Thérapie 2011 Janvier-Février; 66 (1): 81–86
DOI: 10.2515/therapie/2011006

Heptavalent Pneumococcal Conjugate Vaccine (PCV7): French Survey of Serious Adverse Reactions

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Text received May 31, 2010; accepted July 29, 2010

Keywords:
heptavalent pneumococcal conjugate vaccine; adverse drug reaction; children; invasive pneumococcal disease

Abstract – Purpose. Previous study did not reveal any particular heptavalent pneumococcal conjugate vaccine (PCV7) related risk. However, french drugs agency (Afssaps) requested the continuation of its surveillance. **Methods.** All serious PCV7-related adverse drug reactions spontaneously reported between October 1, 2004 and December 31, 2007 to the French pharmacovigilance centers or to Wyeth Pharmaceutical France were included. Vaccine failure was defined as an invasive pneumococcal infection due to vaccine serotype which occurs at least 15 days after the third dose of vaccine. Incidence rates were estimated according to the doses number except for vaccine failure estimated according to the vaccinated children number. **Results.** During the 39-month follow-up period, 154 serious adverse drug reactions were spontaneously reported: convulsions (17%), fever (13%), hypotonia (10%), sudden death (7%) and thrombopenic purpura (6%). Evolution was recovery in 72% of cases. PCV7 was the only suspect medication in 28% of cases. The median age was 4 months (range 1-108), and the children's sex was male in 53%. The adverse drug reaction recurred after a subsequent injection in six cases. Among the 24 pneumococcal infections PCV7 failure was certain in 4 cases. The incidences of serious adverse drug reactions did not differ from our previous survey, except the incidence of thrombopenic purpura and of PCV7 failure which seems to be increasing. **Conclusions.** This new study confirms the risk of vascular purpura, raises the thrombopenic purpura issue, and the emergence of PCV7 failures which will need a strict monitoring of the future 13 valences vaccine.

Mots clés :
vaccin conjugué heptavalent contre le pneumocoque ; PCV7 ; effets indésirables médicamenteux ; enfant ; infection à pneumocoque

Résumé – Vaccin heptavalent conjugué contre le pneumocoque (PCV7) : surveillance française des effets indésirables graves. Introduction. Deux études n'ont pas mis en évidence un risque particulier associé au vaccin conjugué heptavalent contre le pneumocoque (PCV7). Cependant, la poursuite de la surveillance des effets graves a été souhaitée par l'Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps). **Matériel et méthode.** Tous les effets indésirables (EI) graves associés au PCV7 notifiés entre le 1er octobre 2004 et le 31 décembre 2007 aux Centres régionaux de Pharmacovigilance ou à Wyeth Pharmaceutical France ont été inclus. Un échec vaccinal était défini par une infection due à un sérotype vaccinal et survenant au moins 15 jours après la troisième dose de PCV7. Les taux d'incidence ont été calculés en fonction du nombre de doses vendues sauf pour les échecs rapportés au nombre d'enfants vaccinés. **Résultats.** Durant les 39 mois de suivi, 154 EI graves ont été notifiés : convulsions (17 %), fièvre (13 %), hypotonie (10 %), mort subite (7 %) et purpura thrombopénique (6 %). L'évolution a été une guérison dans 72 % des cas. Le PCV7 était le seul médicament suspect dans 28 % des cas. L'âge médian était de 4 mois (extrêmes 1-108), et le sexe était masculin dans 53 % des cas. L'EI a récidivé lors d'une injection suivante dans six cas. Parmi les 24 infections à pneumocoque, un échec du PCV7 est certain dans 4 cas. Les incidences des EI graves sont proches de celles estimées lors de notre étude précédente, excepté celle du purpura thrombopénique et des échecs du PCV7 qui ont tendance à augmenter. **Conclusion.** Cette nouvelle étude confirme le risque de purpura vasculaire, pose le problème d'un risque de purpura thrombopénique et soulève la question de l'émergence d'échecs du PCV7 qui nécessitera une surveillance particulière du futur vaccin conjugué à 13 valences contre le pneumocoque.

Article published by EDP Sciences

1. Introduction

The heptavalent pneumococcal conjugate vaccine (PCV7), marketed in France since April 2001, is indicated for active immunization against infections (including invasive infections defined by a positive culture for *S. pneumonia* from the blood, pleural fluid or cerebrospinal fluid, but also pneumonitis and otitis media) caused by *Streptococcus pneumonia* due to the serotypes contained in the vaccine (4, 6B, 9V, 14, 19F, 23F and 18C). PCV7 is recommended by the "Haut Conseil de la Santé Publique" for all children under 2 years of age and for patients between 2 and 5 years at increased risk of pneumococcal disease.[1]

The vaccine has proven effective in reducing invasive infections due to serotypes contained in the vaccine,[2–5] and to a lesser extent reducing acute otitis media.[6–8] In France,[9] in all ages between the pre (2001/2002) and post vaccine periods (2007) the incidence of invasive pneumococcal infections (IPI) whatever the serotype increased (9.4% *versus* 10.2% per 100,000 *i.e.* +8%) particularly the bacteraemia. In children between 0 to 23 months, the incidence of IPI decreased (meningitis 8% *versus* 6% per 100,000 *i.e.* -26% and bacteraemia 22% *versus* 15% per 100,000 *i.e.* -32%). In this class of age there is a great reduction of IPI due to serotypes contained in the vaccine (meningitis -78% and bacteraemia -85%), but also a clear increase of IPI due to serotypes not contained in the vaccine (meningitis +95% and bacteraemia +82%).

Soon after commercialization of the vaccine in France, our working group conducted, on french drugs agency's (Afssaps or "Agence Française de Sécurité Sanitaire des Produits de Santé") request, a prospective study about tolerance of PCV7. Although this study concluded that the vaccine's safety profile did not differ from what was expected,[10] the French Pharmacovigilance Commission stated on November 29, 2005 that, surveillance of serious adverse drug reactions should be continued by the same team (Clinical Pharmacology Department/Regional Pharmacovigilance Center of Tours).

2. Material and method

All serious adverse drug reactions (ADRs) associated with PCV7, spontaneously reported in France between October 1, 2004 (the end of the preceding study) and December 31, 2007 to the 31 French Regional Pharmacovigilance Centers (RPVC) or to the manufacturer (Wyeth Pharmaceuticals France) were included. Serious ADRs were defined as "having required hospitalization, the prolongation of existing hospitalization, resulted in disability or death, or been life-threatening". Duplicate notifications to both the RPVC and the manufacturer were discarded. Each notification underwent semiological analysis by one of us (EAL) in order to attribute a principal diagnosis, signs associated with the ADR, or other potential ADRs. When several ADRs were observed in the same child, they were classified exclusively in a hierarchical order based on the severity of ADR. When several symptoms could be linked to the same ADR, the most pertinent and/or serious effect was considered, and others were deemed associated signs. For instance, when "apnoea, faintness, and hypotonia" were reported, apnoea was considered the principal diagnosis, while faintness and hypotonia were considered associated signs. Similarly, when "loss of consciousness, hypotonia, and pallor" were reported, loss of consciousness was considered the principal diagnosis, while hypotonia and pallor were considered associated signs. For each principal ADR, the characteristics of the child (age, sex), the vaccine (injection order), the ADR (delay of onset from time of vaccine injection, outcome), and the medications given concomitantly to PCV7, particularly other vaccines, were collected. Pneumococcal infections (including invasive infections, but also pneumonitis, otitis media and arthritis) due to vaccine serotypes or to unspecified serotype were separately analyzed. We considered as a vaccine failure (ADR) infections due to vaccine serotype which occurs at least 15 days after the third dose of vaccine. All principal ADRs were analyzed according to the French imputability method.[11] The incidence rates of notifications were estimated using PCV7 sales figures provided by the manufacturer considering every vaccine sold as an administered vaccine.

3. Results

During the 39-month follow-up period, 157 serious ADRs were spontaneously reported to the manufacturer (151) or to the RPVCs (73). Three were excluded from analysis because the diagnosis indicated that the vaccine was not likely involved [osteoma (1), congenital fibrosarcoma (1), muscular cancer (1)]. Among the remaining 154 ADRs, the most frequent were: convulsions 27 cases (17%), fever 20 cases (13%), hypotonia 16 cases (10%), sudden death 11 cases (7%) and thrombopenic purpura 10 cases (6%) [table I and table II]. Evolution was recovery (72%), unknown (15.8%), deaths (7.9% *i.e.* n=12 including the 11 sudden death) or consequences (4.6%). PCV7 was the only suspect medication in 44 cases (28%). It was associated with another vaccine in 99 cases [Pentavac® (41), Infanrixtetra® (23), Infanrixquinta® (23), other (12)], and with another drug in 21 cases [(paracetamol (7), lidocain/prilocain-gel (5), domperidone (4), other (5)]. The children's median age was 4 months (range 1-108), and was unspecified in four cases. The children's sex was male in 53.2%, female in 44.8%, and unspecified in 1.9%. The ADR occurred after the first (30.5%), the second (28.6%), the third (11%), or the fourth (3.9%) vaccine injection. The PCV7 injection order was