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ABSTRACT

The fifth annual Asian Rabies Expert Bureau (AREB) meeting, held in Vietnam, addressed how to increase rabies awareness and to improve rabies prevention and control. Active participation of Ministries of Health and Education was identified as crucial for the success of rabies programs, and World Rabies Day was considered as one of the best opportunities to increase rabies awareness. AREB strongly recommend implementation of pre-exposure prophylaxis for children living in rabies endemic areas. A review of national and international guidelines concerning rabies prophylaxis and their application in the Asian situation showed that some issues require further evaluation or clarification.

1. Introduction

The fifth annual meeting of the Asian Rabies Expert Bureau (AREB) was held in Vietnam, an AREB country that recently took an important step in rabies prevention by replacing the use of mouse brain tissue rabies vaccine with modern cell-culture rabies vaccines (CCVs). In his introductory speech, Prof Nguyen Tran Hien, Chairman of the National Program for Rabies Prevention and Control, highlighted the fact that rabies continues to be a public health problem in Vietnam. Rabies was responsible for 131 deaths (38% of which occurred in children under 15 years of age) in 2007, and half a million people bitten by dogs seek post-exposure prophylaxis (PEP) in rabies prevention centers annually. "*The Vietnamese government is highly committed to rabies prevention and control*", said Prof Hien. "*The Ministries of Health, Agriculture, Education and others work together for rabies control. A rabies surveillance network is functioning and 936 rabies vaccination centers have been established all over the country*", added Prof Dinh Kim Xuyen, Vice-Chairman of the National Human Rabies Control Program.

India stopped producing sheep brain vaccine and switched to CCVs in 2004. In India the human rabies burden is very high, with an estimated 20,000 human rabies deaths occurring annually. The dog is the main reservoir and transmitter of rabies. With a dog to human ratio of 1:36, there is an overall rate of 2 dog bites per second in India [1]. "*There is an urgent need to increase the use of modern vaccines and rabies immunoglobulin*", declared Prof M.K. Sudarshan, President of the Rabies in Asia Foundation. "*Commitment at all levels, in all countries, is necessary*", emphasized Dr Deborah Briggs, Executive Director of the Alliance for Rabies Control, "*and education and awareness remain the top priorities as they can save lives*."

AREB members reviewed the state of the art in rabies prophylaxis and management, and national and international guidelines [2] and their application in the specific Asian situation.

2. Failure of treatments for symptomatic rabies

The report of the recovery from rabies of an American teenager bitten by a rabid bat raised hope for a cure for symptomatic rabies. The patient, who received neither rabies vaccine nor rabies immunoglobulin, was treated by coma induction and administration of ketamine and antivirals (Milwaukee protocol) [3]. An attempt by Prof Thiravat Hemachudha (Chulalongkorn University Hospital, Bangkok, Thailand) and colleagues to treat a patient with furious rabies with such a protocol was unsuccessful [4]; and none of the 12 other rabies patients treated around the world with the Milwaukee protocol have survived [5]. Further studies on rabies virus neuroinvasiveness and host response are required. Prof Thiravat reported studies in rabid dogs showing that, while the blood–brain barrier remains intact, immune responses are transient and do not fully develop in the brain [6].

Since there is still essentially no treatment for clinical rabies, AREB members consider that resources would be best spent on ensuring administration of proper prophylaxis prior to the development of disease.

3. Post-exposure prophylaxis

Following exposure to a suspected rabid animal, prevention of human rabies consists of prompt and deep wound cleansing followed by the administration of modern CCV and, in case of severe exposure (category III), infiltration of the wound with rabies immunoglobulin (RIG) [2].

3.1. Modern cell-culture rabies vaccines

The list of World Health Organization (WHO)-prequalified modern CCVs for pre- and post-exposure prophylaxis includes lyophilized vaccines prepared on human diploid cells (HDCV), Vero cells (PVRV), chick embryo cells (PCECV), and duck embryo cells

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Table 1
WHO-prequalified cell-culture rabies vaccines.

Vaccine	Commercial name	Producer	Volume per IM dose	Approved for ID use
Purified chick embryo cell vaccine (PCECV)	Rabipur™, Rabavert™	Novartis Vaccines	1.0 ml	Yes
Purified duck embryo cell vaccine (PDECV)	Vaxirab™	Zydus Cadila	1.0 ml	No
Human diploid cell vaccine (HDCV)	Imovax Rabies™	Sanofi Pasteur	1.0 ml	Yes
Purified vero cell vaccine (PVRV)	Verorab™	Sanofi Pasteur	0.5 ml	Yes

(PDECV) (Table 1). These vaccines are intended for intramuscular (IM) use and are packaged as a single IM dose of either 1.0 or 0.5 ml, depending on the manufacturer. They meet the WHO requirements for production and control, including a potency test of at least 2.5 IU per single IM dose.

3.2. ID regimens for PEP

Intradermal (ID) rabies vaccination regimens reduce the total volume of vaccine required for PEP. ID regimens are currently being utilized in several Asian countries as an alternative to the reference standard intramuscular (IM) administration for PEP. Rabies ID vaccination regimens for both pre-exposure (PrEP) and PEP have been recommended by WHO since 1991, and currently two PEP ID regimens are approved for use in persons exposed to confirmed or suspect rabid animals [7,8]: the 2-site updated Thai Red Cross (TRC) regimen and the 8-site (Oxford) regimen.

The 2-site TRC regimen consists of a total of eight ID doses given over a series of four visits. The TRC regimen is currently approved for use with two rabies vaccines (PVRV produced by sanofi pasteur and PCECV produced by Novartis Vaccines) that have been proven to be efficacious when this regimen was administered to patients exposed to proven rabid animals [8].

The 8-site PEP regimen consists of 14 ID doses administered during a series of four visits. It is currently approved for use with two vaccines that are recognized to be safe and efficacious when administered according to this regimen, HDCV produced by sanofi pasteur and PCECV produced by Novartis Vaccines [8].

Recently, a new 4-site ID PEP regimen, with immunogenicity equivalent to the currently approved IM and ID regimens, has been proposed. This new 4-site regimen requires fewer clinic visits and is more convenient than the 8-site ID method. It can be used economically with vaccines formulated in 1.0 or 0.5 ml ampoules, and its margin of safety is assumed to be wider than the 2-site ID regimen [9]. AREB recommends that the 4-site regimen be evaluated by WHO and eventually included into the WHO guidelines.

3.3. Efficacy of PEP using pERIG in patients exposed to laboratory confirmed rabid animals

Data presented by Dr Beatriz Quiambao (Research Institute for Tropical Medicine, Muntinlupa City, Philippines) confirmed the efficacy of the recommended prophylaxis (wound cleaning, RIG and vaccination) for severe rabies exposure in unvaccinated individuals. Of 193 patients with proven category III rabid exposure who received cell-culture rabies vaccine (ID or IM) and purified equine rabies immunoglobulin (pERIG, sanofi pasteur) at the Research Institute for Tropical Medicine (Muntinlupa, Philippines), 192 were alive and healthy one year after the exposure occurred. One rabies death occurred in a patient who was referred to the rabies prevention centre after a delay of 2 days. The patient received pERIG and a first ID dose of vaccine on day 0 (2 days after exposure) followed by two additional (IM) doses on days 3 and 7. This single rabies fatality was in fact a treatment failure due to the late referral and demonstrates the importance of ensuring immediate and complete application of recommended PEP protocols. This underlines the importance of sustained education and training in rabies management.

3.4. PEP in HIV-infected patients

Published data indicates that HIV-infected patients with low CD4+ T-lymphocyte levels (<300–400 ml^{-1}) have a poor neutralizing antibody response to pre- and post-exposure vaccination [10]. In light of this data WHO specifies that for "*immunocompromised individuals, including patients with HIV/AIDS, comprehensive wound management and local infiltration with RIG, in combination with a complete intramuscular CCV series, are of utmost importance for the successful prevention of rabies. In these situations, the virus neutralizing antibody (VNA) response should be determined 2–4 weeks following vaccination to assess the possible need for an additional dose of the vaccine*" [2]. *Immunocompromised patients with category II exposures should receive rabies immunoglobulin in addition to a full post-exposure vaccination series as listed above* [8].

Prof Terapong Tantawichien (Chulalongkorn University, Bangkok) presented the potential strategies that have been proposed and/or tested to overcome the poor immunological response of HIV-infected patients to rabies vaccines. The strategies proposed for HIV-infected patients with low CD4+ lymphocyte levels who have unacceptable VNA responses to PEP include using a 4-site ID rabies vaccination, administering frequent booster injections, using adjuvanted vaccines for IM administration, increasing the dose of vaccine administered either IM or ID, or using sequential doses of immunoglobulin.

Considering that HIV infection is highly prevalent in many countries where canine rabies is also endemic, AREB members recommend that data from recent studies on the immune response to rabies vaccines in HIV patients be further evaluated by WHO.

3.5. Rabies immunoglobulin for passive immunization

Rabies immunoglobulin should be administered for all category III exposures. According to the WHO position paper published in December 2007, "*The dose for HRIG [human rabies immunoglobulin] is 20 IU/kg body weight, and for ERIG and F(ab′)2* [pERIG] *products 40 IU/kg body weight. All of the RIG, or as much as anatomically possible, should be administered into or around the wound site(s). Any remaining RIG should be injected IM at a site distant from the site of vaccine administration*" [2].

Considering cumulative data and their experience regarding administration of RIG, the AREB members discussed whether the current WHO recommendation of dose calculated by body weight is still valid and whether the recommendation to administer additional RIG (that cannot be injected into the wound area) into the gluteal muscle is scientifically reasonable. AREB members suggest that the volume of RIG required for PEP should rather be calculated according to the size and the number of the wounds, providing that a reproducible scale can be defined. Therefore, AREB respectfully recommends that the current recommendation for calculation of RIG dosage be reviewed by WHO.

4. Pre-exposure prophylaxis

WHO recommends pre-exposure vaccination using any of the modern CCVs for persons at increased risk of exposure to rabies