Reactogenicity and immunogicity of a new measles-mumps-rubella vaccine containing RIT 4385 mumps virus strain in healthy Turkish children

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A total of 44 children aged between 15-18 months were randomly vaccinated either with a new measles-mumps-rubella (MMR) vaccine (Priorix®, SmithKline Beecham) or a commercially available MMR vaccine (MMR-II®, Merck) to compare the reactogenicity and immunogenicity. No local symptoms or fever was reported. Seroconversion rates of the study vaccine were 100, 95 and 100 percent for measles, mumps and rubella, respectively. The seroconversion rates for the control vaccine were 100, 94.7 and 95.5 percent, respectively. The geometric mean titers (GMT's) for the study and control groups were 1695, 95, 58; and 2198, 1183 and 47; respectively.

In conclusion, the new MMR vaccine containing RIT 4385 mumps strain derived from the Jeryl Lynn strain was shown to be immunogenic and safe in healthy Turkish children. Further post-marketing surveillance should be conducted.

Key words: measles, mumps, rubella, immunization, Jeryl Lynn strain.

Vaccination is the most effective method for prevention of mumps[1]. The Jeryl Lynn and Urabe Am 9 mumps virus strains have been most commonly used for the production of the live attenuated mumps vaccine. Both have been shown to be immunogenic and to protect against mumps infection, although the Jerly Lynn strain has seemed less immunogenic[2,3]. Cases of vaccine-associated meningitis have been reported, especially with the Urabe strain[4,5].

A new mumps strain, indistinguishable from the Jeryl Lynn strain in terms of post-vaccinal meningitis, was combined with Schwarz measles and rubella 27/3 strains in a new measles-mumps-rubella (MMR) vaccination (Priorix®, SmithKline Beecham). The presented study was conducted to compare the reactogenicity and immunogenicity of the new measles-mumps-rubella vaccine with the commercially available MMR-II (Merck) vaccine in healthy Turkish children.

Material and Methods

This single blind, randomized, controlled study was conducted between 1 December 1993-19 January 1994 at the Etimesgut Health Center. A total of 44 healthy children between 15-18 months of age were enrolled and randomly assigned to one of the two vaccine groups. Written informed consent was obtained from all parents. Children with any of the following were excluded from the study: clear history of clinical measles infection or vaccination against measles, significant exposure to mumps within the previous four weeks, administration of immunoglobulin during the last three months, history of allergic reactions to any previous vaccination, neomycin and/or egg allergy, history of seizure or encephalopathy, episode of acute febrile illness at the time of vaccination, any continued chronic drug therapy, administration of other parenteral vaccines during the study or within the previous four weeks, or simultaneous participation in any other study.

Monodose vials of vaccines were coded according to a randomization list. Children received either the new MMR vaccine [SKB, Lot MJR111D42 containing per dose a mean titer of $10^{3.8}$ 50% cell-culture infectious dose

($CCID_{50}$) of Schwarz measles strain, $10^{4.4}$ $CCID_{50}$ of RIT 4385 mumps strain and $10^{4.1}$ $CCID_{50}$ of RA 27/3 rubella strain) as study vaccine or MMRI-II (Merck Sharp Dohme Lot 80391OU containing per dose $\geq 10^3$ $CCID_{50}$ of Edmonston Enders measles strain, $\geq 10^{3.7}$ $CCID_{50}$ of Jeryl Lynn mumps strain and $\geq 10^{3.0}$ $CCID_{50}$ of RA 27/3 rubella strain] as the control vaccine. Each vaccine was reconstituted with an individual ampule of water for injection, and a 0.5 ml dose was administered subcutaneously in the left upper arm.

This study was conducted according to the Declaration of Helsinki and Good Clinical Practice. On day 0 of the study all previously screened subjects underwent a complete physical examination, including palpation of the parotid gland and recording of rectal temperature. A prevaccination blood sample was collected and a dose of vaccine injected. At 15 and 30 minutes after injection, swelling or pain at the injection site, or any other symptom, was recorded on a diary card.

On days 7, 14, 21 and 28 postvaccination, a nurse visited the child at home to evaluate the presence of any adverse reactions, especially parotid gland swelling. On day 42 a complete physical examination was performed and a post-vaccination blood sample was collected.

Separated pre- and post-vaccination serum samples were stored at -20 °C until they were titrated at SmithKline Beecham Biological Laboratory in Belgium. Antibody titers against measles, mumps and rubella were determined by commercial kits: Enzygost anti-measles virus/IgG (Behringwerke AG, Marburg, Germany) and expressed as mIU/ml; Enzygost anti-parotitis virus/IgG (Behring) and expressed as U/ml; and Enzygost anti-rubella virus/IgG (Behring) and expressed as U/ml, respectively.

Serconversion was defined as the appearance of a detectable level of antibodies in the serum of subjects who were seronegative before vaccination: for measles < 180 to ≥ 180 mIU/ml, mumps < 230 to ≥ 230 U/ml and for rubella < 4 to ≥ 4 IU/ml[6,7] A booster response was defined as a four-fold or greater increase of a previously positive titer. Subjects with parotid/salivary gland enlargement were examined as soon as possible by the investigator.

Statistical analyses were performed by SAS computer programs. Geometric mean titers (GMT) of antibodies against mumps, measles and rubella and their 95% confidence intervals were calculated in all pre- and post-vaccination sera. GMTs were calculated by taking the anti-log of the mean of the log transformation of non-zero titers. The seroconversion rate in initially seronegative subjects and the percentage of initially seropositive subjects demonstrating a booster response against measles, mumps and rubella on day 42 after vaccination were determined. The seroconversion rates in the two groups were compared using chi-square test.

Results

All subjects were included in the analysis of reactogenicity and immunogenicity. Mean age of subjects was 16.3 ± 0.84 months in the study group and 16.2 ± 0.81 months in the control group. The male to female ratio was 1:0.69 in both groups.

Safety and Reactogenicity

Neither fever nor local symptoms were reported in any case. Parotid gland swelling was reported in one case in the study group on the first day postvaccination. A viral study was not performed but the swelling occurred following exposure to natural mumps infection in the sibling.

There were no unsolicited signs or symptoms reported during the 42 day follow-up period nor any serious adverse events.

Immunogenicity

All subjects were included in the analysis. The seroconversion rate and the GMT values of each group are shown in Table I.

Table I. Serconversion* Rates and GMTs of the Two Vaccine Groups for Measles, Mumps and Rubella

Antibody	Priorix group	MMR-II group
Anti-measles		
Sreconversion rate (%)	100	100
$GMT_{[95\% CI]}$	$1695_{[1163-2468]}$	$2198_{[1532-3153]}$
Anti-mumps		
Seroconversion rate (%)	95	94.7
$GMT_{[95\% CI]}$	$1359_{[934-1978]}$	$1183_{[786-1781]}$
Anti-rubella		
Seroconversion rate (%)	100	95.5
$GMT_{[95\% CI]}$	$58_{[42-80]}$	$47_{[33-69]}$

* Seroconversion was defined as either appearance of antibodies (i.e.titer ≥ cut-off) or in prevaccination seropositive subjects as a four-fold or greater rise in the prevaccination titer. $p < 0.05$ for seroconversion rate of all three antibodies.

GMT: geometric mean titer; 95% CI: 95% confidence interval.

Discussion

This study indicates that Priorix®, containing the new RIT 4385 mumps strain, is safe and immunogenic. No difference could be found between the groups. In eight other recent single blind, randomized, controlled studies conducted in Chile, the Czech Republic, Germany, Lithuania, Switzerland and Taiwan, where 4.702 children were vaccinated either with Priorix or MMR-II, results were similar to those of our study[6,7]. In those studies, local symptoms were reported less frequently after Priorix as compared to after MMR-II. General symptoms and all other events were similar in both groups. The GMTs for all three antibodies were higher for MMR-II, but the clinical significance was not determined. Aseptic meningitis is a rare complication, and was not detected in any of the vaccinees.

The new SmithKline Beecham Biologicals MMR vaccine Priorix® was well tolerated; no local reactions, fever or serious adverse event was reported. The seroconversion rates were similar. Although the study sample was small, still this study points to the safe alternative use of the new vaccine in Turkish children. Further safety studies should be conducted to determine rare events post-marketing.

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