



Chlorpheniramine use for infants: risks more than benefits

Sharon Tsui-Hang FUNG 馮翠姪* and Eric Yat-Tung CHAN 陳日東
Department of Paediatrics, Kwong Wah Hospital, Hong Kong

Introduction

Nasal symptoms are common in infants. Most of the times they are due to benign condition such as common cold or upper respiratory tract infection (URTI). First generation antihistamines are usually used in treating common cold. However, its use in infants could be associated with apparent life-threatening events, apnoea and sudden infant death syndrome. We reported two infants who were admitted and had desaturation after taking oral chlorpheniramine.

Case 1

A 41-day-old girl, who enjoyed good past health, had cough, runny nose and blocked nose for four days. There was no fever. On the day before admission, she was seen by a private doctor and the following medications were prescribed, paracetamol (31.25 mg po qid), chlorpheniramine (1 mg po qid) and bisolvon (1.5 mg po qid). Medications were taken as instructed and total 6 doses of chlorpheniramine were taken before admission. However, her symptoms persisted, appetite became poor and she was brought to the emergency room and was admitted for further management. On admission, she had desaturation with SpO₂ 89-90% in room air, respiratory rate was 38/min and shallow breathing was noted. Physical examination showed nasal blockage and fine crepitations over both lungs. She was afebrile and heart rate was 142/min. Oxygen therapy, 1 L/min oxygen via nasal cannula, was required to maintain SpO₂ above 95%. Gentle nasal suction was done. Oxygen was taken off after half an hour and there was no desaturation afterward. CXR showed hyperinflated chest with bilateral streakiness, compatible with acute bronchiolitis. Venous blood gas on admission revealed a normal pH, 7.34, with increased bicarbonate level, 25.9 mmol/L. She developed fever up to 39.4°C after admission. Nasopharyngeal aspirate showed

respiratory syncytial virus (RSV). Complete blood picture showed neutropenia, 0.8 x 10⁹/L. C-reactive protein, electrolytes were normal. Pernal swab for pertussis was negative. Blood, cerebral spinal fluid and urine cultures showed no growth. She remained oxygen free. Fever gradually subsided. The diagnosis was RSV bronchiolitis.

Case 2

A 38-day-old girl, who enjoyed good past health, was admitted because of blocked nose, noisy breathing sound, severe cough and runny nose for three days. There was no fever all along. She had recently travelled to Shenzhen, China one week ago. Both parents had symptoms of upper respiratory tract infection. On the first day of illness, around four days before admission, the baby was brought to see a doctor in Shenzhen and was given ribavirin (25 mg/dose, po tds) and cefaclor (62.5 mg /dose po tds). Two doses of each medication were taken and she was brought back to Hong Kong for further medical consultation. She was seen by a private doctor on the second day of illness, chlorpheniramine 0.4 mg po qid, mucospect 20 mg po qid and children cough syrup (a mixture of cocillana, liquid NH₃ acetate, senega liquid, seillae liquid; 1 ml po qid) were prescribed, these medications were taken as instructed and eight doses of each medication were taken. However, there was blocked nose and difficulty in breathing and appetite was poor. She was then brought to the emergency room and was admitted to this department. Soon after admission, she was noted to have desaturation, SpO₂ was 80%, with no respiratory effort and sinus tachycardia with heart rate up to 180-200/min. Oxygen therapy 2 L/min via nasal cannula and tactile stimulation were required to maintain SpO₂ above 95%. She was then transferred to the paediatric intensive care unit for close observation. Arterial blood gas on admission to intensive care unit showed hypercapnia with metabolic compensation pH, 7.30, pCO₂, 9.0kp, HCO₃, 33.2 mmol/L, BE 4.4. Oxygen 0.5 L/min via nasal cannula was required. She had recurrent episodes of apnoea. The apneic episodes consisted of central

*Author to whom correspondence should be addressed.

Email: fung_tsui_hang@hotmail.com



apnoea, obstructive and mixed apnoea. Chest radiograph was normal. Ultrasound brain was normal. Complete blood picture was normal. Full septic work up showed no bacterial growth. No more clinically apparent apnoea was noted twelve hours after admission. Oxygen therapy was taken off the next day. There were occasional desaturations following the bouts of cough. Blood gases gradually normalised. Pernal swab returned positive for pertussis, a course of azithromycin was given. The nasopharyngeal aspirate was positive for influenza A also. The baby remained well after. The diagnoses were pertussis and influenza A.

Discussion

First generation antihistamines are commonly used to treat nasal symptoms. It competitively antagonises histamine at the H1 receptor. However, its efficacy in treating nasal symptoms of upper respiratory tract infection is controversial. Double blinded, randomised, placebo-controlled trials failed to show significant improvements of URTI symptoms in children who received an antihistamine-decongestants.^{1,2} Its adverse effects include sedation, dizziness, headache, insomnia, nervousness, nausea, vomiting, constipation, diarrhoea, dry mouth, urinary retention, impotence, appetite stimulation and body weight gain.³ United State Food and Drug Administration termed first generation antihistamines as 'sedating antihistamines'.⁴ First generation antihistamines may induce sedation by their direct antagonism of centrally located H1 receptors⁵ and centrally located acetylcholine receptors,⁶ other anticholinergic effects and antagonism of central H1 receptors may permit circulating histamine to interact with other receptors, such as central H3 receptors which results in the sedative effect.^{3,7}

In the first case of RSV bronchiolitis, the patient's condition was much improved after clearing the nasal blockage and the bronchiolitis was mild in terms of respiratory distress. In infants with bronchiolitis, they usually had respiratory distress. However, the patient had shallow breathing, normal respiratory rate and desaturation. We suggested that chlorpheniramine thickened the nasal secretions and aggravated the nasal blockage in an obligate nasal breather and the sedating effect impaired the respiratory drive. The combined effects led to desaturation. Moreover, the

chlorpheniramine dosage, 1 mg qid, was too high for a young infant. There is no recommended dosage of chlorpheniramine for young infants under 1 year old as it is generally not recommended in children under 1 year old. For children aged 1-2 years old, the dosage recommended should be 1 mg bd with maximum daily dose of 2 mg.⁸

Infant with pertussis may have recurrent apnoea. In case two, the patient had recurrent central apnoea in the first few hours of admission. We suggested that the sedating effect of chlorpheniramine further aggravated the respiratory insufficiency of the patient. With appropriate treatment, the condition improved in around twelve hours. Management of pertussis included macrolide, close monitoring, oxygen, infection-control precaution and close-contact prophylaxis.

Promethazine, phenothiazine derivative, were shown to be associated with apparent life threatening events, sleep apnoea, sudden infant death syndrome (SIDS) and near-miss SIDS.⁹ A population based prospective cohort study reported in 1997 also found an association between the administration of antihistamine medication and infant cyanosis.¹⁰ In 1985, Kahn et al showed that promethazine at a usual dose of 1 mg/kg/day caused an increase in sleep time and a reduction in the number and duration of awakenings, an increase in non-rapid eye movement sleep and a reduction in body movements in the first night after promethazine use. There was an increase in the number of central apnoeas, and several episodes of obstructive apnoeas were also noted in the second night after promethazine use in infant.¹¹

Although chlorpheniramine was shown to be less sedating when compared with promethazine,³ these two cases served to remind medical practitioners and the general public that it was still risky for use in young infants and we should avoid using chlorpheniramine to treat nasal symptoms in infant. When one encounters a neonate with nasal blockage and respiratory distress, one should check the patency of both nostrils by passing a French 8 catheter to rule out nasal obstruction.¹² If other symptoms are present, such as severe cough, other underlying causes, such as pertussis or RSV, should be entertained. To treat nasal blockage and secretions, our experience with 1.5% NaCl nasal drops were good in thinning the nasal secretions; gentle mechanical suction may help to clear the nasal block temporarily.



0.06% nasal ipratropium bromide was shown to be effective in treating rhinorrhoea in pre-school children.¹³ Data in infant was not available. We should avoid nasal decongestant containing phenylpropanolamine or imidazoline in young infant as these nasal vasoconstrictor may have severe central nervous system and cardiovascular system side effect.¹⁴⁻¹⁶ For infants older than 6-month, a third generation antihistamine, cetirizine, was reported to be safe with therapeutic dose of 0.25 mg/kg twice daily.¹⁷

In conclusion, first generation antihistamine is dangerous in young infants and should not be used. Specific treatment targeted at the etiology should always be employed. If the nasal symptoms are secondary to self-limited illness, the benefits of first generation antihistamine is outweighed by its adverse effects. If the nasal symptoms are secondary to severe illnesses, e.g. choanal stenosis or pertussis, antihistamines are not effective.

References

- Hutton N, Wilson MH, Mellits ED, Baumgardner R, Wisow LS, Bonuccelli C, et al. Effectiveness of antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. *J Pediatr* 1991; 118:125-30.
- Clemens CJ, Taylor JA, Almquist JR, Quinn HC, Mehta A, Naylor GS. Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children? *J Pediatr* 1997;130:463-46.
- Simons F, Simons K. H1 Receptor antagonists: clinical pharmacology and use in allergic disease. *Pediatr Clin North Am* 1983;30:899-914.
- Nolen TM. Sedative effects of antihistamines: safety, performance, learning, and quality of life. *Clin Ther* 1997;19: 39-55; discussion 2-3.
- Monti JM. Involvement of histamine in the control of the waking state. *Life Sci* 1993;53:1331-8.
- Diffley D, Tran V, Snyder S. Histamine H1-receptors labeled in vivo: antidepressant and antihistamine interactions. *Eur J Pharmacol*. 1980 Jun 13;64(2-3):177-81.
- Ten Eick AP, Blumer JL, Reed MD. Reed. Safety of Antihistamines in Children. *Drug Saf* 2001;24:119-47.
- British National Formulary. British Medical Association. Royal Pharmaceutical Society of Great Britain.
- Kahn A, Blum D. Phenothiazines and sudden infant death syndrome. *Pediatrics* 1982;70:75-8.
- Ponsonby AL, Dwyer T, Couper D. Factors related to infant apnea and cyanosis: a population-based study. *J Paediatr Child Health* 1997;33:317-23.
- Kahn A, Hasaerts D, Blum D. Phenothiazine-induced sleep apneas in normal infants. *Pediatrics* 1985;75:844-7.
- Chan EY, Ng DK, Chong AS, Hui Y, Fu YM. Congenital nasal pyriform aperture stenosis with semilobar holoprosencephaly. *Int J Pediatr Otorhinolaryngol* 2005;69:93-6.
- Kim KT, Kerwin E, Landwehr L, Bernstein JA, Bruner D, Harris D, et al. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. *Ann Allergy Asthma Immunol* 2005;94:73-9.
- Hamilton RS, Sharieff G. Phenylpropanolamine-associated intracranial hemorrhage in an infant. *Am J Emerg Med* 2000; 18:343-5.
- Claudet I, Fries F. Danger of nasal vasoconstrictors in infants. Apropos of a case. *Arch Pediatr* 1997;4:538-41.
- Bucaretschi F, Dragosavac S, Vieira RJ. Acute exposure to imidazoline derivatives in children. *J Pediatr (Rio J)* 2003;79: 519-24.
- Simons FE, Silas P, Portnoy JM, Catuogno J, Chapman D, Olufade AO, et al. Safety of cetirizine in infants 6 to 11 months of age: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2003;111:1244-8.