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Original article

Safety and immunogencity of rabies pre- and post-exposure intradermal regimens using Abhayrab, a purified vero cell rabies vaccine (PVRV) produced in India in healthy volunteers: towards greater affordability of rabies prophylaxis

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Background : Rabies is 100% fatal, but is preventable. However, due to the high cost of vaccines and immunoglobulins, as well as their limited availability, many dog-bite victims in the Philippines do not complete the required PEP regimen. This concern may be addressed by the introduction of various new brands of affordable rabies vaccines and biologicals for use with the ID regimen.

Objective : Study the safety and immunogenicity of rabies pre- and post-exposure intradermal regimens using Abhayrab, a purified vero cell rabies vaccine (PVRV) produced by the human biological institute of Ooty India in healthy volunteers.

Methods : In a randomized, single blind, unicentric trial, 149 healthy volunteers (5-50 years in age) were recruited to the study. The subjects were then randomized into two groups. Group 1 (pre-exposure) (73 subjects) followed the standard ID regimen using a dose of 0.1 mL PVRV (Abhayrab) given intradermally on either deltoid on days 0, 7 and 28. Group 2 (post-exposure) (76 Subjects) followed the modified Thai Red Cross ID regimen (2-2-2-0-2) using a dose of 0.1 mL PVRV (Abhayrab) each given intradermally on both deltoids on days 0, 3, 7 and 28. Following administration of vaccine, subjects were observed closely for 30 minutes at the site for adverse reactions. Four ml of blood from each subject was drawn on days 0, 14 and 28 for anti-rabies antibody titres. Safety and immunogenicity were assessed through follow-up of adverse events and anti rabies antibody response, respectively.

Results : Eventually, 120 subjects, 60 in each group, completed the day 28 ID immunization. All the 120 subjects demonstrated seroconversions with antibody titers greater than the WHO recommended cut-off level of 0.5 IU/mL on days 14 and 28. The GMC values for Group 1 were 3.30 IU/ml and 4.37 IU/mL on days 14 and 28, respectively, while those of Group 2 were 3.73 IU/mL and 4.82 IU/ml respectively. These GMC values were within their 95% Cis. Only a few mild adverse events were observed with no incidences of moderate or severe events.

Conclusion : Abhayrab is a safe and immunogenic rabies vaccine when administered intradermally.

Keywords : Human rabies, PVRV, Intradermal, post-exposure treatment, RFFIT

Rabies is one of the major public health concerns in the Philippines. It is estimated that 200 to 300 Filipinos die every year of rabies [Phil. Department of Health - DOH]. Of the estimated 150,000 dog-bite consultations [Phil.DOH] in the entire country each year, at least 60,000 are estimated to be severe bites for which complete post-exposure prophylaxis (PEP) is indicated. A review of single point data from the Research Institute for Tropical Medicine (RITM) Out-Patient Department in the Philippines revealed that of 14,449 consults for dog bites, 98% were prescribed PEP [RITM Public Library of Science 2008].

Since rabies is known to be 100% fatal once symptoms have set in, prevention through PEP is the only proven means to save rabies-infected patients. Considering the gravity of rabies, and that dog vaccination and control measures for dogs in the country are far from ideal, pre-exposure and PEP are of utmost importance. However, it is not surprising to find that many Filipinos bitten by suspected rabid animals do not complete the required PEP regimen. This is mainly due to the high cost of PEP vaccines and immunoglobulins, as well as to their limited availability [1].

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The Philippine Department of Health (DOH), in partnership with other government agencies, particularly the Department of Agriculture, aims to eliminate rabies and declare the Philippines rabies free by 2020. One of DOH's major strategies for rabies elimination is the provision of affordable rabies PEP through the more than 200 animal bite treatment centers distributed all over the country. In order to do this, a reliable supply of affordable vaccines and the use of the economical reduced-dose multi-site intradermal (ID) schedule must be ensured. The two site intradermal regimen of rabies vaccination has been well established in Thailand and in the Philippines since 1984 and 1993, respectively, and it has offered patients significant amounts of savings of up to 80% compared with the application of the standard full-course regimen using the same vaccine [WHO Recommendation on PEP 24 June 2009]. The WHO Expert Committee on Rabies has recommended the use of the ID regimen for rabies PEP since 1991 [2, 3].

As there are now a growing number of rabies vaccine manufacturers able to supply affordable quality rabies vaccines and biologicals, the introduction of various new brands in the Philippine market is expected to benefit the general public through competition, the direct reduction in cost of PEP. However, such new products should be proven first to be safe, immunogenic and efficacious through the conduct of clinical trials.

A vaccine that is considered to be an affordable alternative was recently introduced in the Philippines, Abhayrab, is a purified vero cell rabies vaccine (PVRV) manufactured in India by Human Biologicals Institute. Since its introduction in the Philippines, it has been used in both pre-exposure and post-exposure regimens. The vaccine has previously been proven safe and immunogenic by the intramuscular regimen in India, where it has been used extensively since 2000 [4-6]. In 2006, based on an independently conducted ID safety and immunogenicity study, the Indian government permitted the ID use of four types of rabies vaccines, including Abhayrab, to significantly bring down the cost and ensure the provision of effective rabies PEP, replacing the use of the low quality and dangerous semple vaccine [7].

This randomized controlled clinical trial documented the safety and immunogenicity of PVRV (Abhayrab) when used in both pre-exposure and post exposure rabies prophylaxes by following the Thai Red Cross ID regimen. In this study, we conducted the trial in healthy volunteers in whom safety was evaluated through clinical observations for local and systemic reactions. Immunogenicity was likewise determined through RFFIT assays of rabies neutralizing antibodies.

Materials and methods

Ethical approval and GCP

Approval to conduct the study was obtained from the Ethics Review Committee of the Philippine Department of Health (DOH) prior to the start of the study. The study was conducted following the international guidelines on Good Clinical Practice.

Study location

The trial was conducted at the Reference Laboratory of the Collaborating Centre for Disease Prevention and Control, Department of Health (DOH) Centre for Health Development for Central Luzon, in the city of San Fernando, Pampanga. The determination of the antibody responses of the subjects was done at the Rabies Research Laboratory of the Research Institute for Tropical Medicine, Department of Health, Alabang, Muntinlupa City.

Pampanga is among the 10 Philippine provinces with the most number of animal rabies. The Provincial Health Office (PHO) reported 2,033 cases of animal bites (27.52 per 100,000 populations) in 2008. In 2007, there were five reported cases of human deaths due to rabies in the province.

Sample size

The sample size was computed based on the formula for the estimation of a single proportion with allowance for dropouts.

Inclusion and grouping of volunteer subjects

All subjects were healthy volunteers recruited from the city of San Fernando, Pampanga between September and November 2006. Written informed consent was obtained from all the subjects or from the legal guardians for subjects below 18 years of age. The inclusion/exclusion criteria for both groups were the same. The subjects were all healthy volunteers from 5 to 50 years of age. The subject exclusion criteria were: had previously received anti-rabies vaccination; pregnant or lactating; blood extraction was judged to be difficult; had no permanent address or had plans of traveling within the next three months; unable to comply with the visit schedule of the protocol; enrolled in another clinical trial; with signs of rabies; receiving immunosuppressive therapy or cytotoxic drugs; with prior history of dog/cat bite where the biting animal died or outcome is unknown; have received blood and/or plasma transfusion within the past three months; with known chronic illness; who