

Anaphylaxis to simultaneous administration of inactivated tissue culture hepatitis A vaccine and purified chick embryo cell rabies vaccine after multiple doses

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SUMMARY

Both the inactivated hepatitis A vaccine (Aimmugen) and purified chick embryo cell rabies vaccine (PCECV, Rabipur) are well tolerated. Anaphylaxis has rarely been reported as an adverse reaction of these vaccines. There have been no reports or published case reports of anaphylaxis due to Aimmugen. According to the Japanese Ministry of Health, Labour and Welfare Aimmugen adverse reaction report, no cases of anaphylaxis have been reported from April 2013 to August 2016. Twenty cases of anaphylaxis due to PCECV (RabAvert) have been reported from 1997 to 2005 in USA, whereas 2 cases have been reported from 2006 to 2016. We report a case of anaphylaxis after multiple vaccinations in a 24-year-old man with ulcerative colitis, previous medical history of tonsillectomy for IgA nephropathy and no history of allergies.

BACKGROUND

Anaphylaxis is a serious and fatal systemic allergic reaction that occurs after exposure to an allergen, which may be caused by food, drugs or vaccination.¹ Anaphylaxis occasionally returns after an asymptomatic period without further exposure to the causative antigen (biphasic reaction). Anaphylaxis after vaccination rarely occurs, in the analysis performed by McNeil and colleagues, the incidence rate was 1.31 episodes per 1 million vaccinations.² In the analysis performed by John R Su and colleagues, 40% of patients with anaphylaxis have never had any allergies to foods, drugs or so on.³

In Japan, Aimmugen, a freeze-dried inactivated tissue culture hepatitis A vaccine (HAV) has been approved. Three doses of Aimmugen are generally required to complete the HAV series. In the prospective study performed by Endo and colleagues, the seroconversion rate was reported to be 94.4% for two doses and 100% for three doses.⁴ HAV is recommended when travelling to high risk areas such as Southeast Asia, South America and Africa.⁵

Rabipur is a purified chick embryo cell rabies vaccine (PCECV) for pre-exposure and postexposure prophylaxis (PEP) against rabies virus and was approved in Japan in March 2019. Two doses of pre-exposure vaccination against rabies are recommended before travel to high-risk areas in addition to the HAV,^{6,7} whereas Ministry of Health, Labour and Welfare (MHLW) recommend three doses pre-exposure rabies prophylaxis.⁸

Here, we report a case of anaphylaxis that occurred after sequential doses of Aimmugen and Rabipur in a 24-year-old man with no known history of allergies.

CASE PRESENTATION

A 24-year-old Japanese man visited our travel clinic before his trip to South Africa 3 months later. He has been treated for ulcerative colitis with mesalazine and had a history of tonsillectomy for IgA nephropathy during his childhood. He took no other medication. He had no history of allergy to any drug, vaccine or foods. He had already been given usual vaccines such as diphtheria, tetanus, pertussis, measles, rubella, mumps, Bacille Calmette-Guérin, Japanese encephalitis and hepatitis B vaccine. We scheduled to give Rabipur and Aimmugen as pretravel vaccinations. The inactivated typhoid vaccine was also considered, but it was not given since it is not approved in Japan. The first doses of both vaccines were given on day X-28, and no adverse events occurred. On day X-21, the second dose of Rabipur was administered. On day X, he received the second dose of Aimmugen and the third dose of Rabipur.

Ten minutes after the vaccinations, he felt sick and reported itchiness of the face, abdominal pain and sore throat. On physical examination, he was alert and oriented. His blood pressure was 150/70 mm Hg, heart rate was 90 bpm, respiratory rate was 16/min, oxygen saturation was 98% on room air and body temperature was 36.8°C at axillary measurement. There was urticaria on his face. There were no abnormal respiratory sounds such as wheeze or stridor. There was slight tenderness on the entire abdomen. A few minutes later, his blood pressure dropped to 90/60 mm Hg and pulse rate increased from 90 bpm to 100 bpm.

Since he did not have any food or medications before vaccinations, diagnosis of anaphylaxis secondary to Aimmugen or Rabipur or the combination was made. We immediately administered 0.3 mg of intramuscular epinephrine to the mid-outer aspect of the thigh. After that, famotidine and methylprednisolone were given intravenously.

OUTCOME AND FOLLOW-UP

Shortly after the injection, urticaria disappeared and abdominal pain was improved. He was admitted for close observation. Since the biphasic reaction did



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Case report

not occur, he was discharged home the next day. Epinephrine for intramuscular injection was prescribed to prevent further anaphylaxis if receiving rabies vaccination for PEP after animal exposure abroad.

With regards to HAV, our patient had already received two doses of Aimmugen and the antibody titre might be sufficiently elevated. A third dose would be administered to further increase the seroconversion rate. However, because Aimmugen was also the suspected vaccine for anaphylaxis, we did not give the third dose.

DISCUSSION

We experienced a case of anaphylaxis caused by Aimmugen or Rabipur or the coadministration of both vaccines after giving sequential doses of them despite the absence of allergic symptoms at the time of the first dose.

As far as searching in PubMed and Google Scholar, we could not find any reports of confirmed anaphylaxis due to Aimmugen. According to the MHLW report, a total of approximately 910 000 HAVs were used from April 2013 to August 2019 in Japan, but there was no report of anaphylaxis.⁹

For Rabipur, Dobardzic *et al* reported of 20 patients with anaphylaxis after PCECV vaccination. Six developed anaphylaxes after the first dose, three after the second dose, seven after the third dose and four patients' reports did not list number of doses.¹⁰

Moro *et al* also reported of two patients with anaphylaxis after PCECV vaccination from 2006 to 2016.¹¹

In our case, it is difficult to determine which vaccine caused the reaction because of the simultaneous vaccination, but based on the previous reports, it was more likely due to Rabipur than Aimmugen.

Two doses of PCECV are recommended as PEP against animal bites in high-risk areas of rabies, if three doses were completed before exposure to rabies virus.⁷ Since there is the equivalence and interchangeability of PCECV to human diploid cell culture rabies vaccine (HDCV),¹² patients who are immunised with PCECV as pre-exposure prophylaxis can receive HDCV as PEP. As there is possible cross-sensitisation between HDCV and PCECV, a case of recurrent anaphylaxis after PCECV already sensitised by HDCV has been described.¹⁰ Therefore, if HDCV is administered as either pre-exposure or PEP for our patient instead of PCECV, anaphylaxis could occur again.¹⁰

In addition, we may have an opportunity to give unapproved vaccines at a travel clinic. In Japan, adverse events associated with the use of approved vaccines are covered by the relief system for sufferers from vaccination. However, we should fully inform patients that those adverse events resulted from simultaneous vaccinations with unapproved vaccines that may be excluded. If there is enough time for vaccination, it may be better to avoid simultaneous vaccinations of approved and unapproved vaccines.

In conclusion, we experienced a rare case of anaphylaxis after multiple simultaneous inoculations of Aimmugen and Rabipur. Although anaphylaxis is a rare adverse reaction, physicians should keep this possibility in mind.

We reported this adverse reaction to the Pharmaceuticals and Medical Devices Agency in Japan.

Learning points

- ▶ Anaphylaxis after vaccination is extremely rare, but we should never forget.
- ▶ We should pay attention to adverse events including anaphylaxis that may occur after sequential doses of vaccines, even if there were no adverse events at the time of the initial dose.
- ▶ When diagnosing a severe side effect, it is necessary to appropriately follow the country's system and consider the indication of compensation for the side effect.
- ▶ Adverse reactions resulted from simultaneous vaccinations with approved and unapproved vaccines may not be covered by the relief system for injury from Vaccination in Japan.

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REFERENCES

- 1 Sampson HA, Muñoz-Furlong A, Campbell RL, *et al*. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.
- 2 McNeil MM, Weintraub ES, Duffy J, *et al*. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol* 2016;137:868–78.
- 3 Su JR, Moro PL, Ng CS, *et al*. Anaphylaxis after vaccination reported to the vaccine adverse event reporting system, 1990–2016. *J Allergy Clin Immunol* 2019;143:1465–73.
- 4 Endo O, Tanaka K, Iwata K. Long term follow-up of antibody after immunization with inactivated hepatitis A vaccine. *Clinical Virology* 1997;25:43–7.
- 5 WHO position paper on hepatitis A vaccines: June 2012–recommendations. *Vaccine* 2013;31:285–6.
- 6 De Pijper CA, Stijnis C, Grobusch MP. WHO bites back rabies pre-travel vaccination schedules - Implications for travel medicine. *Travel Med Infect Dis* 2018;23:4–5.
- 7 O'Brien KL, Nolan T, SWo R, SAGE WG on Rabies. The WHO position on rabies immunization - 2018 updates. *Vaccine* 2019;37(Suppl 1):A85–7.
- 8 The Ministry of Health LaW. Questions and answers about rabies. Available: <https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou10/07.html> [Accessed 15 Dec].
- 9 The Ministry of Health LaW. Report of suspected adverse reactions to freeze-dried inactivated hepatitis A vaccine. Available: <https://www.mhlw.go.jp/content/10906000/000569143.pdf> [Accessed 15 Dec].
- 10 Dobardzic A, Izurieta H, Woo EJ, *et al*. Safety review of the purified chick embryo cell rabies vaccine: data from the vaccine adverse event reporting system (VAERS), 1997–2005. *Vaccine* 2007;25:4244–51.
- 11 Moro PL, Lewis P, Cano M. Adverse events following purified chick embryo cell rabies vaccine in the vaccine adverse event reporting system (VAERS) in the United States, 2006–2016. *Travel Med Infect Dis* 2019;29:80–1.
- 12 Briggs DJ, Dreesen DW, Nicolay U, *et al*. Purified chick embryo cell culture rabies vaccine: interchangeability with human diploid cell culture rabies vaccine and comparison of one versus two-dose post-exposure booster regimen for previously immunized persons. *Vaccine* 2000;19:1055–60.

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