Pediatr* 2014;164:992–8.
- 26 Hassanein SM, Gad GI, Ismail RI, *et al*. Effect of caffeine on preterm infants' cerebral cortical activity: an observational study. *J Matern Fetal Neonatal Med* 2015;28:2090–5.
- 27 Schmidt B, Roberts RS, Davis P, *et al*. Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;354:2112–21.
- 28 Schmidt B, Roberts RS, Davis P, *et al*. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;357:1893–902.
- 29 Schmidt B, Anderson PJ, Doyle LW, *et al*. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012;307:275–82.
- 30 Henderson-Smart DJ, Steer PA. Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst Rev* 2010;12:CD000140.
- 31 Aranda JV, Beharry K, Valencia GB, *et al*. Caffeine impact on neonatal morbidities. *J Matern Fetal Neonatal Med* 2010;23(Suppl 3):20–3.
- 32 Davis PG, Schmidt B, Roberts RS, *et al*. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. *J Pediatr* 2010;156:382–7.
- 33 Lodha A, Seshia M, McMillan DD, *et al*. Association of early caffeine administration and neonatal outcomes in very preterm neonates. *JAMA Pediatr* 2015;169:33–8.
- 34 Tobias JF. Caffeine in the treatment of apnea associated with respiratory syncytial virus infection in neonates and infants. *South Med J* 2000;93:294–6.
- 35 Duffett M, Liu D, Deshpande A, *et al*. Caffeine in bronchiolitis associated apnea: a retrospective cohort study. *J Pediatr Intensive Care* 2012;01:095–8.
- 36 Cesar K, Iolster T, White D, *et al*. Caffeine as treatment for bronchiolitis-related apnoea. *J Paediatr Child Health* 2012;48:619.
- 37 Alansari K, Toaimah FH, Khalafalla H, *et al*. Caffeine for the treatment of apnea in bronchiolitis: a randomized trial. *J Pediatr* 2016;177:204–11.
- 38 Nicolai A, Nenna R, Stefanelli P, *et al*. Bordetella pertussis in infants hospitalized for acute respiratory symptoms remains a concern. *BMC Infect Dis* 2013;13:526.
- 39 Ralston S, Hill V. Incidence of apnea in infants hospitalized with respiratory syncytial virus bronchiolitis: a systematic review. *J Pediatr* 2009;155:728–33.
- 40 Vyas-Read S, Kanaan U, Shankar P, *et al*. Early characteristics of infants with pulmonary hypertension in a referral neonatal intensive care unit. *BMC Pediatr* 2017;17:163.
- 41 Bishop NC, Fitzgerald C, Porter PJ, *et al*. Effect of caffeine ingestion on lymphocyte counts and subset activation in vivo following strenuous cycling. *Eur J Appl Physiol* 2005;93:606–13.
- 42 Ritter M, Hohenberger K, Alter P, *et al*. Caffeine inhibits cytokine expression in lymphocytes. *Cytokine* 2005;30:177–81.
- 43 Timson J. The effect of caffeine on the mitosis of human lymphocytes in culture. *Br J Pharmacol* 1970;38:731–4.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact [consortiasales@bmjgroup.com](mailto:consortiasales@bmjgroup.com)

Visit [casereports.bmj.com](http://casereports.bmj.com) for more articles like this and to become a Fellow