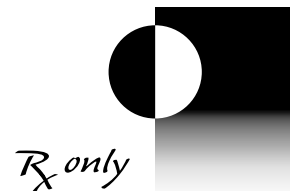


Rabies Vaccine

IMOVAX[®] RABIES



WISTAR RABIES VIRUS STRAIN PM-1503-3M GROWN IN HUMAN DIPLOID CELL CULTURES

DESCRIPTION

The Imovax[®] Rabies Vaccine produced by Aventis Pasteur is a sterile, stable, freeze-dried suspension of rabies virus prepared from strain PM-1503-3M obtained from the Wistar Institute, Philadelphia, PA.

The virus is harvested from infected human diploid cells, MRC-5 strain, concentrated by ultrafiltration and is inactivated by beta propiolactone. One dose of reconstituted vaccine contains less than 100 mg albumin, less than 150 µg neomycin sulfate and 20 µg of phenol red indicator. This vaccine must only be used intramuscularly and as a single dose vial.

The vaccine contains no preservative or stabilizer. It should be used immediately after reconstitution, and if not administered promptly, discard contents.

The potency of one dose (1.0 mL) Aventis Imovax Rabies Vaccine is equal to or greater than 2.5 international units of rabies antigen.

CLINICAL PHARMACOLOGY

Pre-exposure immunization

High titer antibody responses of the Aventis Imovax Rabies Vaccine made in human diploid cells have been demonstrated in trials conducted in England¹, Germany^{2,3} France⁴ and Belgium.⁵ Seroconversion was often obtained with only one dose. With two doses one month apart, 100% of the recipients developed specific antibody and the geometric mean titer of the group was approximately 10 international units. In the US, Aventis Imovax Rabies Vaccine resulted in geometric mean titers (GMT) of 12.9 IU/mL at Day 49 and 5.1 IU/mL at Day 90 when three doses were given intramuscularly during the course of one month. The range of antibody responses was 2.8 to 55.0 IU/mL at Day 49 and 1.8 to 12.4 IU at Day 90.⁶ The definition of a minimally accepted antibody titer varies among laboratories and is influenced by the type of test conducted. CDC currently specifies a 1:5 titer (complete inhibition) by the rapid fluorescent focus inhibition test (RFFIT) as acceptable. The World Health Organization (WHO) specifies a titer of 0.5 IU.

Postexposure immunization

Postexposure efficacy of Aventis Imovax Rabies Vaccine was successfully proven during clinical experience in Iran⁷ in conjunction with antirabies serum. Forty-five persons severely bitten by rabid dogs and wolves received Aventis vaccine within hours of and up to 14 days after the bites. All individuals were fully protected against rabies.

There have been reports of possible vaccine failure when the vaccine has been administered in the gluteal area. Presumably subcutaneous fat in the gluteal area may interfere with the immunogenicity of human diploid cell rabies vaccine (HDCV).^{26,29} For adults and children, Rabies Vaccine should be administered in the deltoid muscle. (See DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

1. Rationale of treatment

Physicians must evaluate each possible rabies exposure. Local or state public health officials should be consulted if questions arise about the need for prophylaxis.⁸

In the United States and Canada, the following factors should be considered before antirabies treatment is initiated.

Species of biting animal

Carnivorous wild animals (especially skunks, raccoons, foxes, coyotes, and bobcats) and bats are the animals most commonly infected with rabies and have caused most of the indigenous cases of human rabies in the United States since 1960. Unless an animal is tested and shown not to be rabid, postexposure prophylaxis should be initiated upon bite or nonbite exposure to the animals. (See definition in “Type of Exposure” below.) If treatment has been initiated and subsequent testing in a competent laboratory shows the exposing animal is not rabid, treatment can be discontinued.⁸

The likelihood that a domestic dog or cat is infected with rabies varies from region to region; hence the need for postexposure prophylaxis also varies.⁸

Rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats and mice) and lagomorphs (including rabbits and hares) are rarely found to be infected with rabies and have not been known to cause human rabies in the United States. In these cases, the state or local health department should be consulted before a decision is made to initiate postexposure antirabies prophylaxis.⁸

Circumstances of biting incident

An UNPROVOKED attack is more likely than a provoked attack to indicate the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as PROVOKED.

Type of exposure

Rabies is transmitted by introducing the virus into open cuts or wounds in skin or via mucous membranes. The likelihood of rabies infection varies with the nature and extent of exposure. Two categories of exposure should be considered.

Bite: Any penetration of the skin by teeth.

Nonbite: Scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material, such as brain tissue, from a rabid animal. Casual contact, such as petting a rabid animal (without a bite or nonbite exposure as described above), does not constitute an exposure and is not an indication for prophylaxis. There have been two instances of airborne rabies acquired in laboratories and two probable airborne rabies cases acquired in a bat-infested cave in Texas.^{8,9}

The only documented cases for rabies from human-to-human transmission occurred in four patients in the United States and overseas who received corneas transplanted from persons who died of rabies undiagnosed at the time of death.^{9,10} Stringent guidelines for acceptance of donor corneas should reduce this risk. Bite and nonbite exposure from humans with rabies theoretically could transmit rabies, although no cases of rabies acquired this way have been documented. Each potential exposure to human rabies should be carefully evaluated to minimize unnecessary rabies prophylaxis.^{8,11}

2. Pre- and postexposure treatment of rabies

A. Pre-exposure - See Table 1

Pre-exposure immunization may be offered to persons in high risk groups, such as veterinarians, animal handlers, certain laboratory workers, and persons spending time (e.g. 1 month or more) in foreign countries where rabies is a constant threat. Persons whose vocational or avocational pursuits bring them into contact with potentially rabid dogs, cats, foxes, skunks, bats, or other species at risk of having rabies should also be considered for pre-exposure prophylaxis.⁸

Vaccination is recommended for children living in or visiting countries where exposure to rabid animals is a constant threat. Worldwide statistics indicate children are more at risk than adults.

Pre-exposure prophylaxis is given for several reasons. First, it may provide protection to persons with inapparent exposure to rabies. Secondly, it may protect persons whose postexposure therapy might be expected to be delayed. Finally, although it does not eliminate the need for additional therapy after a rabies exposure, it simplifies therapy by eliminating the need for globulin and decreasing the number of doses of vaccine needed. This is of particular importance for persons at high risk of being exposed in countries where the available rabies immunizing products may carry a higher risk of adverse reactions.

Pre-exposure immunization does not eliminate the need for prompt prophylaxis following an exposure. It only reduces the postexposure treatment regimen.⁸

PRE-EXPOSURE RABIES TREATMENT GUIDE

1. Pre-exposure immunization: Consists of the three doses of HDCV, 1.0 mL, intramuscularly (deltoid area), one each on Days 0, 7 and 21 or 28. Administration of routine booster doses of vaccine depends on exposure risk category as noted in Table 1. Pre-exposure immunization of immunosuppressed persons is not recommended.⁸

TABLE 1⁸

| CRITERIA FOR PRE-EXPOSURE IMMUNIZATION | | | |
|---|---|--|--|
| Risk category | Nature of risk | Typical populations | Pre-exposure regimen |
| Continuous | Virus present continuously often in high concentrations. Aerosol, mucous membrane, bite or nonbite exposure possible. Specific exposures may go unrecognized. | Rabies research lab workers.* Rabies biologics production workers. | Primary pre-exposure immunization course. Serology every 6 months. Booster immunization when antibody titer falls below acceptable level.* |
| Frequent | Exposure usually episodic, with source recognized, but exposure may also be unrecognized. Aerosol, mucous membrane, bite or nonbite exposure. | Rabies diagnostic lab workers*, spelunkers, veterinarians, and animal control and wildlife workers in rabies epizootic areas. | Primary pre-exposure immunization course. Booster immunization or serology every 2 years.† |
| Infrequent (greater than population-at-large) | Exposure nearly always episodic with source recognized. Mucous membrane, bite or nonbite exposure. | Veterinarians and animal control and wildlife workers in areas of low rabies endemicity. Certain travelers to foreign rabies epizootic areas. Veterinary students. | Primary pre-exposure immunization course. No routine booster immunization or serology. |
| Rare (population-at-large) | Exposure always episodic, mucous membrane, or bite with source recognized. | US population-at-large, including individuals in rabies epizootic areas. | No pre-exposure immunization. |

* Judgement of relative risk and extra monitoring of immunization status of laboratory workers is the responsibility of the laboratory supervisor (see US Department of Health and Human Service's Biosafety in Microbiological and Biomedical Laboratories, 1984).

† Pre-exposure booster immunization consists of one dose of HDCV, 1.0 mL/dose, IM (deltoid area). Acceptable antibody level is 1:5 titer (complete inhibition in RFFIT at 1:5 dilution). (See CLINICAL PHARMACOLOGY). Boost if titer falls below 1:5.

B. Postexposure - See Table 2

The essential components of rabies postexposure prophylaxis are local treatment of wounds and immunization, including administration, in most instances, of both globulin and vaccine (Table 2).^{8,13}

1. Local treatment of wounds: Immediate and thorough washing of all bite wounds and scratches with soap and water is perhaps the most effective measure for preventing rabies. In experimental animals, simple local wound cleansing has been shown to reduce markedly the likelihood of rabies.^{8,11}

Tetanus prophylaxis and measures to control bacterial infection should be given as indicated.

2. Specific treatment: Postexposure antirabies immunization should always include administration of both antibody (preferably RIG) and vaccine, with one exception: persons who have been previously immunized with the recommended pre-exposure or postexposure regimens with HDCV or who have been immunized with other types of vaccines and have a history of documented adequate rabies antibody titer should receive only vaccine. The combination of globulin and vaccine is recommended for both bite exposures and nonbite exposures regardless of the interval between exposure and treatment.^{14,15} The sooner treatment is begun after exposure, the better. However, there have been instances in which the decision to begin treatment was made as late as 6 months or longer after the exposure due to delay in recognition that an exposure had occurred.^{8,13}

3. Treatment outside the United States: If postexposure is begun outside the United States with locally produced biologics, it may be desirable to provide additional treatment when the patient reaches the US. State health departments should be contacted for specific advice in such cases.⁸

POSTEXPOSURE TREATMENT GUIDE

The following recommendations are only a guide. In applying them, take into account the animal species involved, the circumstances of the bite or other exposure, the vaccination status of the animal, and presence of rabies in the region. Local or state public health officials should be consulted if questions arise about the need for rabies prophylaxis.⁸

TABLE 2⁸

| Animal species | Condition of animal at time of attack | Treatment of exposed person* |
|---|---|--|
| DOMESTIC: Dog and cat | Healthy and available for 10 days of observation. Rabid or suspected rabid. Unknown (escaped). | None unless animal develops rabies. † RIG§ and HDCV. Consult public health officials. If treatment is indicated, give RIG§ and HDCV. |
| WILD: Skunk, bat, fox, coyote, raccoon, bobcat and other carnivores | Regard as rabid unless proven negative by laboratory tests. £ | RIG§ and HDCV. |
| OTHER: Livestock, rodents and lagomorphs (rabbits and hares) | Consider individually. Local and state public health officials should be consulted on questions about the need for rabies prophylaxis. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits and hares, almost never call for antirabies prophylaxis. | |

* All bites and wounds should immediately be thoroughly cleansed with soap and water. If antirabies treatment is indicated, both rabies immune globulin (RIG) and human diploid cell rabies vaccine (HDCV) should be given as soon as possible regardless of the interval from exposure. Local reactions to vaccines are common and do not contraindicate continuing treatment. Discontinue vaccine if fluorescent antibody tests of the animal are negative.

† During the usual holding period of 10 days, begin treatment with RIG and HDCV at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.

§ If RIG is not available, use antirabies serum, equine (ARS). Do not use more than the recommended dosage.

£ The animal should be killed and tested as soon as possible. Holding for observation is not recommended.

CONTRAINDICATIONS

For postexposure treatment, there are no known specific contraindications to the use of Aventis Imovax Rabies Vaccine. In cases of pre-exposure immunization, there are no known specific contraindications other than situations such as developing febrile illness, etc.

WARNINGS

Rabies Vaccine in this package is a unit dose to be delivered intramuscularly in the deltoid area.⁸

This vaccine must not be used intradermally or as a multiple dose dispensing unit. In both pre-exposure and postexposure immunization, the full 1.0 mL dose should be given intramuscularly.

In the case of pre-exposure immunization, recently a significant increase has been noted in “immune complex-like” reactions in persons receiving booster doses of HDCV.¹⁶ The illness characterized by onset 2-21 days post-booster, 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. Preliminary data suggest this “immune complex-like” illness may occur in up to 6% of persons receiving booster vaccines and much less frequently in persons receiving primary immunization. Additional experience with this vaccine is needed to define more clearly the risk of these adverse reactions.^{8,17}

Two cases of neurologic illness resembling Guillain-Barré syndrome^{18,19} a transient neuroparalytic illness, that resolved without sequelae in 12 weeks and a focal subacute central nervous system disorder temporally associated with HDCV, have been reported.²⁰

All serious systemic neuroparalytic or anaphylactic reactions to a rabies vaccine should be immediately reported to the state health department or Aventis Pasteur Inc., 1-800-VACCINE/1-800-822-2463.⁸

PRECAUTIONS

IN ADULTS AND CHILDREN THE VACCINE SHOULD BE INJECTED INTO THE DELTOID MUSCLE. IN INFANTS AND SMALL CHILDREN THE MID-LATERAL ASPECT OF THE THIGH MAY BE PREFERABLE.

General

When a person with a history of hypersensitivity must be given rabies vaccine, antihistamines may be given; epinephrine (1:1000) should be readily available to counteract anaphylactic reactions, and the person should be carefully observed after immunization.

While the concentration of antibiotics in each dose of vaccine is extremely small, persons with known hypersensitivity to any of these agents could manifest an allergic reaction. While the risk is small, it should be weighed in light of the potential risk of contracting rabies.

Drug interactions

Corticosteroids, other immunosuppressive agents, and immunosuppressive illnesses can interfere with the development of active immunity and predispose the patient to developing rabies. Immunosuppressive agents should not be administered during postexposure therapy, unless essential for the treatment of other conditions. When rabies postexposure prophylaxis is administered to persons receiving steroids or other immunosuppressive therapy, it is especially important that serum be tested for rabies antibody to ensure that an adequate response has developed.⁸

Usage in pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Imovax Rabies Vaccine. It is also not known whether the product can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Rabies vaccine should be given to a pregnant woman only if clearly needed.

Because of the potential consequences of inadequately treated rabies exposure and limited data that indicate that fetal abnormalities have not been associated with rabies vaccination, pregnancy is not considered a contraindication to postexposure prophylaxis.^{8,21} If there is substantial risk of exposure to rabies, pre-exposure prophylaxis may also be indicated during pregnancy.⁸

Pediatric use

Both safety and efficacy in children have been established.

ADVERSE REACTIONS

ALSO SEE WARNINGS AND CONTRAINDICATIONS SECTIONS FOR ADDITIONAL STATEMENTS.

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 anti-inflammatory and antipyretic agents (e.g. aspirin).

Reactions after vaccination with HDCV are less common than with previously available vaccines.^{12,16,17} In a study using five doses of HDCV, local reactions, such as pain, erythema, and swelling or itching at the injection site were reported in about 25% of recipients of HDCV, and mild systemic reactions such as headache, nausea, abdominal pain, muscle aches and dizziness were reported in about 20% of recipients.⁸

Serious systemic anaphylactic or neuromuscular reactions occurring during the administration of rabies vaccines pose a 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 to treat life-threatening neuromuscular 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 patient be tested for rabies antibodies. Advice and assistance on the management of serious adverse reactions in persons receiving rabies vaccines may be sought from the state health department.⁸

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstitute the freeze-dried vaccine in its vial with the 1.0 mL of diluent supplied in the disposable syringe using the longer of the two needles. Gently swirl the contents until completely dissolved and withdraw the total amount of dissolved vaccine into the syringe by setting the vial in an upright position on the table. Remove the reconstitution needle and replace it with the smaller needle.

The reconstituted vaccine should be used immediately.

After preparation of the injection site, immediately inject the vaccine intramuscularly. For adults and children, the vaccine should be injected into the deltoid muscle.^{22-27,29} In infants and small children, the mid lateral aspect of the thigh may be preferable. Care should be taken to avoid injection into or near blood vessels and nerves. After aspiration, if blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedure using a new dose of vaccine, at a different site.

NOTE: The freeze-dried vaccine is creamy white to orange. After reconstitution it is pink to red.

A. Pre-exposure dosage

1. Primary vaccination: In the United States, the Immunization Practices Advisory Committee (ACIP) recommends three injections of 1.0 mL each, one injection on Day 0 and one on Day 7 and one either on Day 21 or 28.⁸

2. Booster dose: Persons working with live rabies virus in research laboratories and in vaccine production facilities should have rabies antibody titers checked every six months and boosters given as needed to maintain an adequate titer. (For definition of adequate titer, see CLINICAL PHARMACOLOGY.) Only laboratory workers, such as those doing rabies diagnostic tests, spelunkers and veterinarians, animal control and wildlife officers in areas where rabies is epizootic should have boosters every 2 years or have their serum tested for rabies antibody every 2 years and, if the titer is inadequate, have a booster dose. Veterinarians and animal control and wildlife officers, if working in areas of low rabies endemicity, do not require routine booster doses of HDCV after completion of primary pre-exposure immunization (Table 1).⁸

Persons who have experienced "immune complex-like" hypersensitivity reactions should receive no further doses of HDCV unless they are exposed to rabies or they are truly likely to be inapparently and/or unavoidably exposed to rabies virus and have unsatisfactory antibody titers.

B. Postexposure dosage

The World Health Organization established a recommendation for six intramuscular doses of human diploid cell vaccine (HDCV) based on studies in Germany and Iran.^{3,7} Used in this way, a total of 6 injections of a 1.0 mL dose of vaccine are given according to the following schedule: on Day 0, 3, 7, 14, 30 and 90. The first dose should be accompanied by Rabies Immune Globulin (RIG) or Antirabies Serum (ARS). If possible, up to half the dose of RIG or ARS should be used to infiltrate the wound, and the rest administered intramuscularly, in a different site from the rabies vaccine, preferably in the gluteal region.

Studies conducted at the CDC in the United States have shown that a regimen of 1 dose of Rabies Immune Globulin (RIG) and 5 doses of HDCV induced an excellent antibody response in all recipients. Of 511 persons bitten by proven rabid animals and so treated, none developed rabies.⁸

Based on these data, the ACIP recommends a 5-dose regimen for postexposure situations. Five 1.0 mL doses are given intramuscularly on Day 0, 3, 7, 14 and 28 in conjunction with RIG on Day 0.⁸

Because the antibody response following the recommended vaccination regimen with HDCV has been so satisfactory, routine postvaccination serologic testing is not recommended. Serologic testing is indicated in unusual circumstances, as when the patient is known to be immunosuppressed. Contact state health department or CDC for recommendations.^{8,28}

C. Postexposure therapy of previously immunized persons

When an immunized person who was vaccinated by the recommended regimen with HDCV or who had previously demonstrated rabies antibody is exposed to rabies, that person should receive two IM doses (1.0 mL each) of HDCV, one immediately and one 3 days later. RIG should not be given in these cases. If the immune status of a previously vaccinated person who did not receive the recommended HDCV regimen is not known, full primary postexposure antirabies treatment (RIG plus 5 doses of HDCV) may be necessary. In such cases, if antibody can be demonstrated in a serum sample collected before vaccine is given, treatment can be discontinued after at least two doses of HDCV.⁸

HOW SUPPLIED

Imovax Rabies Vaccine is supplied in a tamperproof unit dose plastic box with:

- One vial of freeze-dried vaccine containing a single dose.
- One disposable needle and syringe containing diluent for reconstitution.
- One smaller disposable needle for administration.

Product No. 49281-250-10

STORAGE

The freeze-dried vaccine is stable if stored in the refrigerator between 2°C and 8°C (35°F to 46°F). Do not freeze.

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