Negative pressure pulmonary oedema: a potential hazard of muscle relaxants in awake infants

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We report two cases of healthy infants who were given an IV intubating bolus of a nondepolarizing muscle relaxant (0.1 mg · kg^{-1} vecuronium) at the beginning of an inhalational induction of anaesthesia. Shortly after the introduction of low concentrations of gaseous agents, both infants exhibited airway obstruction although inspiratory muscle activity was still vigorous. The airway obstruction was due to approximation of the tongue to the posterior pharyngeal wall, and was easily corrected by insertion of an oral airway. The infants immediately exhibited fulminant pulmonary oedema, which responded to conventional therapy. It is postulated that paralysis of glossal muscles occurred prior to diaphragmatic paralysis, creating upper airway obstruction while preserving inspiratory muscle activity. This can rapidly lead to negative pressure pulmonary oedema in the small infant. Meticulous attention to the maintenance of an unobstructed upper airway is required if muscle relaxants are administered to the awake infant.

Peu après l'injection intraveineuse de 0,1 mg · kg^{-1} de vécuronium en bolus, au début d'une induction par anesthésique en inhalation, deux bébés en bonne santé développèrent une obstruction respiratoire tandis que persistait une activité importante des muscles inspiratoires. L'insertion d'une canule oropharyngée corrigea rapidement l'obstruction causée par l'accolement de la langue à la paroi postérieure du pharynx. Dans les deux cas, il s'ensuivit toutefois un œdème pulmonaire fulminant que l'on traita de façon conventionnelle. Nous postulons que la paralysie des muscles de la langue survint avant celle du diaphragme, amenant une obstruction des voies aériennes sur une mécanique inspiratoire intacte. Chez les bébés, cela peut facilement entraîner un œdème pulmonaire par pression négative. Mieux vaut donc s'assurer de la perméabilité des voies aériennes lorsque qu'on injecte un curare à un enfant éveillé.

Key words
AIRWAY: obstruction, iatrogenic;
ANAESTHESIA: paediatric;
LUNG: oedema, negative pressure;
NEUROMUSCULAR RELAXANTS: complications.

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We recently reported an infant who developed negative pressure pulmonary oedema (NPPE) upon emergence from general anaesthesia as a result of an obstructed tracheal tube.[1] Subsequently, we have observed two infants who have experienced NPPE secondary to airway obstruction occurring early in the course of an inhalational induction of anaesthesia. Both had received vecuronium while awake (crying, moving all extremities) to facilitate early control of the airway.

Case reports

A fullterm four-week-old male infant was scheduled for cystoscopy and possible pyeloplasty. He entered the operating room with an IV infusion in place. Precordial stethoscope, ECG and pulse oximetry sensor were positioned and the alarm set at 90 per cent oxygen saturation. As the administration of 0.25 per cent halothane and 50 per cent N_2O by mask was commenced, 0.1 mg · kg^{-1} vecuronium was given IV. Within 30 sec, the oximeter alarm sounded, and the infant was observed making two maximal inspiratory efforts, with sternal collapse evident with both inspiratory attempts. The baby was cyanotic. Immediately, an oral airway was inserted and positive pressure ventilation was accomplished with 100 per cent O_2. However, O_2 saturation remained below 85 per cent and bloody foam was observed under mask. A tracheal tube was quickly inserted in spite of poor visualization of the glottis due to copious amounts of frothy fluid. Surgery was cancelled. In the recovery room, the infant's lungs were mechanically ventilated with the addition of 5 cm H_2O PEEP, and he was given 1 mg · kg^{-1} furosemide for diuresis and 2 μg · kg^{-1} fentanyl for sedation. The chest *x*-ray, which showed fluffy exudates soon after the event,

was clear the next morning; arterial blood gas tensions were normal while breathing room air, and the trachea was successfully extubated.

A healthy fullterm six-week-old male infant presented for excision of a dermal sinus of the sacrum. An IV infusion was in place. In the operating room, the following monitors were placed: precordial stethoscope, ECG, automatic blood pressure cuff, pulse oximeter and axillary temperature probe. While 100 per cent O_2 was insufflated by mask, 0.1 $mg \cdot kg^{-1}$ vecuronium was administered IV. The gaseous mixture was then changed to 0.25 per cent isoflurane and 50 per cent N_2O. Soon afterwards, airway obstruction was noted and the O_2 saturation had decreased to 85 per cent. The anaesthetic agents were discontinued and the airway obstruction was corrected with insertion of an oral airway combined with the jaw-thrust manoeuvre, which ruled out isoflurane-induced laryngospasm. Oral tracheal intubation was quickly performed; copious amounts of pink-tinged fluid instantly poured from the tracheal tube. With suction and vigorous hyperventilation, O_2 saturation increased to 96 per cent with an FiO_2 of 1.0. In the recovery room, the infant was given 1.0 $mg \cdot kg^{-1}$ furosemide and his lungs were mechanically ventilated with 5 cm H_2O PEEP added. Chest *x*-ray revealed bilateral fluffy exudates consistent with pulmonary oedema; echocardiogram was normal. With the return of spontaneous respiration, CPAP of 5 cm H_2O was instituted. Within a few hours, the oedema had cleared as evidenced by auscultation and chest *x*-ray, and arterial blood gas tensions were normal while breathing room air. The trachea was successfully extubated approximately four hours after the initial insult.

Discussion

In healthy infants, NPPE is a rarely recognized event in the perianaesthetic setting. We are aware of only three reported cases, all occurring upon emergence – one due to tracheal tube occlusion by bronchial impaction,[1] and two due to laryngospasm.[2,3] The two cases described in this report represent NPPE occurring upon induction of general anaesthesia.

The pathophysiology of NPPE was discussed in a previous paper,[1] so will not be commented upon at this time, except to say that the exact mechanism has not been adequately defined. In fact, the entity has not been unequivocally reproduced in laboratory animals (Staub NC, personal communication). Two conditions must be present: (1) inspiratory airway obstruction and (2) spontaneous inspiratory effort(s). In awake infants with total airway obstruction, NPPE can develop very rapidly, in a matter of seconds.

Pulmonary aspiration of gastric contents may produce clinical findings similar to NPPE, namely, pulmonary oedema, hypoxia and decreased compliance. However, the presence of these signs following correction of an airway obstruction in a spontaneously breathing patient merits the presumptive diagnosis of NPPE. If frothy pink-tinged fluid pours from the upper airway immediately after reestablishment of airway patency in a previously healthy child, the diagnosis of NPPE is almost certain. Early chest *x*-ray shows bilateral fluffy infiltrates in a central (butterfly) pattern. Appropriate therapy will correct both clinical and *x*-ray signs within 24 hr, unless tissue damage has occurred.[1] If the onset of clinical signs is delayed beyond the time of airway correction, aspiration should be considered in the differential diagnosis. Massive aspiration of gastric acid can produce the same *x*-ray picture as NPPE, but aspiration of a lesser amount most commonly involves the posterior segments or the right side. Roentgenographic changes typically lag behind the development of clinical signs and take at least a week to resolve.[4] The clinical course is also more protracted and severe because of chemical injury to the alveolar and bronchiolar epithelium. Some cases of "mild aspiration" or "silent regurgitation" may have been due to NPPE.

It is postulated that airway obstruction in the two infants reported above was the result of paralysis of the muscles protecting the upper airway, allowing the tongue to fall back and occlude the oropharynx, and that NPPE developed because the diaphragm was still functionally adequate. A difference in sensitivity to neuromuscular blockade between the muscles that protect the upper airway from obstruction and/or aspiration, and the muscles involved in inspiration was demonstrated in a recent study by Pavlin *et al.* who gave small incremental doses of d-tubocurarine to conscious adults.[5] When paralysis had progressed to the point that the subjects were unable to approximate the incisors, or to swallow, or to hold the tongue away from the posterior pharyngeal wall, maximal inspiratory pressures of 48, 47 and 43 per cent, respectively, could still be produced.

The above study[5] evaluated dose-related sensitivities at subparalytic steady-state blood concentrations in awake subjects. To our knowledge, time-related sensitivities (i.e., onset times for paralysis) among the different muscle groups involved with respiration have not been specifically studied in subjects given a paralytic (intubating) IV bolus – a situation in which a true steady state is never achieved. However, there have been studies in awake subjects given a small (priming) bolus of vecuronium, where relative sensitivities were evaluated 3 min after drug administration. Taboada *et al.*[6] reported that the majority of patients given 0.02 $mg \cdot kg^{-1}$ were unable to protrude the tongue and/or experienced difficulty in swallowing (which involves masseter contraction and

tongue elevation), but had no difficulty breathing. In a study by Engbaek *et al.*,[7] most awake volunteers given 0.015 $mg \cdot kg^{-1}$ noted dysphagia, but no breathing difficulties; and the measured inspiratory force was 86 per cent of control. Musich and Walts[8] reported a sedated adult who became agitated and complained of weakness and difficult breathing within one minute of receiving 0.02 $mg \cdot kg^{-1}$ vecuronium.

The onset time for full paralysis after an IV intubating bolus has been assessed by measuring the degree of peripheral paralysis, usually in muscles of the hand.[9] Two recent studies have compared the onset times for paralysis of the adductor pollicis with diaphragmatic or masseter paralysis and suggest that the onset time for paralysis of muscles maintaining the upper airway may precede the onset time for paralysis of the inspiratory muscles following an intubating bolus of vecuronium. In adults anaesthetized with N_2O, fentanyl and thiopentone, Chauvin *et al.*[10] found that a 0.1 $mg \cdot kg^{-1}$ IV bolus of vecuronium produced complete diaphragmatic paralysis at 1.6 min. Nakatsuka *et al.*[11] in assessing masseter muscle activity in adults, found that the muscle was unresponsive to train-of-four stimulation of the mandibular nerve 1 min after the administration of 0.1 $mg \cdot kg^{-1}$ of vecuronium. In both studies, peripheral paralysis occurred later. Since the onset of vecuronium-induced paralysis is more rapid in infants than in adults – possibly due to a higher cardiac output,[12] an onset time of less than 30 sec for paralysis of muscle protecting the upper airway in the infant receiving 0.1 $mg \cdot kg^{-1}$ of vecuronium does not seem unreasonable and, at this time, diaphragmatic activity may still be adequate. Variations in onset times among specific muscle groups are thought to be dependent upon differences in local blood flow and differences in muscle structure, which may govern accessibility of the relaxant to the motor endplate.[10]

The IM administration of intubating doses of succinylcholine may also produce a time-related differential in paralysis between upper airway and inspiratory muscles, and a brief period of unrecognized or uncorrected airway obstruction may produce NPPE. This might explain the pulmonary oedema found in awake infants following IM succinylcholine, reported by Cook *et al.*[13] Indeed, in a study by Williams and Bourke,[14] a semirecumbent awake adult given low-dose succinylcholine by infusion developed upper airway obstruction, although the generated inspiratory pressure was 63 per cent of control.

The genioglossal muscles play an important role as accessory muscles of respiration. Reflex phasic inspiratory genioglossal activity helps to maintain a patent pharyngeal airway by pulling the tongue forward when negative pressure is sensed during inspiration. In animals, paralysis of the genioglossal muscles leads to collapse of the pharyngeal airway when negative pressure is applied.[15] Head position also plays an important role in maintaining a patent upper airway, especially if genioglossal activity is depressed, as during sleep, general anaesthesia or muscle paralysis. Neck extension increases the rigidity of the upper airway, making it more resistant to collapse from negative transmural pressure.[16] The infant – with a relatively larger tongue than the adult – is especially vulnerable to both genioglossal depression and head position. It is possible that some degree of neck flexion contributed to early upper airway obstruction in our two infants.

Airway management during induction of general anaesthesia in the infant less than two months of age requires a high level of experience and skill. All infants in this age group should be intubated. Awake tracheal intubation is usually reserved for those infants who are at risk for aspiration, or have an upper airway problem or are unstable. In most other circumstances, tracheal intubation is performed following induction of general anaesthesia. Although an intravenous sequence can be used if an IV infusion is in place, an inhalational technique with gradually increasing concentrations of gaseous agents is preferred at our institution. However, if volatile agents alone are employed for laryngoscopy and tracheal intubation, the depth of anaesthesia (MAC) required to prevent reflex closure of the vocal cords and/or coughing may be sufficient to cause myocardial depression.[17] Therefore, muscle relaxants are commonly given IV to facilitate laryngoscopy at a lower MAC. Ideally, their administration should be timed so that maximal paralysis is present when a light surgical plane of anaesthesia has been reached. The slower onset of action of nondepolarizing drugs, compared with succinylcholine, permits their earlier administration, with the added objective of facilitating control of the airway and ventilation during the early stages of induction. The two infants in this report had IV infusions in place, so vecuronium was electively administered as the gaseous agents were introduced. Unfortunately, this sequence precipitated upper airway obstruction which was neither anticipated nor corrected in time.

In conclusion, the administration of intubating doses of muscle relaxants to awake infants at the beginning of an inhalational induction may selectively paralyze muscles protecting the upper airway from obstruction, before there is significant depression of inspiratory muscle activity from either the relaxant or inhalational agent. In this situation, expert airway management is required to prevent negative pressure pulmonary oedema, which can develop rapidly in the infant with total upper airway obstruction and spontaneous inspiratory activity.

References

1 *Warner LO, Beach TP, Martino JD.* Negative pressure pulmonary oedema secondary to airway obstruction in an intubated infant. Can J Anaesth 1988; 35: 507–10.

2 *Lee KWT, Downes JJ.* Pulmonary edema secondary to laryngospasm in children. Anesthesiology 1983; 59: 347–9.

3 *Deisering LF, Douglass DA.* Post-laryngospasm pulmonary edema. American Association of Nurse Anesthetists Journal 1988; 56: 246–8.

4 *Kuhn JP.* The Thorax. *In*: Silverman FN (Ed.). Caffey's Pediatric X-Ray Diagnosis: An Integrated Imaging Approach. 8th ed. Chicago: Year Book Medical Publishers, Inc., 1985: 1245–64.

5 *Pavlin EG, Holle RH, Schoene RB.* Recovery of airway protection compared with ventilation in humans after paralysis with curare. Anesthesiology 1989; 70: 381–5.

6 *Taboada JA, Rupp, SM, Miller RD.* Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. Anesthesiology 1986; 64: 243–7.

7 *Engbaek J, Howardy-Hansen P, Ørding H, Viby-Mogensen J.* Precurarization with vecuronium and pancuronium in awake, healthy volunteers: the influence on neuromuscular transmission and pulmonary function. Acta Anaesthesiol Scand 1985; 29: 117–20.

8 *Musich J, Walts LF.* Pulmonary aspiration after a priming dose of vecuronium. Anesthesiology 1986; 64: 517–9.

9 *Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ.* Clinical pharmacology of vecuronium and atracurium. Anesthesiology 1984; 61: 444–53.

10 *Chauvin M, Lebrault C, Duvaldestin P.* The neuromuscular blocking effect of vecuronium on the human diaphragm. Anesth Analg 1987; 66: 117–22.

11 *Nakatsuka M, Franks P, Keenan RL.* A method of rapid-sequence induction using high-dose narcotics with vecuronium or vecuronium and pancuronium in patients with coronary artery disease. Journal of Cardiothoracic Anesthesia 1988; 2: 177–81.

12 *Fisher DM, Miller RD.* Neuromuscular effects of vecuronium (ORG NC45) in infants and children during N_2O, halothane anesthesia. Anesthesiology 1983; 58: 519–23.

13 *Cook DR, Westman HR, Rosenfeld L, Hendershot RJ.* Pulmonary edema in infants: possible association with intramuscular succinylcholine. Anesth Analg 1981; 60: 220–3.

14 *Williams JP, Bourke DL.* Effects of succinylcholine on respiratory and nonrespiratory muscle strength in humans. Anesthesiology 1985; 63: 299–303.

15 *Brouillette RT, Thach BT.* Control of genioglossus muscle inspiratory activity. J Appl Physiol 1980; 49: 801–8.

16 *Wilson SL, Thach BT, Brouillette RT, Abu-Osba YK.* Upper airway patency in the human infant: influence of airway pressure and posture. J Appl Physiol 1980; 48: 500–4.

17 *Berry FA* (Ed.). Anesthetic Management of Difficult and Routine Pediatric Patients. New York: Churchill Livingstone, 1986; 68–74.