BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03771.x

Letter to the Editors

Case discussion of an immediate serious reaction to hexavalent vaccine mistaken for anaphylaxis

Giovanna Zanoni,[1] Leonardo Gottin,[2] Attilio Boner,[3] Giorgio Piacentini,[3] Diego Peroni[3] & Michael Gold[4]

[1]Immunology Unit, University Hospital, Verona, [2]Anaesthesiology and Surgery, University of Verona, [3]Pediatric Department, University of Verona, Verona, Italy and [4]School of Pediatrics and Reproductive Health, University of Adelaide, Adelaide, Australia

Anaphylaxis is rarely associated with vaccination. Clinical presentation may include a variety of non-specific symptoms, making a clinical diagnosis uncertain. Therefore, it is important to distinguish anaphylaxis from other adverse events following immunization (AEFIs), particularly in children, to manage subsequent immunizations where necessary. For administration of additional doses a specialist evaluation is recommended to confirm the diagnosis and consider if re-vaccination is appropriate. A post-event evaluation is based on an in-depth history and skin and *in vitro* testing to identify specific sensitizations. Applying a standardized AEFI case definition, such as the Brighton Collaboration [1], is also helpful for individual cases as well as pharmacovigilance activities.

We describe the case of a child with an immediate reaction to hexavalent vaccine which was mistakenly diagnosed as anaphylaxis. The baby, born in the 34th week, reported no perinatal problems and was breast and artificial milk fed. In good health, he received the first dose of hexavalent vaccine (diphtheria-tetanus-pertussis-polio-hepatitis B-haemophilus influenzae type B) at 3 months of age. Upon injection he cried, then he manifested atony, pallor, apnoea and flaccidity. Treated with mouth-to-mouth ventilation, he responded by crying, gasping, ocular reversion and generalized hypotonia. He was then treated with intramuscular epinephrine. On arrival in the emergency department. oxygen was admininistered and he became responsive, reactive and began to breathe normally. He was treated with i.m. methylprednisolone. A transient papular skin rash was observed on the trunk. The vaccination schedule was interrupted and he was referred to a specialized consultation service [2] for further vaccination. Serum analysis showed total IgE = 10 kU l^{-1} and IgE level to tetanus toxoid <0.10 kUA l^{-1} (Unicap, Phadia, Sweden). Since there were doubts about the anaphylaxis diagnosis, the following hypotheses were evaluated with international vaccine safety collaborators:

a) *Anaphylaxis*: the diagnosis was unlikely because the symptoms and signs did not fulfil the Brighton anaphylaxis case definition. Skin changes were not typical of a hypersensitivity reaction nor did he manifest respiratory or cardiovascular features. Additional factors which make this unlikely include his initial response to mouth-to-mouth ventilation prior to administration of epinephrine and this was his first exposure to the hexavalent vaccine.
b) *Hypotonic-hyporesponsive episode (HHE)*: he had pallor, hyporesponsiveness and hypotonia, which are symptoms of HHE, but also apnoea, which is not part of HHE [3].
c) *Apparent life-threatening event (ALTE)*: sudden episode of a combination of apnoea, change in colour, change in muscle tone, coughing or gagging [4].
d) *Apnoea in ex-premature infant*: condition described in infants mostly born before and up to 32 weeks gestation; immunization is one of the triggers [5].
e) *Reflex Anoxic Seizure*: exaggerated vagal response to pain resulting in extreme bradycardia or even asystole, possibly causing post-vaccination collapse [6].

This was considered the most likely hypothesis, but skin testing was performed with hexavalent vaccine and was negative. As a precaution hexavalent vaccine was consequently administered in two graded doses (0.1 and 0.4 ml), without subsequent reactions.

Anaphylaxis is often considered to be the cause of acute and unexpected events following immunization in infants. Careful consideration of the history, application of Brighton Collaboration case definition and specialist evaluation allows for accurate diagnosis [7]. If anaphylaxis is excluded, revaccination under supervision should be

All authors significantly contributed in the management of this case and therefore their names should be included.

considered. This case illustrates these issues because anaphylaxis was excluded. Data on outcome of revaccinations in particular situations and on AEFI surveillance activities should be shared at a global level.

Competing interests

There are no competing interests to declare.

The authors are grateful to A. Muraro and D.Villalta for sending the patient, and blood sample, respectively, I. Lucchi, S. Mondino and A. Chizzoni Susani for their assistance, to the Brighton Collaboration Anaphylaxis Working Group, especially J. Gidudu for helpful discussion, and the Veneto Region Public Health Authority for funding.

REFERENCES

1 Rüggeberg JU, Gold MS, Bayas JM, Blume MD, Bonhoeffer J, Friedlander S, Brito GS, Heininger U, Imoukhuede B, Khamesipour A, Erlewyn-Lajeunesse M, Martin S, Mäkelä M, Nell P, Pool V, Simpson N. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25: 5675–84.

2 Zanoni G, Ferro A, Valsecchi M, Tridente G. The 'Green Channel' of the Veneto Region as a model for vaccine safety monitoring in Italy. Vaccine 2005; 23: 2354–58.

3 Bonhoeffer J, Gold MS, Hejbel H, Vermeer P, Blumberg D, Braun M, Brito GS, Davis RL, Halperin S, Heininger U, Khuri-Bulos N, Menkes J, Nokleby H. Hypotonic-Hyporesponsive Episode (HHE) as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004; 22: 563–68.

4 Hall KL, Zalman B. Evaluation and management of Apparent Life-Threatening Events in children. Am Fam Physician 2005; 71: 2301–8.

5 Cooper PA, Mahdi SA, Huebner RE, Mbelle N, Karim SSA, Kleinschmidt I, Forrest BD, Klugman KP. Apnea and its possible relationship to immunization in ex-premature infants. Vaccine 2008; 26: 3410–3.

6 Appleton RE. Reflex anoxic seizures. BMJ 1993; 307: 214–5.

7 Wood A, Berger M, Dreskin SC, Setse R, Engler RJM, Dekker CL, Halsey NA. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Pediatrics 2008; 122: e771–77.

RECEIVED
16 April 2010

ACCEPTED
22 July 2010

CORRESPONDENCE
Dr Giovanna Zanoni, Immunology Unit, University Hospital Policlinico G.B. Rossi, 37134 Verona, Italy.
Tel.: + 0039 45 8124256
Fax: + 0039 45 8126455
E-mail: giovanna.zanoni@univr.it