København 31. maj 2005

Sundhedsudvalget
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Ved vores foretræde for Sundhedsudvalget den 18. maj 2005 blev der spurgt, om vi havde kendskab til eller en forestilling om at tilføjelse af yderligere en komponent (Hepatitis B) til det eksisterende børnevaccinationsprogram, ville kunne give anledning til bekymringer hos fx forældre og dermed svække tilslutningen til børne-vaccinationsprogrammet.
I den forbindelse blev der omtalt en artikel omhandlende nogle uforklarlige dødsfald hos børn kort efter deres vaccination med en sekskomponent vaccine.
Der blev ytret ønske fra flere af udvalgets medlemmer om vi kunne fremskaffe denne artikel.

Artiklen er fra tidsskriftet Vaccine og er p.t. "Article in press" og et "Uncorrected Proof".
Se vedlagte dokument.

Sluttelig vil vi gerne gentage vores invitation til Sundhedsudvalget om et besøge på Statens Serum Institut.

Med venlig hilsen

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Lisbeth Holm Petersen, HK-Stat, Dansk Laborantforening.

Kurt Dröscher, Lager og Handel.

Jørgen B. Møller, Dansk Farmaceutforening.

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Unexplained cases of sudden infant death shortly after hexavalent vaccination

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Abstract

Vaccinations are considered to be the most effective and safe method preventing infectious diseases. Although hexavalent vaccines like Hexavac® and Infanrix Hexa® are assumed to be well tolerated and safe regarding the rate of immunity [Liese JG, Stojanov S, Berut F, Minini P, Harzer E, Jow S, et al. Large scale safety study of a liquid hexavalent vaccine (D-T-acP-IPV-PRP-T-HBs) administered at 2, 4, 6 and 12–14 months of age. Vaccine 2002;20:448–54; Mallet E, Fabre P, Pines E, Salomon H, Staub T, Schödel F, et al. Immunogenicity and safety of a new liquid hexavalent combines vaccine compared with separate administration of reference licensed vaccines in infants. Pediatr Infect Dis J 2000;19:1119–27], it was noticed that several cases of death occurred shortly after the vaccination.

We report six cases of sudden infant death that occurred within 48 h after hexavalent vaccination. At post-mortal examination, those cases showed unusual findings, especially in the brain and in laboratory tests.

Crude calculations of local epidemiology are compatible with an association between hexavalent vaccination and unusual cases of sudden infant death. If confirmed in systematic studies, our findings would have potentially serious clinical implications.

Keywords: Hexavalent vaccination; Sudden infant death; Increased death rate

1. Introduction

Polyvalent vaccines like Hexavac® and Infanrix Hexa® were developed to increase acceptance of vaccinations by decreasing the number of necessary injections. Compared to their pentavalent predecessors, these hexavalent vaccines additionally contain hepatitis B serum. They are used for immunisation against diphtheria, pertussis, tetanus, influenza, poliomyelitis and hepatitis B. Hexavac® and Infanrix Hexa® are available in European markets since October 2000. Until April 2003, approximately 3 million children have been vaccinated in this way and about 9 million doses were sold in the European union during this time [3]. Children are to be vaccinated with these vaccines at the age of 2, 4, 6 and 12–14 months.

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2. Case reports

We report six cases of sudden infant death after hexavalent vaccination were autopsied and examined at the Munich Institute of Legal Medicine from 2001 to 2004.

Among those investigated children, three were male and three female, ageing between 4 and 17 months. Five children had been vaccinated with Hexavac®, one with Infanrix Hexa® during the past 48 h before death. Shortly after the vaccination, three of the children developed symptoms like tiredness, loss of appetite, fever up to 39 °C and insomnia. All children were found dead without explanation 1–2 days after the vaccination.

2.1. Post-mortem examination

These children underwent a forensic post-mortem examination. They were assumed to be typical cases of SID (sudden

infant death) because there was no history of a serious illness, and since all children died suddenly and unexpectedly.

In addition to neuropathologic and histologic abnormalities, all of these children showed an extraordinary brain edema, which made them exceptional to other SID cases. After the third of such extraordinary cases had been identified, we decided to further investigate the pathological findings.

2.2. Neuropathology

Abnormal neuropathologic findings were acute congestion, defective blood–brain barrier, slight infiltration of the leptomeninx by macrophages and lymphocytes, perivascular lymphocytic infiltration, diffuse infiltration of the pons, mesencephalon and cortex by T-lymphocytes, microglia in the hippocampus and pons, and in one case a necrosis in the cerebellum.

2.3. Histological examination

In four cases, a slight infiltration of the liver by lymphocytes and eosinophile granulocytes was diagnosed, in two cases also in the lung, and in one case in the spleen.

We were able to do histological examinations at the cutaneous injection site in one child and found an infiltration of the cutaneous and subcutaneous layer by lymphocytes and eosinophile granulocytes.

2.4. Laboratory testings

Three of these six cases could be investigated concerning increased serum levels of mast cell tryptase and IgE. Mast cell-tryptase concentration was slightly above normal in one, and markedly elevated in the other two children (18, 100 and 108 μg/l). On the other hand, IgE levels were normal and specific IgE against tetanus toxoid and latex could not be detected.

Autopsy and all further investigations did not reveal other serious abnormalities that could have lead to the deaths of the children.

3. Discussion

The neuropathological findings in the investigated cases are unlikely to explain the deaths, since early post-vaccinal encephalopathy is mostly associated with a congestive and edematous brain without relevant inflammatory infiltration. Post-vaccinal encephalopathies are mentioned especially in relation with vaccinations against pertussis [4,5]. Such cases, however, typically show clinical symptoms like somnolence, convulsion, headache or paresis [4]. Such or similar symptoms could not be found in any of the examined cases.

Increased brain weights either which result from edema or hyperemia, and in which clinical symptoms are lacking, are described as "benign intracranial hypertension", and are reported mainly after DTP-vaccinations [6].

At the moment, to our knowledge, there are no reference values available regarding mast cell-tryptase plasma concentrations in children up to the age of 12 years. For older children the 95.0 percentile is 11.4 μg/l. Increased tryptase levels were repeatedly described in SID [7,8]. It is unlikely that our children had a predisposition for an atopic diathesis, since mast cell-tryptase plasma concentrations were increased while IgE levels were normal. The increased tryptase levels and numbers of eosinophile granulocytes suggest that an anaphylactic reaction developed after the vaccination. As time to death seems comparably long for an acute anaphylactic reaction, a delayed immune reaction has to be discussed.

Prior to the release of hexavalent sera (in the years 1994–2000), we observed only one child out of 198 cases with sudden unexplained infant death who died shortly after vaccination (DTP). However, between 2001 and 2004 five of such cases were identified in our institution among 74 children with SID. This would indicate a 13-fold increase (the local autopsy rate for infants is about 70%). A recent analysis of all cases known German authorities [9] showed death rates that were to be expected statistically for the first day after vaccination. As four of those 10 cases were autopsied at Munich, although the Munich institute represents just 7.8% of the German population, a real number of about 50 cases might be expected, that is, 500% of the statistic figures to be expected.

We reported these six cases to direct attention to a possibly serious vaccination side effect. So far, there is no way to proof that these infant deaths are caused by vaccination. Therefore, the relation between the vaccinations and the death of the children must remain uncertain. Nevertheless, we feel that it is important to inform vaccinating physicians and pediatricians as well as parents about such possibly fatal complications after application of hexavalent vaccines. Especially, physicians and pediatricians should be also informed about the possibility of using pentavalent vaccines, which seem to be associated with lesser complications.

Finally, if broad use of hexavalent vaccines continues, extensive studies are most likely required to assess or exclude a relation between vaccination and death in infants.

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[1,2].

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