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Safety review results of Pneumococcal conjugate vaccine and Haemophilus influenzae type b(Hib) vaccine for pediatrics

March 24, 2011

The joint meeting of
Subcommittee on Drug Safety of Committee on Drug Safety
Vaccine Adverse Reaction Review Committee for Carcinoma of the Uterine Cervix

1. The review of reported seven cases

Seven fatal cases have been reported in infants who simultaneously received multiple vaccinations including pediatric pneumococcal conjugate vaccine and Hib vaccine since March 2 2011. The joint meeting evaluated those cases based on the detailed information which was newly obtained from autopsy reports, medical records etc. on their courses and severities of the illnesses of these cases, including the 6th and the 7th fatal cases reported after the joint meeting held on March 8.

1) All the 7 fatal cases were 0- to 2-year-old infants. Three of them had underlying diseases, and the other 4 cases were not confirmed whether they had underlying diseases.

2) Three infants died on the day following the vaccination, 1 died two days later, 2 died three days later, and 1 died 7 days later.

3) Case summaries of these seven cases and the expert evaluation on the causes of deaths of these cases are shown in the attached sheet.

4) Having reviewed those seven cases based on the post-vaccination course and findings currently available, it is considered that there is no clear or direct causality with the vaccinations in the 7 fatal cases based on the information at this moment. Meanwhile, some of the fatal cases involved infants with underlying heart disease. Therefore, sufficient precautions should be taken for patients with serious underlying disease, such as severe congenital heart disease, depending on their disease conditions.

2. Situations in foreign countries

1) For each of pneumococcal conjugate vaccine and Hib vaccine, fatal cases are reported with a certain level of frequency after vaccination according to the published papers on their use result in the United States of America and the adverse reaction reports from the companies.

2) Frequencies of reported fatal cases overseas are approx.0.1-1 cases per 100,000 vaccinations for pneumococcal conjugate vaccine and approx.0.02-1 cases per 100,000 vaccinations for Hib vaccine.

3) Most of the causes of deaths among the fatal cases reported in foreign countries are infections and SIDS (Sudden infant death syndrome).The causal relationship between the vaccination and the death is not clear in any case. Considering the frequencies (approx. 0.1-0.2 cases per 100,000 vaccinations for both vaccines) and the contents of fatal cases reported this time in Japan, there is not much difference between the situations in Japan and those in foreign countries, and thus it is unlikely that the safety of the vaccinations of these vaccines in Japan are particularly questioned.

Reference information

From year 2011, there is tendency of increase in the number of vaccines in Japan.

3. Simultaneous vaccination

1) According to the e-mail survey conducted by the Ministry of Health and Welfare (there were responses from 866 medical institutions), approx. 75% of the vaccinations of pneumococcal conjugate vaccine or the Hib vaccine conducted during one month of February 2011, were simultaneous vaccination with some other vaccine. A similar survey by the manufacturer also showed the similar tendency.

2) Post-marketing surveys and clinical trials conducted by the manufacturers in Japan showed the tendency of higher frequencies of adverse reactions in simultaneous vaccination than single vaccination when simultaneous vaccination of pneumococcal conjugate vaccine and DPT

vaccine, that of Hib vaccine and DPT vaccine, that of pneumococcal conjugate vaccine and Hib vaccine are compared to the single vaccination of each vaccine respectively. On the otherhand, a research by the Kagoshima University shows no significant difference between the frequency of simultaneous vaccination of pneumococcal conjugate vaccine and Hib vaccine and that of single vaccination of each vaccine. In both results, increase of severe adverse reactions is not shown.

3) Also from experiences of vaccination to patients with underlying diseases up to this time in Japan, there is no particular concern about safety reported.

4) In Europe and the United States, there are reports showing that simultaneous vaccination of pneumococcal conjugate vaccine and Hib vaccine does not increase the frequency of severe adverse reactions although it increases the frequency of local adverse reactions and pyrexia compared to the single vaccination , and it is regarded that there is no problem in the safety of simultaneous vaccination of these vaccines. Thus simultaneous vaccination of these vaccines is recommended. Based on the above, data in Japan and overseas reviewed this time shows no increase of severe adverse reactions although there are some reports showing higher frequency of adverse reactions in simultaneous vaccination compared to single vaccination, and there is no particular safety concern about vaccination of these vaccines.

4. Tests results of the vaccines and quality control

The inspection conducted by the National Institute of Infectious Diseases showed that vaccine lots given to fatal cases was within the acceptable criteria and no deviation was found. Since the same lot number of pneumococcal vaccines was used in cases occurred in Takarazuka and Nishinomiya, it was investigated whether there was deviation in manufacturing process of the relevant vaccine, but no problem was recognized. For the issue of foreign substances contained in Hib vaccine, safety problem concerned is limited to the local irritation, and it is reported that there were no foreign substances observed in the vaccines used in fatal cases where infants were injected vaccines of recalled lots. Thus it is not considered that the contamination by foreign substances is associated with the fatal cases.

5. Measures to be taken

1) Based on the information of cases and the information in Japan and overseas collected so far, it is considered that there was no direct or clear causality between pediatric pneumococcal conjugate vaccine or Hib vaccine.

2) Based on the information on simultaneous vaccinations of both vaccines, there considered to be no safety concerns. On the basis of this fact, the following precautions should be taken when using pediatric pneumococcal conjugate vaccine and Hib vaccine.

A) For pneumococcal conjugate vaccine and Hib vaccine, Physicians should explain that simultaneous vaccinations can efficiently achieve the preventive effect within a short period of time and that single vaccinations are also available. If simultaneous vaccinations are to be carried out, physicians should determine the necessity of the vaccination and should obtain the consent of the child's guardian.

B) Vaccinations should be performed in infants with serious underlying diseases including severe cardiac diseases, to prevent severe infectious disorders such as meningitis, and vaccines should be carefully administered after checking the infant's clinical condition. In such cases, single vaccinations should be considered, and physicians should determine the necessity of simultaneous vaccinations.

3) Under the national vaccination project of pneumococcal conjugate vaccine and Hib vaccine, the reporting system of adverse reactions requires reporting more widely than the previous reporting system even when there is no causal relationship between the event and the vaccine. For example, reporters of adverse reactions are explicitly required to report adverse events even when the causality evaluation with vaccines is "Not related", or "unable to evaluate".

4) Therefore, it is likely that report of fatal cases within several days after vaccination will continue. In receiving new report of fatal cases after vaccination, it is pertinent to continuously collect as detailed information as possible, and to quickly conduct evaluation by experts about the causal relationship with vaccines.

5) In that case, considering the reporting situation of fatal cases after vaccination in foreign countries, it is pertinent to discuss about the measures to be taken based on the review by the meeting of experts in timely manner, in case, for example, that the frequency of fatal cases exceed 0.5 per 100,000 vaccination in 6 months regardless of causal relationship.

6) Moreover, in order to validate the relationship between the fatal/severe adverse events and vaccines, it is necessary to construct a mechanism to conduct positive epidemiological survey in the future.