Human diploid-cell-culture vaccine for rabies prophylaxis

In Canada in 1977, 40 000 doses of three different rabies vaccines were distributed for pre- and postexposure prophylaxis (R.S. Dolman, E.W. Pearson: personal communication, 1975). This figure demonstrates the magnitude of the perceived need for rabies vaccine in Canada. The use of three different vaccines suggests that, although the currently available vaccines are acceptable, none is ideal.

A potent and perhaps safer vaccine may soon become generally available to Canadian physicians; a limited supply is already available for emergency use.[1] Human diploid-cell-culture rabies vaccine is a new biologic agent prepared by concentration and inactivation of a vaccine strain of rabies virus grown in WI-38 (human embryonic lung fibroblast) cell culture. This method of vaccine production, with human non-neural cells used as the substrate for virus replication, has yielded a vaccine that has several advantages over current rabies vaccines produced in bird and animal cells. Human diploid vaccine has been administered to more than 100 000 persons in Europe.[2] It has been found to be more immunogenic than other rabies vaccines and less likely to cause serious adverse reactions. Accumulating data indicate that human diploid vaccine is effective in preventing rabies in persons bitten by rabid animals.[2] A more detailed comparison of the relative merits of this vaccine and other currently available vaccines requires consideration of both pre- and postexposure prophylaxis because clinical problems and immunization practices differ in these two areas.

Pre-exposure prophylaxis is recommended for individuals such as veterinarians who are at an increased risk of exposure to rabies because of their occupation.[3] Duck embryo vaccine (a suspension of embryonic duck tissue infected with a vaccine strain of rabies virus) and hamster kidney vaccine (a suspension of fixed rabies virus prepared in cultures of baby hamster kidney cells) are the two vaccines currently used for pre-exposure prophylaxis in Canada. Two to three injections are administered a month apart, then a booster dose is given 3 to 7 months later. About 3 or 4 weeks after the last dose has been administered the serum is tested for the presence of neutralizing antibody as a marker for immunity. Even though no exact correlation has been established between the titre of circulating antibody and protection against rabies in humans, studies in animals suggest such an association.[4] Hattwick,[5] in an extensive review, observed: "No case of human rabies has occurred in persons who are known to have had rabies antibodies in their serum at the time of exposure". Hence, it is practice to gauge the adequacy of immunization and the need for booster doses from the antibody titres in the serum. By this criterion, duck embryo and hamster kidney vaccines induced adequate immunity in 90%[6] and about 95% (E.W. Pearson: personal communication, 1975) respectively of vaccinated persons.

In a prospective study of 1679 persons administered duck embryo vaccine according to the recommended schedule local skin reactions occurred in 67%, constitutional symptoms in 10% and anaphylaxis in 0.5%.[7] Neuroparalytic reactions, the other life-threatening side effect of administration of duck embryo vaccine, were observed in 13 of approximately 424 000 persons who had received an average of 14 doses of this vaccine, mainly as postexposure treatment.[7] Of the 13 persons 2 died of encephalitis; however, the encephalitis may have been caused by clinical rabies rather than the vaccine. From 1971 to 1978 approximately 35 000 doses of hamster kidney vaccine were administered to persons in Canada; seven cases of nonfatal anaphylactoid reactions were reported (E.W. Pearson: personal communication, 1978). Local and other systemic side effects are apparently uncommon. Although rare, these adverse reactions to duck embryo and hamster kidney vaccines may be partly responsible for the reluctance of physicians to recommend pre-exposure vaccination to healthy veterinarians and their staff.

The new human diploid vaccine may prove a suitable substitute for pre-exposure prophylaxis. In one study 77 previously unimmunized volunteers were each given three doses of vaccine at monthly intervals; the vaccine stimulated the production of detectable neutralizing antibody in all 77.[8] The antibody persisted for at least 24 months, and an anamnestic response was elicited by a booster dose given at 6, 12 or 24 months. Reactions at the injection site were minor. Among the 77 persons hypersensitivity-type adverse reactions, including breathlessness and wheezing, occurred in 3.[8] In a study of 14 persons given an intradermal booster dose of this vaccine generalized urticaria developed in 2.[9] These reactions may have been due to sensitivity to traces of fetal bovine serum in the cell-culture medium of some batches of the vaccine. Theoretically, neuroparalytic reactions to human diploid vaccine should not occur, and to date none have been observed.

For postexposure prophylaxis of rabies, the administration of rabies antiserum and vaccine combined with cleaning of the wound provide the best specific therapy.[3] The aim of combined antiserum and vaccine therapy is to achieve early and sustained titres of antibody in the serum. Antiserum, however, blunts the antibody response to the vaccine, so that with the use of homologous antiserum and duck embryo vaccine 23 doses (21 initial doses followed by 2 booster doses) are required for postexposure prophylaxis to ensure sustained antibody titres.[10] A vaccine of nervous tissue origin (Semple vaccine) is also used for postexposure prophylaxis. Initially 14 to 21 doses are required when antiserum is administered. Hamster kidney vaccine is not approved for postexposure prophylaxis, although it can be used as a booster vaccine in the three doses (at 10, 20 and 90 days after the

primary series of injections of Semple vaccine) recommended in the product monograph when antiserum is used.[3]

Semple vaccine is prepared as a suspension of brain tissue from adult rabbits infected by intracerebral inoculation with a vaccine strain of rabies virus. Duck embryo and Semple vaccines have similar immunogenic properties; however, Semple vaccine causes a 20-fold greater frequency of neuroparalytic reactions.[5]

Although the effectiveness of duck embryo and Semple vaccines in preventing the development of clinical rabies has never been formally studied, it has been estimated as similar from a review of the failure rates: between 1957 and 1971, when both vaccines and antiserum were used in the United States, 12 of 310 000 persons (1:25 000) given duck embryo vaccine died, as did 6 of 125-000 (1:20 000) persons given Semple vaccine.[11]

Duck embryo vaccine is a less potent immunogen when administered with antiserum: in a study of 46 persons immunized with 23 doses each of this vaccine, 20% failed to produce active antibodies;[12] all nine persons given heterologous rabies antiserum on day 1, plus 12 daily injections of Semple vaccine and 2 booster doses at days 23 and 33, had detectable antibodies at day 50.[13]

In a prospective study of 116 persons given duck embryo vaccine as postexposure prophylaxis, local irritation at the injection site occurred in all persons and systemic reactions developed in 33%.[7] Anaphylaxis occurred in one patient. In spite of these reaction rates, Rubin and colleagues[7] concluded that duck embryo vaccine was acceptable for rabies prophylaxis since serious complications were uncommon and fatal reactions rare.

Semple vaccine may cause local adverse reactions less frequently. A retrospective analysis was done of the results of questionnaires on adverse reactions to Semple vaccine in 1149 persons in Ontario in 1972.[14] Replies were received from 969 persons (84.3%), 32% of whom reported local reactions and 4% systemic reactions. No cases of anaphylaxis were reported, but symptoms and signs suggesting a neuroparalytic reaction developed in one person. In the United States, however, Semple vaccine has caused neuroparalytic reactions 20 times more frequently than the duck embryo vaccine and therefore has been replaced by the latter for rabies prophylaxis.[7]

Human diploid vaccine is a better immunogen than both duck embryo and Semple vaccines. In one study six doses of human diploid vaccine administered with heterologous antiserum on the day of exposure produced antibodies in all recipients.[2] However, the extent of postexposure protection produced by human diploid vaccine has not been fully determined. To date 76 persons bitten by rabid animals and given postexposure prophylaxis with human diploid vaccine, with or without rabies antiserum, have survived, and clinical rabies has not developed.[2] It therefore appears that this vaccine provides simpler and safer postexposure than duck embryo and Semple vaccines, and should prove to be just as efficacious.

In this issue of the Journal (beginning on page 1069) Dempster and colleagues describe their experience with duck embryo and human diploid vaccines given to 41 persons exposed to a rabid dog. Of the 41 persons 15 had been in contact with the dog's urine or had handled the dog, but they had not been contaminated by saliva or infected tissues. Procedures for managing persons in these circumstances are not detailed in standard references on indications for postexposure prophylaxis.[3,15] In 4 of the 29 persons given more than one dose of duck embryo vaccine, this vaccine had to be discontinued because of adverse reactions; all tolerated further prophylaxis with human diploid vaccine.

Dempster and colleagues have recommended more thorough and systematic pre-exposure vaccination of veterinary staff and early licensing of human diploid vaccine, which would probably make pre-exposure prophylaxis more acceptable to veterinarians and others who are at an increased risk of rabies because of their occupation. It will certainly ease the presently formidable task of administering 14 to 23 doses of duck embryo or Semple vaccine for postexposure prophylaxis of rabies.

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