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Procedia in Vaccinology 2 (2010) 147–150

Procedia in Vaccinology

www.elsevier.com/locate/ procedia

Ninth Global Vaccine Research Forum and Parallel Satellite Symposia
Bamako, Mali, 6-9 December 2009

Measles Aerosol Vaccine Project

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Abstract

Aerosol delivery of measles vaccine to the respiratory mucosa, mimicking the natural route of transmission for measles virus, is the most promising non-injectable method of measles vaccination studied so far. A phase II/III study is underway in India to confirm that its efficacy is equivalent to that of existing routes of administration. Studies suggest aerosolized measles vaccine appears to be equally or more immunogenic than subcutaneous vaccine in children 9 months and older. Aerosol delivery devices are available or being developed, and could be used by lay people with limited training, and would avoid issues of injection safety. Measles vaccine is not licensed for respiratory administration. Administration of the current measles vaccine via the respiratory route is being comprehensively studied to achieve licensure for international use under the auspices of the WHO's Measles Aerosol Project. The most suitable aerosol administration device for use in low resource environments is being evaluated in such studies.

Keywords: Aerosol; live attenuated measles vaccine; mucosal delivery; safety

1. Introduction

The current route of administering measles vaccine, via subcutaneous injection with a syringe and needle, while very effective, is challenging because it requires trained medical personnel and may be a source of injection hazards due to the difficulty in disposing used syringes and needles and the heightened potential for reuse with resultant spread of blood-borne pathogens (11-15). Auto-disable syringes decrease the risks of reuse, but increase the cost of vaccination, and contribute to many countries not being able to afford to fully vaccinate their children (15). Respiratory administration of live measles vaccine closely mimics the natural route of measles infection. It is already established that current measles vaccines are at least as effective in inducing antibody production when delivered by nebulisation as when delivered parenterally (19, 21). Maternal antibody interference might be avoided and mucosal immunity might be enhanced (20 -

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[1] The WHO Measles Aerosol Product Development Group (PDG) is an expert clinical and scientific advisory body to WHO established to advise the Initiative for Vaccine Research independently and with scientific rigour regarding the development plan of the measles aerosol vaccine. Members of the PDG (current): Chairperson: Mr Michel Greco. Members: Prof Andrew Hall, Dr Rita Helfand, Dr Nick Andrews, Dr Odile Leroy, Dr Jorge Fernandez de Castro, Mrs Teeranart Jivapaisarnpong and, Prof Nirmal Ganguly (Ad-hoc member)

1877-282X © 2010 Published by Elsevier Ltd.
doi:10.1016/j.provac.2010.07.007

22). Aerosol measles vaccine appears to be equally immunogenic as subcutaneous vaccine when administered to children aged 10 months and older (9, 10, 23). No increase in adverse side effects of respiratory administration has been noted compared to current injectable vaccine. In 2002 the World Health Organization (WHO), the Centers for Diseases Control and Prevention (CDC) and the American Red Cross (ARC) established the Measles Aerosol Project (MAP) with the purpose of undertaking the necessary non-clinical and clinical trials required to achieve the licensure of a product (i.e., a device and a vaccine) for aerosol administration. WHO has since been leading the Measles Aerosol Vaccine Project funded by the Bill and Melinda Gates Foundation that has made substantial step-wise progress towards the goal of achieving licensure of an aerosol measles vaccine product.

2. Preclinical studies

The "classic Mexican device" (CMD) described elsewhere (20, 21) is an aerosol delivery device used in early studies of aerosol measles vaccination in Mexico (21, 23). It was studied to determine the output of particles and mean mass diameters (MMD) of these particles to create a reference device of nebuliser output for performance characteristics of devices that could be considered for use in the proposed clinical trials. Current technology has produced many aerosol generating devices with better properties than the original Mexican device. Although studies using the CMD reported good immunogenicity results, the CMD is heavy, cumbersome, and noisy, requires electricity, and is not ideal for use in the field. New nebulisers are compact units which are quiet; driven by AC, solar power, batteries, or a cranking system; and some have patient interfaces that can eliminate any risk of contamination to the device or user. The studies on the CMD showed that more than 50% of the particles in the output stream from the nebuliser at the settings used in the Mexican trials (47 psi and a flow of approximately 10 L/min) had a diameter of ≤5 micrometers (1, 2). Several modern devices (jet nebulisers and vibrating element nebulisers) were evaluated for selection for clinical trials. WHO invited almost two dozen aerosol device makers globally to participate in a detailed comparison of devices to identify three that would be suitable for further evaluation in Phase I trials in India. Each of these devices was assessed with respect to the character of the aerosol (i.e., aerosol output and aerosol size that they generate, vaccine potency retained in aerosol outputs from nebulisers by each device (5), as well as criteria that addressed practicality/field usability (size, portability, ease of use, power requirements, robustness, risk of cross infection), and cost per dose delivered. Subsequently, WHO set the standard procedure for the performance evaluation of the devices, the manufacturers carried out the characterization, and a global measles specialized laboratory carried out the vaccine potency retention (5). A panel of experts was convened to conduct a review of the available information including: device performance characteristics; vaccine potency retention during nebulisation; results from the Phase I trial in India (safety and immunogenicity); and review of device field usability. One device was chosen for the pivotal trial that was licensed in the country of manufacture. It matched the performance characteristics of the CMD for output flows and particle size, satisfactorily retained virus potency during nebulisation, avoided risk of contamination and also met WHO criteria for availability and practicality.

With the aim of establishing a standard operating procedure (SOP) for measles plaque reduction neutralization test (PRNT), that could be used internationally (to assess new measles vaccines or new routes of administration in the field), a standardized laboratory protocol for measles PRNT was established and validated for use in clinical trials of aerosolized measles vaccines (7). A study to evaluate measles PRNT and measles-specific IgG ELISA for use in the WHO measles aerosol vaccination project was conducted (8).

A single dose animal safety and efficacy study in 45 Cynomolgus monkeys (Macaque fascicularis), which are susceptible to measles infection, was carried out with measles aerosol vaccines (Edmonston Zagreb strain). The animals were treated with immunosuppressants to give a "worst case" scenario. The immunogenicity and protective efficacy of aerosol vaccination using devices similar to those previously used in humans were comparable to those in animals vaccinated by injection.. The immunogenicity and protective capacity to a challenge dose of measles vaccine administered by jet nebuliser or by injection were comparable. The level of protection produced to measles virus challenge was similar in all immunized groups. No evidence for a safety hazard associated with the route of vaccination was detected. (3). A GLP toxicology study in Cynomolgus monkeys (Macaque fascicularis) was performed to evaluate the potential toxicity of measles vaccine (Edmonston-Zagreb strain) following two doses by inhalation. Two nebulisers were used, one which supplies predominantly low droplet size and one which supplies predominantly high droplet size particles. Forty eight monkeys were included in the study and divided in 4 groups, each with 6 animals of each sex. The animals were subjected to vaccine or placebo (excipients) at approximately 5 times the human daily dose. All animals

received the first dose of vaccine or placebo (excipients) on day 0. At day 7, when measles viremia was expected to be at a peak, half of the animals/sex/group were sacrificed for analysis of toxicity. The remaining animals received a second dose on day 21, and were sacrificed on day 42. The results of the study showed the vaccine was well tolerated and did not result in any evidence of local or systemic toxicity when given by inhalation with any of the two nebulizers. A positive immune response was detected in all vaccine treated animals (4).

3. Clinical studies

During a Phase I trial in India, the measles aerosol vaccine was administered to healthy measles immune volunteers 1-35 years of age using three different devices with comparable performance characteristics to the CMD in three different sites in India. In total we followed up 145 volunteers. The measles aerosol vaccine was safe, well tolerated and immunogenic in three different sites in India (WHO unpublished data). In 2009, WHO initiated a phase II/III pivotal trial of the measles vaccine in healthy infants from 9-11.9 months of age who were eligible for their first measles vaccination. This study used the selected device as previously described. The study design is that of a randomized, open-label, active-control, parallel group, non-inferiority trial. The same dose (NLT 1000 CCID50) will be administered by aerosol or by subcutaneous injection (currently licensed route of inoculation). A total of 2000 infants will be enrolled in the study, randomized 1:1 to the two arms (aerosol 1000; subcutaneous 1000). A subset of 100 subjects per arm will be followed-up for 364 days for any serious or unexpected adverse events. Blood samples for assessment of the post vaccination levels of anti-measles antibody will be taken at baseline and 91 days post-vaccination. Subjects in the sub-set will also have blood samples taken at 28 days and 364 days post vaccination.

4. Discussion

Measles – a vaccine preventable disease – remains a major cause of morbidity and mortality in some countries. Alternative routes of vaccine administration, like aerosol delivery, using existing measles vaccine, may enhance control of the disease and reduce logistic and safety concerns.

A number of theoretical safety concerns with this route of administration have been identified and are being considered, such as risk in HIV-seropositive and immunosuppressed individuals, adverse events in the respiratory tract and the central nervous system and, risk of environmental contamination. GLP animal safety and immunogenicity and toxicology studies results confirmed good immune responses and no evidence of local or systemic toxic effects. Preliminary results form the non clinical and clinical studies suggest a very good immunogenicity and safety profile.

The assumptions are that the aerosol devices will use currently licensed Edmonston-Zagreb measles vaccine, and target children between 9 and 59 months of age for routine vaccination, and nine months up to 18 years of age for mass campaigns. The objective is to complete clinical testing by 2010. Licensure of a measles aerosol vaccine will be a critical step towards making the promise of aerosol delivery of other vaccines a reality (16, 17, 18, 24).

5. Acknowledgments

WHO/IVR coordinates the Measles Aerosol Project (MAP). The Centers for Disease Control and Prevention (CDC), USA and, the American Red Cross (ARC) are partners to the project. The MAP has received financial support from the Bill and Melinda Gates Foundation.

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