RABIES PROPHYLAXIS OF PEOPLE

Persons can be protected against rabies through a vaccine -- the vaccine which is currently being used is Rabies Human Diploid Cell Vaccine (HDCV). The pre-exposure series can be given intradermally (ID) or intramuscularly (IM). The post-exposure series must be given intramuscularly.

Rabies vaccine is a sterile, stable, inactivated cell-culture rabies vaccine for human use by injection. The vaccine is derived from material that is grown in rabbit brain. It is refined and cultured with the Human Diploid Cell strain to create the vaccine.

Pre-exposure Vaccine should be given to high-risk groups so that these individuals do have some protection if they come in contact with an infected animal. This group includes:

Veterinarians (a large animal practice probably provides more risk than a small animal clinic), animal handlers, certain lab workers, persons living in countries where rabies is a threat, and persons who work with potentially rabid animals -- zoo keepers, trappers, etc..

There are three doses of pre-exposure vaccine given IM or ID on Day 0, Day 7, and Day 21 or 28. The administration of the inactivated rabies vaccine stimulates rapid production of specific antibodies. In pre-exposure trials involving more than 2,000 volunteers, at least 99% of the recipients developed antibodies after 3 injections over a four-week period. Serological testing (or titers of the antibodies in the blood that can fight rabies virus), is performed 3 weeks after the pre-exposure series of HDCV or after a primary post-exposure series to ensure that antibodies to rabies have been acquired.

Booster doses of Vaccine are recommended every two years for those individuals who continue to be at increased risk of contracting rabies and whose rabies antibody titer is less than 1:5. Repeat booster doses increase the risk of allergic reaction to rabies vaccine by 6%. Therefore, a titer is recommended prior to receiving a booster dose of rabies HDCV vaccine. If the titer is 1:5 or greater, a booster dose is not indicated. A titer should be repeated again in two years.

Post-exposure vaccine is given to individuals who have exposure to rabies virus through bites of an infected animal, through abrasions, etc. The number of doses required is determined by the previous immunization status of an individual.

An immunized person is "any person who has received a complete intramuscular (IM) or intradermal (ID) pre-exposure or intramuscular post-exposure series of human diploid cell rabies vaccine regardless of follow-up serology, or a person who has received a pre-exposure or post-exposure regimen of any rabies

vaccine administered by IM or ID who has had a rabies antibody titer of 1:5 or greater at any time in the past".

An unimmunized person will be given a series of five total injections of IM HDCV on Day 0, 3, 7, 14 and 28 of the exposure. In addition, rabies immune globulin (RIG) will be given according to your weight on Day 0. This injection will provide some protection from the virus, while the antibodies to the vaccine are being produced.

Rabies Post-exposure Prophylaxis: The essential components of rabies post-exposure prophylaxis are immediate local wound treatment and the administration of both Human Rabies Immune Globulin (HRIG) and rabies vaccine. Persons who are bitten by, or have significant exposure to the saliva or nervous system tissue of a confirmed rabid animal should begin treatment as soon as possible (within 24 hours of exposure). Persons so exposed to a suspected rabid animal should begin treatment if rabies testing on the animal is not immediately available.

Post-exposure prophylaxis should not be denied due to a prolonged time interval between exposure and starting treatment. There have been many instances in which treatment was not begun until many months after exposure due to delays in recognition of the exposure. Incubation periods well in excess of one year have been reported.

Local Treatment of Wounds: Immediate and thorough washing of any bite or scratch wound with soap and water may be the most important measure in preventing rabies. Simple local wound cleaning has been shown to markedly reduce the likelihood of rabies in animal experiments. Tetanus and antibiotic prophylaxis should be given as indicated.

Active Immunization - Vaccine: Either Rabies Vaccine Adsorbed (RVA) or Human Diploid Cell Vaccine (HDCV) is administered in conjunction with HRIG at the beginning of post-exposure treatment. A regimen of five 1-ml doses of RVA or HDCV is given intramuscularly. The first dose should be given as soon as possible following an exposure. The other doses are given on days 3, 7, 14 and 28 after the first dose. Vaccine should always be administered by the IM route in the lateral deltoid area. For children, intramuscular administration in the anterolateral aspect of the thigh is acceptable. Rabies vaccine should never be administered in the gluteal region. Administration in the gluteal area may result in lower or inadequate neutralizing antibody titers.

Post-exposure rabies prophylaxis should always include both vaccine and HRIG except in persons who have previously received complete prophylaxis regimens (pre- or post-exposure prophylaxis) with a cell culture vaccine, or persons previously vaccinated with other types of vaccine that have had documented protective rabies antibody titers. These persons should immediately receive a 1-

ml booster vaccination of RVA or HDCV administered intramuscularly, and a second booster three days later.

Because antibody response in persons receiving post-exposure prophylaxis has been universally satisfactory, post-treatment serological testing is not routinely recommended. Serology testing may be indicated in unusual circumstances, as when the patient is known to be immunosuppressed. Immunosuppressive agents should not be administered during post-exposure prophylaxis unless essential for the treatment of other conditions. Acute Communicable Disease Control (213-240-7941) may be contacted for recommendations in these cases.

Passive Immunization - HRIG:

HRIG is given only once at the beginning of treatment to provide immediate antibodies while active immunization from vaccination is developing. If HRIG is not given with the first dose of vaccine, it can be given through the seventh day following administration of the first vaccine dose. Beyond the seventh day, an active immune response is presumed to have occurred. HRIG should be administered at a dose of 20 IU/kg body weight for all age groups. No more than the recommended dose should be used due to a potential partial suppression of active immunization by HRIG. If anatomically feasible, the full dose should be infiltrated in the area around the wound. Any remaining HRIG is administered intramuscularly at a site distant from vaccination administration. HRIG should never be administered in the same syringe or at the same anatomical site as vaccine.

The combination of HRIG and vaccine is recommended for both bite and non-bite exposures regardless of the interval between exposure and initiation of treatment.

Pre-exposure Prophylaxis: In California, pre-exposure vaccination should be offered to persons at increased risk of rabies exposure. This "frequent risk" category includes veterinarians, animal handlers, animal control officers, laboratory workers, and persons traveling to and spending time (e.g., >1 month) in foreign countries where canine rabies is endemic. Pre-exposure vaccination should be considered for other persons whose vocations or avocations bring them into frequent contact with potentially rabid dogs, cats, skunks, bats or other species at risk of having rabies.

Pre-exposure vaccination for persons at risk has several potential advantages. Most importantly, it may protect persons with unrecognized exposures to rabies. Second, it simplifies and saves money on required treatment following a rabies exposure by eliminating the need for HRIG and decreasing the number of vaccine doses to be given. Finally, pre-exposure vaccination may protect persons exposed in areas where immunizing products are not available, carry a

high risk of adverse reactions, or where treatment may be delayed (e.g., travelers).

Primary Preexposure Vaccination:

Intramuscular Primary Immunization: Three 1.0 ml injections of HDCV or RVA should be given intramuscularly in the lateral deltoid on days 0, 7, and 21. Development of antibodies in patients vaccinated using this regimen has been 100% successful in several studies conducted. Based on results of these studies, routine post-primary immunization serological testing is not necessary except for persons suspected of being immunosuppressed. Persons who are immunosuppressed due to medication or illness should postpone preexposure vaccination if possible. Immunosuppressed persons who are at risk of rabies exposure can be vaccinated and should have their antibody titers checked.

Intradermal Primary Immunization: Three 0.1 ml intradermal injections of HDCV have also been recommended as an alternative to the intramuscular primary immunization regimen. Intradermal (ID) injections of IMOVAXR- ID are accurately administered over the lateral deltoid region on days 0, 7 and 21 or 28. The 1.0 ml HDCV vial is not approved for multi-dose ID use and should not be administered in this way. RVA is not to be given by the ID route.

Chloroquine phosphate and related antimalarial drugs (e.g., mefloquine) used for malaria chemoprophylaxis may interfere with the antibody response to HDCV. HDCV should not be administered by the intradermal route to persons receiving such drugs for malaria chemoprophylaxis. For further information, please refer to the Recommendations on Rabies Prevention published by the Advisory Committee on Immunization Practices [MMWR January 8, 1999;48(RR-1):1-21].

Booster Vaccination:

Persons classified as having "frequent risk" for rabies exposure include rabies diagnostic laboratory workers, spelunkers, veterinarians and their staff, animal control officers, wildlife officers and international travelers visiting areas where canine rabies is endemic. Such persons should receive pre-exposure immunization and have a serum sample tested for rabies antibody every two years. If the titer is less than complete neutralization at 1:8 by the Rapid Fluorescent Focus Inhibition Test (RFFIT), the person should receive a booster dose of rabies vaccine. Alternatively, a booster can be administered in lieu of titer determination. Two commercial sources for RFFIT testing are currently (December 2002) available at a cost of approximately $25.00 - $30.00 per sample:

Instructions for submission of samples are available by calling the numbers below:

Department of Veterinary Diagnostics, Veterinary Clinical Science Building, Kansas State University, (785) 532-4483

Department of Pathobiology, Virology Lab, 261 Greene Hall, Auburn University, (334) 844-2659

Atlanta Health Associates, Inc., (770) 205-9091

Maryland State Rabies Lab, Maryland Department of Helath, (410) 767-6177

Rabies Immunizing Products Available in the United States:

Human Rabies Vaccine Produces an active immune response including production of neutralizing antibodies. This antibody develops in approximately 7-10 days and usually persists for at least 2 years.

Human Diploid Cell Vaccine (HDCV) - Intramuscular (IMOVAX) and Intradermal (IMOVAX I.D.) HDCV is prepared from the Pitman-Moore rabies virus strain grown in MRC-5 human diploid cell culture. The vaccine is concentrated by ultrafiltration and inactivated with beta propiolactone. IMOVAX and IMOVAX I.D. are distributed by Aventis Pasteur, Inc. [(800) VAC-CINE {822-2463}].

Intramuscular (IM) administration: A single dose vial containing lyophilized vaccine (IMOVAX) that is reconstituted with diluent to a volume of 1.0 ml just before administration. The average wholesale price for IMOVAX as of 1/1/2000 is approximately $151 per dose.

Intradermal (ID) Administration: A single dose syringe containing lyophilized vaccine (IMOVAX I.D.) that is reconstituted to a volume of 0.1 ml just before administration. The average wholesale price for IMOVAX I.D. as of 1/1/2000 is approximately $91 per dose.

Rabies Vaccine Adsorbed (RVA). RVA is prepared from the Kissling strain of Challenge Virus Standard rabies virus adapted to fetal rhesus lung diploid cell culture. The vaccine is inactivated with betapropiolactone and concentrated by adsorption to aluminum phosphate to form a final 1.0 ml liquid dose. RVA is manufactured and distributed by Bioport Corporation, Phone (517) 327-1500. The average wholesale price for RVA as of 1/1/2000 is approximately $138 per dose.

The two types of vaccine are considered equally efficacious and safe when used as indicated. The 1.0 ml dose of either RVA or IMOVAX can be used for both pre-exposure and post-exposure prophylaxis. Imovax^{R} I.D. has been approved for intradermal administration for pre-exposure vaccination only, and is not to be

used in post-exposure rabies prophylaxis. The intramuscular dose (IMOVAX) should NOT be split into multiple doses for intradermal administration.

The safety and efficacy of RVA administered by the intradermal route has not been studied; therefore, RVA is not to be used intradermally.

Rabies Immune Globulin - Human: Provides immediate passive immunity that persists only a short time (half-life of approximately 21 days).

BayRab, IMOGAMR® Human rabies immune globulin (HRIG) is available from Bayer Corporation, Pharmaceutical Division, Biological Products (Bayrab), phone (800) 288-8370; and from Aventis Pasteur, Ince (Imogam Rabies HT) phone (800) VAC-CINE or (800) 822-2463.

HRIG is an antirabies gamma globulin concentrated by cold ethanol fractionation from plasma of hyperimmunized human donors. Rabies neutralizing antibody content is standardized to 150 international units (IU) per ml. HRIG is supplied in 2-ml and 10-ml vials for pediatric and adult use, respectively. The average wholesale price for Bayrab as of 1/1/2000 is approximately $750 per 10 ml vial, and $168 per 2 ml vial. The average wholesale price for IMOGAM as of 1/1/2000 is approximately $775 per 10 ml vial, and $155 per 2 ml vial.

Both HRIG preparations are considered equally efficacious and safe when used as indicated.

Adverse Reactions to Rabies Immunizing Products:

Human Diploid Cell Rabies Vaccine: Reactions after vaccination with HDCV and RVA are less serious and common than with previously available vaccines. Local reactions such as pain, erythema, and swelling or itching at the injection site were reported in 30-70 percent of patients receiving a three dose post-exposure regimen of HDCV. Mild systemic reactions such as headache, nausea, abdominal pain, muscle aches, and dizziness have been reported in 5-50 percent of recipients. Anaphylactic, encephalitic or neuroparalytic events are extremely rare, but have been reported.

An "immune complex-like" reaction occurs in approximately 6% of persons receiving booster doses of HDCV. The illness, characterized by onset 2-21 days postbooster, presents with a generalized urticaria and may also include arthralgia, arthritis, angioedema, nausea, vomiting, fever, and malaise. In no cases were the illnesses life-threatening. This reaction occurs much less frequently in persons receiving primary immunization. The reaction appears to be associated with the presence of betapropiolactone-altered human serum albumin in HDCV and the development of IgE to this allergen.

Rabies Immune Globulin, Human: Local pain and low-grade fever may follow receipt of HRIG. Although not reported specifically for HRIG, angioneurotic edema, nephrotic syndrome, and anaphylaxis have been reported after injections of immune globulin (IG). These reactions have occurred predominantly in persons receiving large and frequent doses of IG for various dysgammaglobulinemias. These reactions occur so rarely that the causal relationship between IG and these reactions is not clear.

There is no evidence that hepatitis B virus, human immunodeficiency virus or other viruses have ever been transmitted by commercially available HRIG in the United States.

Management of Adverse Reactions:

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully managed with non-steroidal anti-inflammatory and antipyretic agents (ibuprofen or acetaminophen, for example). For more severe reactions, consideration should be given to switching from one product to another.

When a person with a history of hypersensitivity must be given rabies vaccines, antihistamines may be given; epinephrine should be readily available to counteract anaphylactic reactions, and the person should be carefully observed immediately after immunization.

Systemic anaphylactic or neuroparalytic reactions occurring during the administration of rabies vaccines, though rare, pose a serious dilemma for the attending physician. A patient's risk of developing rabies must be carefully considered before deciding to discontinue vaccination. Moreover, the use of corticosteroids in the treatment of life-threatening neuroparalytic reactions carries the risk of inhibiting the development of active immunity to rabies. It is especially important in these cases that the serum of the patients be tested for rabies antibodies following vaccination.

All serious systemic neuroparalytic or anaphylactic reactions to a rabies vaccine should be immediately reported to the Division of Communicable Disease Control, California Department of Health Services (510) 540-2566 during working hours or (510) 540-2308 at other times, or the Division of Viral and Rickettsial Diseases, Center for Infectious Diseases, CDC ([404] 639-1050 during working hours, or [404] 639-2888 at other times).

References:

Rabies Prevention - United States, 1999. Recommendations of the Immunizations Practices Advisory Committee (ACIP). MMWR January 8, 1999;48(RR-1):1-21.

California Department of Health Services Division of Communicable Disease Control Veterinary Public Health Section (916) 327-0332 January, 2003