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"Review article on anti-rabies vaccine"

shubhangi Dattatray Bhojgude*
1)Mr.L.D.Hingne (M Pharm , PhD Scholar)
2)Mr.L.D.Hingne (M Pharm , PhD Scholar)
Aditya Pharmacy College, Beed. Nalwandi Naka Beed , Maharashtra Pincode : 431127

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ABSTRACT: Rabies is a fatal viral zoonotic disease transmitted to humans through bites or scratches by infected domestic and wild animals. It is present in all continents except Antarctica and mostly endemic in Asian and African countries. In countries like India and China, dogs are one of the major reservoir hosts for the transmission of this disease. This disease is unpreventable with the lack of awareness and proper treatment measures are not being followed up with patients who reside particularly in rural areas. It is because most Post Exposure Prophylaxis (PEP) needs are borne by patients who can least afford to yield. Rabies vaccines have come a long way following the development of a vaccine by Louis Pasteur in 1885 which is still being used to control rabies in animals and humans.

I. INTRODUCTION

Rabies is a disease entrenched in history, dating back to ancient Egypt. Caused by an RNA virus belonging to the Lyssavirus genus, rabies is capable of infecting all mammals. Rabies is primarily a disease of terrestrial and airborne mammals, including dogs, wolves, foxes, coyotes, jackals, cats, bobcats, lions, mongooses, skunks, badgers, bats, monkeys and humans .The dog has been, and still is, the main reservoir of rabies in India. Other animals, such as monkeys, jackals, horses, cattle and rodents, seem to bite incidentally on provocation, and the fear of rabies leads the victim to seek postexposure prophylaxis. Rabies occurs in more than 150 countries and territories .With the expectation of some areas in the South pacific, rabies persists as a major Public Health hazard in many countries across the world .

In India, Some studies have estimated that there are as high as 17 million animal bites per annum and 20,000 human deaths occur due to rabies each year. Based on vaccine utilization, approximately 3 million people receive post-exposure treatment in our country.

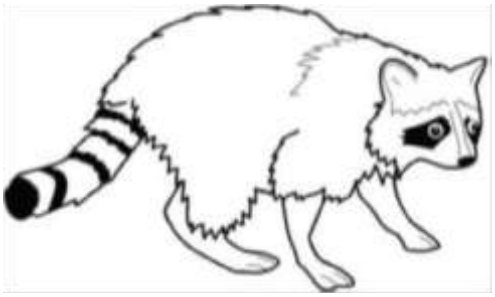

Figure 1: Wild animal (especially bats)

Intradermal Vaccines-

Over the centuries, a number of vaccines have been administered into the skin using a variety of instruments, from simple to sophisticated ones. At the same time as these progresses in administration techniques, advances in the field of immunology have led to an increased understanding of the basic mechanisms of innate and adaptive immunity and the skin has been identified as an attractive site for vaccination, largely due to the presence of a dense network of immune-stimulatory antigen-presenting cells.. The current renewed interest in ID route of vaccination has been largely driven by the perception that it might offer several advantages in terms of both immunogenicity, such as the reduction of antigen concentration (dose-sparing), the ability to improve immune response in low-responders and the avoidance of the need for adjuvants, and some practical issues as the easier and safer administration with the respect to conventional intramuscular route and the reduction in risk of needle-stick injuries for health care workers and blood vessels or nerves injuries for patients.

During the last century, the skin was the subject of numerous studies demonstrating the highly complex and dynamic interplay between the skin and the other components of the immune system and for this reason has been proven to be suitable for vaccine delivery.

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What is Rabies?

Rabies is a serious disease. It is caused by a virus. Rabies is mainly a disease of animals. Humans get rabies when they are bitten by infected animals. At first there might not be any symptoms. But weeks, or even months after a bite, rabies can cause pain, fatigue, headaches, fever, and irritability. These are followed by seizures, hallucinations, and paralysis. Human rabies is almost always fatal. Wild animals especially bats- are the most common source of human rabies infection in the United States. Skunks, raccoons, dogs, cats, coyotes, foxes and other mammals can also transmit the disease. Human rabies is rare in the United States. There have been only 55 cases diagnosed since 1990. However, between 16,000 and 39,000 people are vaccinated each year as a precaution after animal bites. Also, rabies is far more common in other parts of the world, with about 40,000 –70,000 rabies related deaths worldwide each year.

PATHOPHYSIOLOGY CHANGES

Rabies is a zoonotic disease that remains an important public health problem worldwide and causes more than 70,000 human deaths each year. The causative agent of rabies is rabies virus (RV), a negative-stranded RNA virus of the rhabdo virus family. Neuro in vasiveness and neurotropisn are the main features that define the pathogenesis of rabies. Although RV pathogenicity is a multigenic trait involving several elements of the RV genome, the RV glycoprotein plays a major role in RV pathogenesis by controlling the rate of virus uptake and trans-synaptic virus spread and by regulating the rate of virus replication. Pathogenic street RV strains differ significantly from tissue culture-adapted RV strains in their neuro in vasiveness. Whereas street RV strains are highly neuroinvasive, most tissue culture-adapted RV strains have either no or only limited ability to invade the CNS from a peripheral site. The high neuro in vasiveness of pathogenic street RVs is, at least in part, due to their ability to evade immune responses and to conserve the structures of neurons. The finding that tissue culture-adapted RV strains replicate very fast and induce strong innate and adaptive immune responses opens new avenues for therapeutic intervention against rabies.

PHARMACOLOGICAL CHANGES

If preventative treatment is sought promptly, rabies need not be fatal. Immunization is almost always effective if started within two days of the bite. Chance of effectiveness declines, however, the longer vaccination is put off. It is, however, important to start immunizations, even if it has been weeks or months following a suspected rabid animal bite, because the vaccine can be effective even in these cases. If immunizations do not prove effective or are not received, rabies is nearly always fatal with a few days of the onset of symptoms.

Management of a patient following an animal bite –

- Wound should be washed immediately with soap and water for 3-5 min.
- Wounds should be was cleaned thoroughly at the hospital with 70 % alcohol or provide iodine.
- Anti titaneous immunization should be inoculated when necessary.
- Antimicrobial should be prescribed if necessary to control bacterial infection.

Symptoms

The period between infection and the first symptoms (incubation period) is typically 1–3 months in humans. Incubation periods as short as four days as and longer than six years have been documented, depending on the location and severity of the contaminated wound and the amount of virus introduced. Initial signs and symptoms of rabies are often nonspecific such as fever and headache. As rabies progresses and causes inflammation of the brain and/or meninges, signs and symptoms can include slight or partial paralysis, anxiety, insomnia, confusion, agitation, abnormal behavior, paranoia, terror, and hallucinations, progressing to delirium, and coma. The person may also have hydrophobia. Death usually occurs 2 to 10 days after first symptoms. Survival is rare once symptoms have presented, even with the administration of proper and intensive care. Jeanna Giese, who in 2004 was the first patient treated with the Milwaukee protocol, became the first person ever recorded to have survived rabies without receiving successful post-exposureprophylaxis.

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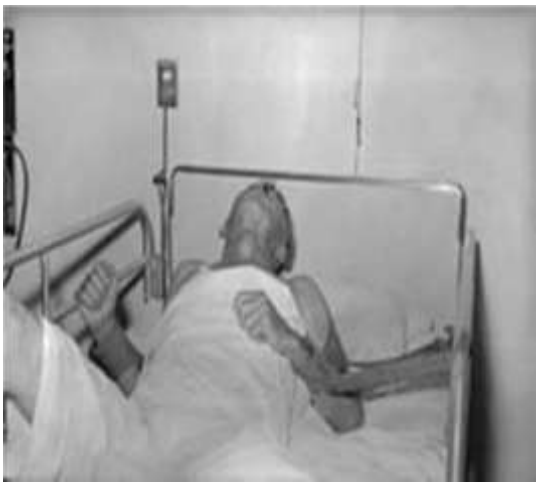

Figure 2: Rabies patient

Prevention

One promising preventive strategy that has been used since the early 2000s is the distribution of wildlife baits containing an oral vaccine against rabies. This strategy has been used in Germany to vaccinate wild foxes, which are frequent carriers of the disease in Europe. In the United States, veterinary researchers at Kansas State University have developed an oral vaccine for fruit bats; early trials of the vaccine have given promising results.The following precautions should be observed in environments where humans and animals may likely come into contact.

Domesticated animals, including household pets, should be vaccinated against rabies. If a pet is bitten by an animal suspected to have rabies, its owner should contact a veterinarian immediately and notify the local animal control authorities. Domestic pets with current vaccinations should be revaccinated immediately; unvaccinated dogs, cats, or ferrets are usually euthanized (put to sleep). Further information about domestic pets and rabies is available on the American Veterinary Medical Association (AVMA) web site. Wild animals should not be touched or petted, no matter how friendly they may appear. It is also important not to touch an animal that appears ill or passive, or whose behavior seems odd, such as failing to show the normal fear of humans. These are all possible signs of rabies. Many animals, such as raccoons and skunks, are nocturnal and their activity during the day should be regarded as suspicious. People should not interfere in fights between animals. Because rabies is transmitted through saliva, a person should wear rubber gloves when handling a pet that has had an encounter with a wild animal.

Diagnosis

After the onset of symptoms, blood tests and cerebrospinal fluid (CSF) analysis tests will be conducted. CSF will be collected during a procedure called a lumbar puncture in which a needle is used to withdraw a sample of CSF from the area around the spinal cord. The CSF tests do not confirm diagnosis but are useful in ruling out other potential causes for the patient's altered mental state. This must be started at the earliest to ensure that the individual will be immunized before the rabies virus reaches the nervous system. However, people who present for treatment even months after a possible rabies exposure should be evaluated and treated as if the event had occurred recently. To bring out uniformity globally, the classification of animal bite for post-exposure prophylaxis has been based on WHO recommendations

The two most common diagnostic tests are the fluorescent antibody test and isolation of the rabies virus from an individual's saliva or throat culture. The fluorescent antibody test involves taking a small sample of skin (biopsy) from the back of the neck of the patient.

If specific proteins, called antibodies, that are produced only in response to the rabies virus are present, they will bind with the fluorescent dye and become visible.

Treatment

Rabies is 100% fatal disease and after development of rabies there is no treatment for it. Only method to prevent rabies is anti rabies prophylaxis. For the prevention of rabies presently two type of vaccine regimen are in practiced in India. In both regimen cell culture vaccine is used. In India, IDRV was recommended for use in the government sector in 2006.

Compliance to post-exposure vaccination is crucial to achieve optimum level of antibody titers. The present study was planned to assess the compliance of 4 dose Intradermal regimen (updated Thai regimen) over 5 dose intramuscular regimen (Essen regimen). It was observed that compliance was more in Intra-dermal regimen as compare to intramuscular regimen and it was found to be statistically significant. Treatment approximately reduces by 80% of intramuscular regimen.

A study conduct by Rohi K R, Mankeshwar R (2014) conducted study on 2051 patients, found that Intradermal regimen is more

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cost beneficial than Intramuscular (Essen) regimen. Present study showed that, 25.67% & 27.99% patients belongs to category III and 72.02% and 71.07% belongs to category II during year 2010-11 &2011-12 respectively. Pattern of distribution was found similar during both year. N.J. Gogtay et al (2014) found that maximum patients belonged to category II (78.3%) followed by category III (21.7%). Contrast to our study, Shah Venu, et al (2012) found that 67.8% were belonged category III followed by 19% to category I and 13.2% to category II exposure. Study shows that as prophylaxis treatment precede dropout rate increased, so counseling part and follow up is very important to avoid dropouts.

Intradermal injection-

Is the injection of a substance into the dermis, just below the epidermis. This route has the longest absorption time as compared to subcutaneous injections and intramuscular injections. As a result, it is used for sensitivity tests, like tuberculin and allergy tests, and for local anesthesia. Additionally, the body's Intramuscular regimens for rabies PEP. Three intramuscular schedules for category 2 and 3 exposures:

- The 5 dose regimen
- The 2-1-1 regimen
- The 4 dose regimen with RIG in both categories 2 and 3 Vaccines should be injected in into the deltoid muscle for adults and children aged 2 years and more.

The anterolateral thigh is recommended for younger children.

Vaccines should not be injected into the gluteal region.

Figure 3: Intra-dermal route of vaccine

Transmission

Rabies is mostly transmitted to humans, and between animals, through the saliva of infected animals. Transmission is generally through a bite from any infected animal. Transmission between humans is extremely rare, although it can happen through organ transplants, or through bites.[citation needed]After a typical human infection by bite, the virus enters the peripheral nervous system. It then travels along the nerves towards the central nervous system.

During this phase, the virus cannot be easily detected within the host, and vaccination may still confer cell-mediated immunity to prevent symptomatic rabies. Once the virus reaches the brain, it rapidly causes encephalitis and symptoms appear. This is called the "prodromal" phase and at this time, treatment is usually unsuccessful. Rabies may also inflame the spinal cord producing myelitis[citation needed].

POST-EXPOSURE PROPHYLAXIS (PEP)-

Post-exposure prophylaxis (PEP) is the immediate treatment of a bite victim after rabies exposure. This prevents virus entry into the central nervous system, which results in imminent death. PEP consists of:

Extensive washing and local treatment of the wound as soon as possible after exposure; A course of potent and effective rabies vaccine that meets WHO standards; and the administration of rabies immunoglobulin (RIG), if indicated.All category II and III exposures assessed as carrying a risk of developing rabies require PEP.

This risk is increased if:

•the biting mammal is a known rabies reservoir or vector species

•the exposure occurs in a geographical area where rabies is still present •the animal looks sick or displays abnormal behavior a wound or mucous membrane was contaminated by the animal's saliva

RABIES VACCINES-Nerve tissue based vaccines

More than 100 years ago, Louis Pasteur and his colleagues developed the first crude rabies vaccine based on attenuated virus in desiccated nerve tissue. Nerve tissue vaccines (NTVs) were intended for post-exposure prophylaxis. Although continuously improved over the years, inactivated NTVs produced in the brains of sheep or goats

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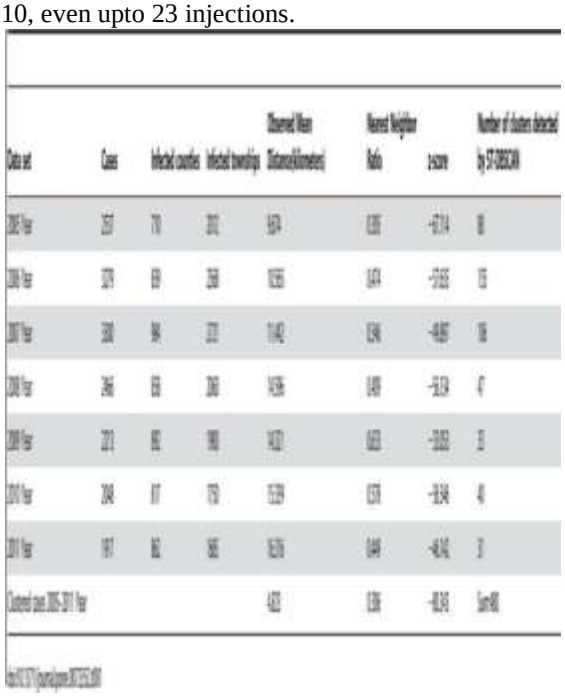
(Sample) or suckling mice (Fuenzalida) are associated with neurological adverse reactions.

Thus, in about 0.3-0.8 persons per 1000 vaccines sensation to contaminating neuroproteins present in the vaccine causes severe allergic encephalomyelitis. Also, these vaccines are inferior to modern CCVs in terms of potency and immunogenicity. A complete post-exposure prophylaxis regimen using NTVs involves a prolonged and painful immunization course of 7-10, even upto 23 injections.



Nerve tissue based vaccines

Table 1: Distance (Euclidian) to the nearest case of annual rabies data and clustered dataset

More than 100 years ago, Louis Pasteur and his colleagues developed the first crude rabies vaccine based on attenuated virus in desiccated nerve tissue. Nerve tissue vaccines (NTVs) were intended for post-exposure prophylaxis.

THE MANUFACTURING PROCESS-

Manufacturing an anti-virus vaccine today is a complicated process even after the arduous task of creating a potential vaccine in the laboratory. The change from manufacturing a potential vaccine in small quantities to manufacturing gallons of safevaccine in a production situation is dramatic, and simple laboratory procedure may not be amenable to a "scale up" situation.

The Seed

Manufacturing begins with small amounts of a specific virus (or seed). The virus must be free of impurities, including other similar viruses and even variations of the same type of virus. Additionally, the seed must be kept under "ideal" conditions, usually frozen, that prevent the virus from becoming either stronger or weaker than desired. Stored in small glass or plastic containers, amounts as small as only 5 or 10 cubic centimeters, but containing thousands if not millions of viruses, will eventually lead to several hundred liters of vaccine. Freezers are maintained at specified temperatures; charts and/or dials outside of the freezer keep a continuous record of the temperature. Sensors will set off audible alarm signals and/or computer alarms if the freezer temperature goes out of range.

Growing the virus

After defrosting and warming the seed virus under carefully specified conditions (i.e., at room temperature or in a water bath), the small amount of virus cells is placed into a "cell factory," a small machine that, with the addition of an appropriate medium, allows the virus cells to multiply. Each type of virus grows best in a medium specific to it, established in pre-manufacturing laboratory procedures, but all contain proteins from mammals in one form or another, such as purified protein from cow blood. The medium also contains other proteins and organic compounds that encourage the reproduction of the virus cells. As far as the virus is concerned, the medium in a cell factory is a host for reproduction. Mixed with the appropriate medium, at appropriate temperature, and with a predetermined amount of time, viruses will multiply.

In addition to temperature, other factors must be monitored, including the pH of the mixture. pH is a measure of acidity or basicity, measured on a scale from 0 to 14, and the viruses must be kept at a defined pH within the cell factory.

Sensors monitor pH and temperature, and there are various connections for adding media or chemicals such as oxygen to maintain the pH, places to withdraw samples for microscopic analysis, and sterile arrangements for adding the components of the cell factory and withdrawing the intermediate product when it is ready.

The virus from the cell factory is then separated from the medium, and placed in a second medium for additional growth. Early methods of 40 or 50 years ago used a bottle to hold the mixture, and the resulting growth was a single layer of

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viruses floating on the medium. It was soon discovered that if the bottle was turned while the viruses were growing, even more virus could be produced because a layer of virus grew on all inside surfaces of the bottle. An important discovery in the 1940s was that cell growth is greatly stimulated by the addition of enzymes to a medium, the most commonly used of which is trypsin. An enzyme is a protein that also functions as a catalyst in the feeding and growth of cells.

In current practice, bottles are not used at all. The growing virus is kept in a container larger than but similar to the cell factory, and mixed with "beads," near microscopic particles to which the viruses can attach themselves. The use of the beads provides the virus with a much greater area to attach themselves to, and consequently, a much greater growth of virus. As in the cell factory, temperature and pH are strictly controlled. Time spent in growing virus varies according to the type of virus being produced, and is, in each case, a closely guarded secret of the manufacturer.

Separation

When there is a sufficient number of viruses, they are separated from the beads in one or more ways. The broth might be forced through a filter with openings large enough to allow the viruses to pass through, but small enough to prevent the beads from passing. The mixture might be centrifuged several times to separate the virus from the beads in a container from which they can then be drawn off still another alternative.

Selecting the strain

The eventual vaccine will be either made of attenuated (weakened) virus, or a killed virus. The choice of one or the other depends on a number of factors including the efficacy of the resulting vaccine, and its secondary effects. Ru vaccine, which is developed almost every year in response to new variants of the causative virus, is always an attenuated vaccine. The virulence of a virus can dictate the choice; rabies vaccine, for example, is always a killed vaccine.

Rabiesvaccine forIntradermaladministration-

Although injection of cell culture and embryonated egg vaccines by the intramuscular route results in higher antibody concentrations, extensive evaluations have shown that similar schedules based on ID injection of 0.10 ml of the vaccine induce equally high protection against rabies. Cost-effective ID regimens using selected CCVs have been successfully introduced for post-exposure prophylaxis in many developing countries.

ID regimens offer a safer and more effective alternative to the use of NTVs and a more economic alternative compared with the intramuscular use of CCVs. For administration by the intradermal route CCVs should meet the samerequirements for production and control as required for intramuscular rabies vaccines, including a test potency of at least 2.5 IU per single intramuscular dose. In addition, the immunogenicity and safety of the vaccine in question should be demonstrated inappropriate clinical trials using WHO PEP regimen

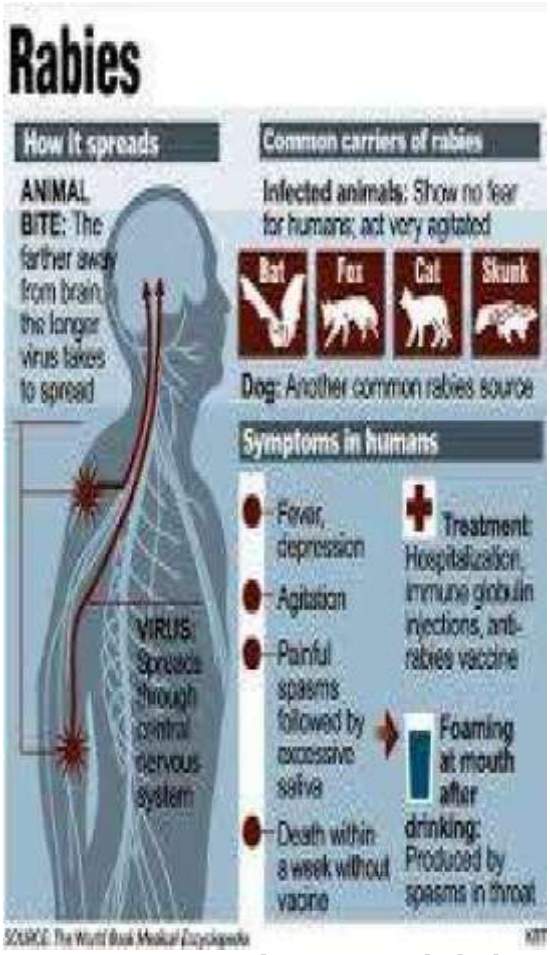

Figure 4: Vaccine administration the body changes

Quality Control

To protect both the purity of the vaccine and the safety of the workers who make and package the vaccine, conditions of laboratory cleanliness are observed throughout the procedure.

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All transfers of virus and media are conducted under sterile conditions, and all instruments used are sterilized in an autoclave (a machine that kills organisms by heat, and which may be as small as a jewel box or as large as an elevator) before and after use. Workers performing the procedures wear protective clothing which includes disposable Tyvek gowns, gloves, booties, hair nets, and face masks. The manufacturing rooms themselves are specially air conditioned so that there is a minimal number of particles.

WHO response

Rabies is included in the neglected tropical disease roadmap of WHO. As a zoonotic disease, it requires close cross-sectoral coordination at the national, regional and global levels. Out of 2051 patients, 1339 patients completed all the 4 doses,347 patients took 3 doses, 264 patients received only 2doses while 101 patients received only 1 dose of ID Anti Rabies vaccine.

Rabies immunoglobulins (RIG) for passive immunization RIG should be administered in all category III exposures and in category II exposures involving immuno deficient individuals.

Drug- Imovax.-

Description

The Imovax® Rabies Vaccine produced by Sanofi Pasteur SA is a sterile, stable, freeze-dried 9 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 13 ultrafiltration and is inactivated by betapropiolactone. One dose of reconstituted vaccine contains less than 100 mg human albumin, less than 150 mcg neomycin sulfate and 20 mcg of phenol red indicator. Betapropiolactone, a residual component of the manufacturing process, is present in less than 50 parts per million.

Clinical pharmacology-

Pre-exposure immunization

1. High titer antibody responses to the Imovax Rabies vaccine made in human diploid cells have been demonstrated in trials conducted in England (1), Germany (2) (3), France (4) and Belgium.
2. Seroconversion was often obtained with only one dose. With two doses one month apart, 8100% of the recipients developed specific antibody, and the geometric mean titer of the groupmean
3. Approximately 10 international units. In the US, Imovax Rabies vaccine resulted in geometric

Contraindications

Do not administer to anyone with a known life-threatening systemic hypersensitivity reaction to 4any component of the vaccine (see WARNINGS, PRECAUTIONS, and

DESCRIPTION

Warning

Do not inject the vaccine into the gluteal area as administration in this area may result in 4 lower neutralizing antibody titers.

The product is provided in a single dose vial. Because the single dose vial contains no preservative, it is not to be used as a multidose vial for intradermal injection. posture and post-exposure immunization, the full 1.0 mL dose should be given intramuscularly.

Serum sickness type reactions have been reported in persons receiving booster doses of rabies 10 vaccine for pre-exposure prophylaxis. The reaction is characterized by onset approximately 11to 21 days post-booster, presents with a generalized urticaria, and may also include arthralgia, arthritis, angioedema, nausea, vomiting, fever, and malaise. None of the reported reactions were life-threatening. This has been reported in up to 7% of persons receiving booster vaccination.

Precaution-

When a person with a history of hypersensitivity must be given rabies vaccine, antihistamines 12may be given. Epinephrine (1:1000) and other appropriate agents should be readily available 13to counteract anaphylactic reactions, and the person should be carefully observed after 14immunization.

Drug interaction-

Corticosteroids, other immunosuppressive agents or treatments, and immunosuppressive illnesses interfere with the development of active immunity and predispose the patient to developing rabies.

Immunosuppressive agents should not be administered during post-exposure therapy.

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Adverse interaction-

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, antihistaminic, and antipyretic agents. local reactions such as pain, erythema, swelling or itching at the injection site were reported in about 25% of recipients of HDCV, and mild systemic reactions such as headache.

Dosage and administration-

Parenteral drug products should be inspected for particulate matter and discoloration prior to 1administration, whenever solution and container permit. The syringe and its package should also be inspected prior to use for evidence of leakage, premature activation of the plunger, or a faulty tip seal. If evidence of such defects is observed, the product should not be used.

How supply-

Imovax Rabies vaccine is supplied in a tamper evident unit dose box with: One vial of freeze-dried vaccine containing a single dose (NDC 49281-248-58). One sterile syringe containing diluent (NDC 49281-249-01). A separate plunger is provided for insertion and use. One sterile disposable needle for reconstitution.

Storage-

The freeze-dried vaccine is stable if stored in the refrigerator between 2°C and 8°C (35°F to46).

II. CONCLUSION

Rabies is a highly contagious, dangerous and potentially fatal virus. It is carried by animals and can be easily contracted by humans as well as other animals. There are numerous symptoms of infection that will appear and there are many diagnostic tests that can confirm the presence of the virus. Treatment is available for rabies in the form of vaccinations. People within rural areas that are heavily populated with stray canines or felines are considered to be at higher risk of contracting rabies.

Result-

The project on review article of anti-rabies vaccine is prepared and submitted successfully.

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