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ORIGINAL PAPER

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Apnoea and bradycardia in preterm infants following immunisation with pentavalent or hexavalent vaccines

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Abstract There is a lack of data regarding the incidence and clinical significance of apnoea or bradycardia (AB) following immunisation with combination vaccines containing an acellular pertussis (Pa) component in respiratory stable preterm infants. Medical records of respiratory stable preterm infants who received a first dose of a combined diphtheria (D) and tetanus (T) toxoids, Pa, *Haemophilus influenzae* type b (Hib), inactivated poliovirus (IPV) vaccine with or without hepatitis B virus (HBV) in the neonatal intensive care unit (NICU) of the University Children's Hospital Basel between January 2000 and June 2003 were analysed. For each infant, clinical data were recorded for a 72 h period before and after immunisation. Of 53 infants with a mean gestational age of 28 weeks, 7 (13%) showed a transient recurrence of or increase in episodes of AB following immunisation. Five of these seven infants required intervention ranging from tactile stimulation to bag and mask ventilation. Regarding risk factors, children with recurrent or increased AB were indistinguishable from those without such events. The rate of fever (>38°C) following immunisation was higher in affected infants compared to those without recurrence of or increase in AB (3/7 vs 2/46, $P = 0.01$). *Conclusion*: Although most infants tolerated immunisation well, the incidence of recurrent or increased apnoea or bradycardia in respiratory stable preterm infants following the first immunisation with penta- or hexavalent vaccines was 13%. Most apnoea or bradycardia events required intervention but did not have serious consequences. Monitoring of all preterm infants following immunisation in the neonatal intensive care unit is recommended.

Keywords Acellular pertussis vaccine · Apnoea · Bradycardia · Immunisation · Preterm infant

Abbreviations AB: apnoea or bradycardia · CPAP: continuous positive airway pressure · D: diphtheria · HBV: hepatitis B virus · Hib: *Haemophilus influenzae* type b · IPV: inactivated polio virus · NICU: neonatal intensive care unit · Pa: acellular pertussis · Pw: whole cell pertussis · T: tetanus

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Introduction

Official guidelines in North America, Australia and various European countries recommend immunising stable preterm infants at the same chronological age as full-term infants because of their increased risk of vaccine-preventable diseases and sufficient immune responses. Concerns have been raised after the recognition of clinically significant apnoea following the immunisation of hospitalised preterm infants with diphtheria (D), tetanus (T), whole cell pertussis (Pw), and *Haemophilus influenzae* type B (Hib) component vaccines [2, 8,9]. Recent studies have shown similar cardiorespiratory events after administration of combination vaccines containing an acellular pertussis (Pa) component in cohorts of former preterm infants with a large proportion of infants on respiratory support or supplemental oxygen at the time of immunisation, both known to be risk factors for post-immunisation apnoea [3, 6,10]. We report on the incidence and clinical significance of post-immunisation apnoea or bradycardia (AB) in former preterm infants not requiring respiratory support or supplemental oxygen and immunised with a pentavalent (DTPa-IPV/Hib) or hexavalent vaccine (DTPa-IPV-HBV/Hib) in the neonatal intensive care unit (NICU).

Subjects and methods

Medical records of all preterm infants, hospitalised for at least 8 weeks after birth, who had received their first Infanrix DTPa-IPV + Hib or Infanrix Hexa (containing DTPa-IPV + Hib + HBV) vaccine (GlaxoSmithKline, Rixensart, Belgium) between January 2000 and June 2003 in the NICU of the University Children's Hospital, Basel, Switzerland, were analysed retrospectively.

Apnoea was defined as ≥20 s without breathing, and bradycardia as a heart rate <100/min for at least 20 s according to our general institutional guidelines for the monitoring of preterm infants. All 60 identified infants had a previous history of typical AB of prematurity. A total of 53 infants were continuously monitored by electrocardiogram and chest wall impedance monitors. Six infants were monitored by pressure sensors only and one infant was without technical monitoring for unknown reasons; the latter seven patients were excluded from the analysis.

Infants were considered to have recurrent or increased AB after immunisation when recurrence of or a ≥50% increase in the frequency of AB episodes occurred in the 72 h period following immunisation compared to the 72 h period preceding immunisation. Bronchopulmonary dysplasia was defined as a need for supplemental oxygen at 36 weeks postmenstrual age or at a chronological age of 4 weeks to maintain an oxygen saturation of at least 88%.

At the time of immunisation, all infants were medically stable and did not require any ventilatory support or continuous supplemental oxygen. Rectal temperature was measured routinely every 8 h and in addition when nursing staff suspected fever. Children with recurrent or increased AB were compared with those without such events in order to identify possible predictive factors. Statistical analysis was performed by the Prism 4 for Mac OS X software package (GraphPad Software, San Diego, USA) using the Student t-test, Mann-Whitney test and Fisher's exact test as appropriate.

Results

In the 72 h control period before immunisation, 16 infants had AB (median 3 episodes, range 1 to 19). In this period, no infant with AB required any intervention. In the 72 h period following immunisation, seven infants (13%) had recurrent or increased AB (median 6 episodes, range 2 to 33) (Fig. 1). Episodes started 8 to 24 h after and settled within 48 h following immunisation. Five infants required repeated tactile stimulation and three of them needed supplemental oxygen. One infant additionally needed resuscitation by brief bag and mask ventilation because of prolonged AB and hypoxaemia. No infant required restart of caffeine treatment, continuous positive airway pressure (CPAP), or re-intubation. Infants showing recurrent or increased episodes of AB were indistinguishable from those without recurrence of or increase in AB (Table 1). A comparison between the proportion of hexavalent and pentavalent vaccinations in both groups revealed no difference regarding recurrence of or increase in AB (2/7 vs. 12/46, $P = 1.0$). The rate of fever (>38°C) following immunisation was higher in the group of apnoeic infants compared to those without recurrence of or increase in AB (3/7 vs. 2/46, $P = 0.01$). There were no signs of late onset sepsis or intercurrent infection in infants who had fever following immunisation.

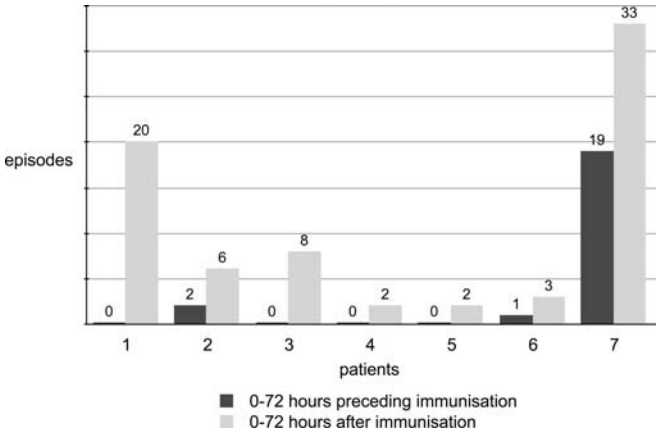

Fig. 1 Individual numbers of AB episodes in seven preterm infants after their first combined immunisation

Discussion

The incidence of apnoea in hospitalised preterm infants following immunisation with DTPw-Hib combination vaccines has been reported to be in the range of 7% to 23% [2, 8,9]. Studies reporting no increased risk of apnoea in preterm infants after the first DTPw vaccination were based on parents' diaries in outpatient settings [1,7]. In such settings without monitoring, however, it may be difficult to recognise apnoea.

Recent studies showed that the use of vaccines incorporating Pa instead of Pw vaccine components does not prevent post-immunisation apnoea in former preterm infants, thus making it very unlikely to suspect endotoxin as an important trigger factor for these events, because Pa does not contain endotoxin [3,10]. The cause of AB after immunisation is not yet identified, and it has been speculated that it might be an unspecific CNS reaction to vaccine-induced stimulation of the immune system [5]. The delay between immunisation and onset of AB was between 8 and 24 h and is in agreement with this hypothesis. Similarly, the onset of fever as a side-effect after immunisation with pertussis component and other killed vaccines usually also occurs after 6 to 24 h [11]. It is therefore tempting to assume that similar underlying immunological mechanisms are responsible for these observations.

Table 1 Basic characteristics and clinical conditions of respiratory stable preterm infants with or without AB following immunisation

	Recurrence of or increase in AB (n = 7)	No recurrence of or increase in AB (n = 46)	P
Basic characteristics			
Sex, male	6 (86%)	25 (54%)	0.22 [c]
Mean gestation (weeks)	27.9 (25.5–30.3)	27.9 (26.0–29.8)	0.94 [a]
Mean birth weight (g)	987 (743–1231)	999 (748–1250)	0.91 [a]
Mean postmenstrual age at immunisation (weeks)	37.3 (35.3–39.3)	38.5 (36.9–40.1)	0.10 [a]
Median chronological age at immunisation (days)	59 (53–92)	68 (54–112)	0.12 [b]
Mean weight at immunisation (g)	2266 (2039–2493)	2428 (2015–2841)	0.32 [a]
Median baseline body temperature at immunisation (°C)	37.3 (37.1–37.7)	37.2 (36.7–37.6)	0.10 [a]
Clinical conditions			
Bronchopulmonary dysplasia	3 (43%)	11 (24%)	0.37 [c]
Intraventricular haemorrhage	0 (0%)	12 (26%)	0.33 [c]
Ongoing methylxanthine therapy	1 (14%)	7 (15%)	1.0 [c]
AB ≤ 72 h before immunisation	3 (43%)	13 (28%)	0.42 [c]
Respiratory support			
Median total days of mechanical ventilation	0 (0–28)	0 (0–54)	0.59 [b]
Median total days of CPAP	1 (0–43)	5 (0–59)	0.36 [b]
Median total days of mechanical ventilation and CPAP	1 (0–51)	8 (0–77)	0.31 [b]

[a]Unpaired Student t -test
[b]Mann-Whitney U-test
[c]Fisher's exact test

Major risk factors for post-immunisation apnoea in the above-mentioned studies were mechanical ventilation, CPAP or continuous supplemental oxygen at the time of immunisation [3, 6,10]. The authors reported an incidence of 13% and 38%, respectively, of post-immunisation apnoea, the difference probably partly being due to different definitions of increased apnoea [3,10]. Our "low risk" study population entirely consisted of infants without respiratory support or supplemental oxygen at the time of immunisation. There was a 13% incidence of recurrent or increased AB in these infants using a relatively rigid definition of "increase in AB". However, reporting bias cannot be excluded as nursing staff documenting AB were aware of the time of immunisation. While recent data from Pfister and colleagues [6] strongly suggests that a severe clinical condition at 8 weeks of age and the persistence of prematurity-associated AB during the 24 h preceding immunisation increases the risk of post-immunisation AB in former preterm infants 5- to 8-fold, it is still advisable to monitor stable preterm infants following immunisation in the NICU, because the majority of events in our "low risk" population transiently required mild to moderate interventions. We detected an increased rate of fever in the group of apnoeic infants, therefore additional temperature monitoring might be helpful in identifying infants at risk of recurrent or increased AB. Regarding risk factors, the retrospective design and small sample size of our study does not allow to draw firm conclusions from the fact that we found no specific risk factors predisposing infants to post-immunisation AB.

Prophylaxis for AB after the first immunisation of preterm infants is not established. The use of methylxanthines could be helpful as shown for the prevention of postoperative apnoea in preterm infants undergoing general anaesthesia for minor surgery [4], but there is no such study for post-immunisation apnoea yet. Furthermore, there is no data available on the safety of the second combined immunisation. It remains unclear if some former extremely low birth weight infants might have cardiorespiratory events in this situation.

In conclusion, most preterm infants tolerated the first immunisation well. There was a 13% risk of developing post-immunisation AB with combination vaccines containing a Pa component in preterm infants not needing mechanical ventilation, CPAP or supplemental oxygen; most events required clinical intervention ranging from tactile stimulation to brief bag and mask ventilation, but they were all transient and without severe consequences on the clinical course. The benefit of timely administration of immunisation in former preterm infants by far outweighs the risk of post-immunisation AB. Monitoring of previously respiratory stable preterm infants for 48 h after their first standard immunisation is justified.

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