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Perspectives: Intradermal Rabies Preexposure Immunization

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Few topics in travel medicine prompt more concern and persistent questions than the prevention of rabies in travelers. Although we understand the basics of rabies prevention for travelers, the logistics of providing this care in a timely fashion remain a challenge. Unimmunized travelers who are exposed to rabies and other lyssaviruses require proper wound care, infiltration of human rabies immune globulin (RIG), and a series of 4 or 5 doses of rabies vaccine intramuscularly over a 2- to 4-week period. Travelers who receive 3 doses of rabies vaccine before travel need to receive 2 more doses of rabies vaccine, 3 days apart, after a viral exposure. Notably, human RIG and equine RIG are often unavailable in developing countries, although modern cell culture rabies vaccines are increasingly available. Thus, preexposure rabies immunization can facilitate the traveler's access to adequate postexposure rabies prophylaxis.

One limiting factor in the use of preexposure rabies immunization is the cost of the vaccine in most developed countries. In the United States, rabies vaccine may cost more than \$300 per dose, resulting in a cost to the patient in excess of \$900 for three 1.0-mL intramuscular injections. As a way of decreasing the cost of preexposure immunization, some practitioners have used a 0.1-mL dose of rabies vaccine administered intradermally.

At approximately \$45 per dose in the early 1980s, many people already considered the vaccine too expensive. Thus, intradermal rabies immunization began almost as soon as the intramuscular human diploid cell vaccine (HDCV) was manufactured. By reconstituting the 1.0 mL of vaccine in the vial, practitioners could draw up approximately eight 0.1-mL doses. One problem was that the entire vial had to be used within a few hours of reconstituting, meaning that a provider had to either be in a busy clinic or line up groups of people, such as families, for rabies immunization at the same time.

Early studies of the immune response to intradermal rabies vaccine, using HDCV and later other rabies vaccines, were uniformly encouraging. Virtually 100% of vaccinees seroconverted. A 1982

statement by the US Advisory Committee on Immunization Practices (ACIP) reviewed data on >1,500 vaccinees and declared, "It appears that, with this vaccine, the 0.1-mL intradermal (ID) regimen is an acceptable alternative to the currently approved 1.0-mL intramuscular (IM) regimen for preexposure prophylaxis." They called upon manufacturers to produce a product with appropriate packaging and labeling.

In 1986, the Mérieux Institute (now Sanofi Pasteur) received approval to market a 0.1-mL dose in an individual syringe. Sharing reconstituted vials of 1.0 mL between patients remained off-label.

Although the new product solved the logistical problem of providing individual travelers with an ID dose, the cost of the prepackaged ID dose was 75% of the full 1.0-mL IM dose.

As ID rabies immunization was being implemented, a death from rabies in an American Peace Corps volunteer in Kenya brought the enthusiasm for ID immunization to a temporary halt. The 23-year-old female volunteer died of rabies after a bite from a stray puppy that she had adopted. She had received 3 doses of ID rabies vaccine in Kenya, finishing 6 months before the bite. She did not suspect that the dog had rabies, even though it died shortly after biting her. As a result, she did not seek postexposure boosters. Serum drawn at the onset of her symptoms revealed she did not have an adequate antibody response. The Peace Corps medical personnel wondered why the recent ID immunization had not been effective. Concerned that she may have had an atypical response to immunization, they tested serum specimens from 11 other Peace Corps volunteers in Kenya who had been immunized at the same time. To their surprise, 9 of 11 also had an inadequate immunologic response. As a control group, Peace Corps volunteers who had received rabies ID preexposure immunization in Nepal and Morocco were also tested, and 31 of 79 had an inadequate antibody response.

Studies were undertaken to confirm the potency of the vaccine lot, maintenance of the cold chain, the method of administration, and the effect of concomitant medication. None of these factors proved to be an entirely adequate explanation. For example, chloroquine taken as an antimalarial medication during ID rabies immunization reduced the levels of antibody induced. However, the seroconversion rate among those taking chloroquine was still adequate, and the volunteers in Morocco and Nepal were not taking chloroquine. After the investigation, it was recommended that people using ID preexposure immunization should complete the course before starting chloroquine and traveling abroad or else use the IM regimen.

ACIP continued to endorse the concept of ID preexposure rabies immunization in a 1999 statement on rabies prevention. However, 3 lots of a prepackaged rabies ID vaccine were recalled in 2000 for

having a potency that fell below the specification level before the expiration date. In 2001, the ID rabies vaccine was withdrawn from the market. Since then, authorities in the United States have not recommended sharing 1.0-mL vials for ID rabies immunization, as the manufacturer has not applied for the appropriate packaging and labeling to the Food and Drug Administration (FDA). This lack of endorsement of ID preexposure immunization has frustrated some travel medicine professionals.

Based on recent data, the World Health Organization has recommended the use of ID preexposure rabies immunization as an alternative to IM immunization. A recent study of 420 Australian travelers given a modified ID rabies preexposure immunization (2 doses on day 0, 2 doses on day 7, and 1 dose on day 21–28) documented a seroconversion rate of 98.3%. Although using only 0.5 mL of vaccine total might save money, this regimen does not alleviate the challenge of needing to identify several travelers in a few hours or use multiple doses from a single-use vial.

Neither ACIP nor FDA are likely to endorse the use of 1.0-mL vials of rabies vaccine for multiple-dose ID use unless the manufacturer requests that indication. Until then, the use of ID rabies vaccine will remain off-label in the United States. The current status of ID rabies immunization in the United States reflects a regulatory situation and ACIP opinion, and is not a comment on the effectiveness of ID rabies preexposure immunization for travelers elsewhere.

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