Apnoea following immunisation of preterm infants

Introduction

Young infants receive four immunisations of DPTP-Hib-HepB and Pneumococcus during their first year in the Dutch childhood immunisation program. Preterm infants receive immunisation according to their chronological age, not corrected for their gestational age.

The currently used vaccines in the program are Infanrix hexa® (DPTP-Hib-HepB) and Synflorix® (10-valent Pneumococcus). Children who were born before August 1, 2011 received DPTP-Hib (Pediacel®) and Synflorix®, children who were born before March 1, 2011 received Pediacel® and Prevenar® (7-valent Pneumococcus). Infanrix hexa® and Synflorix® are given in the current Dutch childhood immunisation program at the age of 2, 3, 4 and 11 months. The number of doses per year is depending on the number of new-borns per year and the vaccination coverage . For the year 2012 the number of new-borns in The Netherlands was almost 175,500 with a vaccination coverage of 95-99% for the vaccination for babies [1,2].

Apnoea is a labelled adverse drug reaction of the vaccines administered to babies in the current Dutch childhood immunisation program. The most widely used definition of (more prolonged and clinically relevant) apnoea in preterm infants specifies a pause of breathing for more than 15-20 seconds, or accompanied by oxygen saturation (SpO2 ≤ 80% for ≥ 4 s) and bradycardia (heart rate < 2/3 of baseline for ≥ 4 s), in infants born less than 37 weeks of gestation [3]. Another definition, that is used by the American Academy of Pediatrics, is "an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or marked hypotonia" [4].
According to the SmPC of Infanrix hexa®, apnoea following immunisation was found in postmarketing surveillance. For very premature infants (≤ 28 weeks of gestation) it should be considered to perform respiratory monitoring for 48-72 hours after the primary series in these very premature infants [5].
According to the SmPC of Synflorix®, apnoea is an uncommon event in very premature infants (≤ 28 weeks of gestation) and it should be considered to perform respiratory monitoring for 48-72 hours after the primary series in these very premature infants [6].

The Netherlands Pharmacovigilance Centre Lareb has received 10 reports of reported apnoea in preterm infants with a gestational age > 28 weeks, an older age as referred to in the SmPCs.

Reports

The database of the Netherlands Pharmacovigilance Centre Lareb was screened for reports of adverse drug reactions in preterm infants. Since prematurity is not recorded in a structural field in the database, the database reports were searched for all words containing "prematu*" and/or "dysmatu*" and/or "immatu*" in the free text fields. The most common reported reaction in this group was apnoea. 39 unique reports where apnoea or symptoms relating to apnoea such as bradycardia, bradypnoea, breath holding, choking, cyanosis, hypotonia, pallor, oxygen saturation decease were reported, were identified in the period between 27-06-2005 and 09-04-2013.
Ten reports concerned preterm infants with an unknown gestational period, five reports concerned preterm infants with a gestational period of ≤ 28 weeks and in 24 reports, the gestational period was > 28 weeks with the longest gestational period of 35 weeks.
After checking the clinical description of these 24 reports with a gestational period of more than 28 weeks, it was concluded that nine reports concerned apnoea, even though it could not be checked whether these cases fulfilled the official definitions for apnoea, because of lack of data concerning heart rate, saturation degree and duration of apnoea. In one report, decreased oxygen saturation was reported and it is not known whether there was cessation

of breathing as well. The assessor at the Pharmacovigilance Centre Lareb concluded this report to be apnoea. In the other fourteen reports, the diagnosis was not clear or appeared to be otherwise (such as convulsion, collapse, breath holding spell, pallor).
The ten reports concerning apnoea are described in more detail in table 1.
In all cases, it concerned the first vaccination in the Dutch routine childhood immunisation program.

Table 1. Reports of apnoea in preterm infants with gestational period between 28 and 35 weeks.

Patient, Sex, Age, Source, Gestational peroid	**Drug Indication for use**	**Concomitant medication**	**Suspected adverse drug reaction**	**Time to onset, outcome**
A 63087 M, 9 weeks Physician Almost 29 weeks	combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus vaccine (INFANRIX-IPV HIB®)		Apparent life threatening event Apnea Fever Common cold Skin discolouration Cough Bradycardia Hypotonia Gastroesophageal reflux Nephrocalcinosis Anemia Choking Rhinorrhea	1 week recovered
B 60144 F, 7 weeks physician 28^{+1} weeks	combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus-hepatitisB vaccine (INFANRIX HEXA®) conjugated pneumococcal vaccine (PREVENAR®)		Body temperature decreased Tachycardia Apnea Pale Loss of consciousness Hard to awaken Cold hands & feet	11 hours unknown
C 70703 F, unknown physician 29 weeks	combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus vaccine (INFANRIX-IPV HIB®)		Apnea Tachypnea Oxygen saturation decreased	1 hours unknown
D 70704 F, 0 years physician 29 weeks	combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus vaccine (INFANRIX-IPV HIB®)		Apnea Oxygen saturation decreased	3 hours unknown
E 74581 F, 2 months physician 30^{+1} weeks	combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus vaccine (Pediacel®)		Apnoea	1 days recovered
F 115747 F, 8 weeks nurse practitioner neonatology. 30^{+3} weeks	combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus-hepatitisB vaccine (INFANRIX HEXA®) conjugated pneumococcal vaccine (PREVENAR®)	PARACETAMOL supp 60MG	Injection site inflammation Apnoea attack	16 hours recovered

Patient, Sex, Age, Source, Gestational peroid	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
G 142892 F, 8 weeks physician (pediatrician) 29 weeks	combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus-hepatitis B vaccine (INFANRIX HEXA®) conjugated pneumococcal vaccine (SYNFLORIX®)		Apnoea attack	30 hours recovered
H 143831 M, 8 weeks community health service nurse 30^{+4} weeks	conjugated pneumococcal vaccine (SYNFLORIX®) combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus-hepatitis B vaccine (INFANRIX HEXA®)		Apnoea attack	immediately recovered
I 143832 M, 8 weeks community health service nurse 29 weeks	conjugated pneumococcal vaccine (SYNFLORIX ®) combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus-hepatitis B vaccine (INFANRIX HEXA®)		Apnoea attack	immediately recovered
J 108933 M, 9 weeks Physician (pediatrician) 31 weeks	combined diphtheria-haemophilus-acellular pertussis-poliomyelitis-tetanus vaccine (Pediacel®) conjugated pneumococcal vaccine (PREVENAR®)	PARACETAMOL supp 60MG	Oxygen saturation decreased	5 hours not applicable recovered

Other sources of information

SmPC

According to the SmPC of Infanrix hexa®, apnoea following immunisation was found in postmarketing surveillance. For very premature infants (≤ 28 weeks of gestation) it should be considered to perform respiratory monitoring for 48-72 hours after the primary series in these very premature infants [5].
According to the SmPC of Synflorix®, apnoea is an uncommon event in very premature infants (≤ 28 weeks of gestation) and it should be considered to perform respiratory monitoring for 48-72 hours after the primary series in these very premature infants [6]. The SmPC does not mention apnoea as an adverse drug reaction in other age groups.

Literature

In a cohort study examining the need for monitoring after the first vaccination at the age of 2 months in preterm infants because of the risk of cardiorespiratory disturbance, 41 preterm infants with a mean gestational age of 30.8 weeks were followed. 10 children experienced a small decrease in oxygen saturation or bradycardia, 3 infants experienced a moderate cardiorespiratory disturbance for which stimulation was needed [7].

In another study, a two-year retrospective study, involving 80 infants with mean gestational age 27.4 weeks and birth weight range 428-1.490 g with median 970 g infants, major

cardiorespiratory events occurred in over 1/3 of all very low birth weight infants after vaccination. Associated factors are low gestational age, bronchopulmonary dysplasia, methylxanthine treatment and persisting oxygen desaturations before vaccination [8].

Databases

Both the WHO-UMC and Eudravigilance database contain reports concerning the used vaccines in the Dutch routine childhood immunisation program and apnoea. However, the analysis concerns the association of these vaccines and apnoea in preterm infants. The WHO- and Eudravigilance database do not provide a category of preterm infants and where therefor not used for this analysis.

Mechanism

Apnoea is a very common symptom in preterm infants. It is likely secondary to immaturity of respiratory control that may be exacerbated by neonatal disease. In the majority of infants, apnoea is a time-limited problem, disappearing by term postconceptional age. The reasons behind the propensity for apnoea in immature infants is not entirely known and the pathogenesis is poorly understood. The occurrence or severity of apnoea in preterm infants may be exacerbated by several coexisting factors or disease states. Among others, thermoregulation may play a role in apnoea. Elevated body temperature increases the incidence of apnoea in preterm infants [9]. It is known that immunisation may lead to a temporary elevated body temperature..

Discussion

In the period between 27-06-2005 and 09-04-2013, Lareb received nine reports of reported apnoea and one report of decreased oxygen saturation, concerning preterm infants with a gestational period of > 28 weeks with the longest gestational period of 35 weeks. The latency period varies from 1 hour after immunisation to 1 week after immunisation, with most latencies reported within 1 day after immunisation. Even though it is not known whether all cases meet exactly the criteria for infant apnoea, it is remarkable that ten reports have been received, whereas the SmPC of the current in the Dutch childhood immunisation program used vaccine for pneumococcus (Synflorix®), only refers to apnoea following immunisation in very premature infants (≤ 28 weeks of gestation) and the need to consider to perform respiratory monitoring for 48-72 hours after the primary series in these very premature infants.

Conclusion

Due to the finding of ten reports concerning apnoea and/or decreased oxygen saturation in preterm infants with a gestational period of > 28 weeks, it should be considered to mention apnoea in premature infants without specification of gestation period in the SmPC of Synflorix®.

- Consider to mention apnoea in premature infants without specification of gestation period in the SmPC of Synflorix®.

References

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Nederlands Bijwerkingen Centrum Lareb
November 2007