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The Safety and Immunogenicity of a Trivalent, Live, Attenuated MMR Vaccine, Priorix™

Seung-In Ahn, M.D., Min-Kook Chung, M.D., Jung-Suk Yoo, M.D.
Hye-Jeon Chung, M.D.*, Jae-Kyun Hur, M.D.†, Young-Kyu Shin, M.D.‡
Jin-Keun Chang, M.D., and Sung-Ho Cha, M.D.*

Department of Pediatrics, Han-il General Hospital,
Department of Pediatrics, College of Medicine, Kyunghee University,*
St. Paul's Hospital, Catholic Medical College†, Seoul,
Ansan Hospital, College of Medicine, Korea University‡, Ansan, Korea

Purpose : This multi-center, open-label, clinical study was designed to evaluate the safety and immunogenicity of a trivalent, live, attenuated measles-mumps-rubella(MMR) vaccine, Priorix™ in Korean children.

Methods : From July 2002 to February 2003, a total of 252 children, aged 12-15 months or 4-6 years, received Priorix™ at four centers : Han-il General Hospital, Kyunghee University Hospital, St. Paul's Hospital at the Catholic Medical College in Seoul, and Korea University Hospital in Ansan, Korea. Only subjects who fully met protocol requirements were included in the final analysis. The occurrence of local and systemic adverse events after vaccination was evaluated from diary cards and physical examination for 42 days after vaccination. Serum antibody levels were measured prior to and 42 days post-vaccination using IgG ELISA assays at GlaxoSmithKline Biologicals (GSK) in Belgium.

Results : Of the 252 enrolled subjects, a total of 199 were included in the safety analysis, including 103 from the 12-15 month age group and 96 from the 4-6 year age group. The occurrence of local reactions related to the study drug was 10.1 percent, and the occurrence of systemic reactions was 6.5 percent. There were no episodes of aseptic meningitis or febrile convulsions, nor any other serious adverse reaction. In immunogenicity analysis, the seroconversion rate of previously seronegative subjects was 99 percent for measles, 93 percent for mumps and 100 percent for rubella. Both age groups showed similar seroconversion rates. The geometric mean titers achieved, 42 days post-vaccination, were : For measles, in the age group 12-15 months, 3,838.6 mIU/mL [3,304.47, 4,458.91]; in the age group 4-6 years, 1,886.2 mIU/mL [825.83, 4,308.26]. For mumps, in the age group 12-15 months, 956.3 U/mL [821.81, 1,112.71]; in the age group 4-6 years, 2,473.8 U/mL [1,518.94, 4,028.92]. For rubella, in the age group 12-15 months, 94.5 IU/mL [79.56, 112.28]; in the age group 4-6 years, 168.9 IU/mL [108.96, 261.90].

Conclusion : When Korean children in the age groups of 12-15 months or 4-6 years were vaccinated with GlaxoSmithKline Biologicals' live attenuated MMR vaccine (Priorix™), adverse events were limited to those generally expected with any live vaccine. Priorix™ demonstrated excellent immunogenicity in this population. **(Korean J Pediatr 2005;48:960-968)**

Key Words : Measles-mumps-rubella vaccine, Immunogenicity, Adverse effects

Introduction

Measles, mumps, and rubella are common infant infections and millions of infants may die or suffer serious complications due to these diseases without proper vaccination[1].

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책임저자 : 차성호, 경희대학교 의과대학 소아과학교실
Correspondence : Sung-ho Cha, M.D.
Tel : 02)958-8303 Fax : 02)967-1382
E-mail : sunghocha@khu.ac.kr

Measles ranks 5th as a cause of death of infants of 5 years or less. In regions where vaccination against it is unavailable, morbidity and mortality are very high[2]. In fact, according to the WHO, 777,000 or 44% of the global total of 1.7 million vaccine-preventable deaths annually are caused by measles[3, 4]. Encephalitis is a complication observed in 0.1% of measles patients, of whom 20% may suffer permanent brain damage[5].

In the US, mumps was previously common among children and adolescents, but since vaccination has become widely adopted, half or more of its victims are now young adults who were not vaccinated. Mumps causes orchitis and rarely, sterility, in about 20% of its victims. Abacterial cerebral meningitis is also a common complication; this disease is usually self-limited, but may cause permanent loss of hearing[6].

Rubella may cause no or very mild symptoms in normal conditions, but in the early stage of pregnancy it may affect the fetus causing the congenital rubella syndrome which leaves serious complications such as cataract, congenital heart disease, lowering of intelligence, and hearing loss[7].

In the 1960s, live attenuated vaccines against measles, mumps, and rubella were separately introduced, resulting in sharp decreases in these viral infections. Nevertheless, sporadic occurrences could not be prevented. In the 1970s, combined live attenuated vaccines against these 3 viruses were introduced, making vaccination more convenient and widening the coverage of vacccination[8]. Until 1992, M-M-R II from Merck & Co. and Pluserix from GlaxoSmithKline were widely used as MMR vaccines, but after a report of increased risk of abacterial cerebral meningitis following vaccination with Pluserix, it gradually disappeared from the market. In 1997, GlaxoSmithKline developed Priorix^{TM}, a new MMR vaccine[8-11]. No assessment of this newly introduced vaccine is presently available in Korea. Thus, the authors of this paper studied the clinical experience after vaccination with Priorix^{TM} to assess its safety and immunogenicity.

Materials and Methods

1. Subjects

From 27 July 2002 to 25 February 2003, a total of 252 healthy male or female children aged 12-15 months or 4-6 years who visited the 4 centers of Han-il General Hospital, Kyunghee University Hospital, St. Paul's Hospital Catholic Medical College in Seoul, and Korea University Hospital in Ansan were selected for this study. Those who had been exposed to measles, mumps, or rubella within 30 days before the initiation of this study; or had experienced anamnesis, or adverse events after other vaccinations, or allergy or allergy aggravation after vaccination; or were suspected of or diagnosed with tuberculosis; or had a history of convulsions (febrile or epileptic) or other central nervous diseases; or were suspected of or confirmed as having an immunosuppressive or immunodeficient state due to HIV infection or other causes; or who subsequently received immunoglobulin or blood agents within 3 months after the vaccination or during the study were excluded. In addition, those who did not have data necessary for safety evaluation; or did not meet the age criteria; or did not meet the selection criteria at the time of enrollment; or violated the protocol (eg. administration of prohibited drugs or vaccines); or withdrew their consent for any reasons except adverse events; or were not available for follow-up; or moved to other regions; or were not available for measles, mumps, and rubella serological analysis were excluded from the final assessment. As a result, among the 252 enrolled subjects, a total of 199 including 103 aged 12-15 months and 96 aged 4-6 years were selected for the evaluation.

2. Study methods

Priorix^{TM}, the study drug, includes live attenuated measles virus (Schwarz measles strain, $10^{3.0}$ $TCID_{50}$ or more), live attenuated mumps virus (RIT 4385 mumps strain, $10^{3.7}$ $TCID_{50}$ or more) and live attenuated rubella virus (RA 27/3 rubella strain, $10^{3.0}$ $TCID_{50}$ or more). This vaccine was injected subcutaneously on the upper arm after dilution with separate water for injection ampoules. Vaccinated subjects were observed for at least 30 minutes in the hospital to allow for prompt treatment of rare but possible anaphylactic reactions. Blood samples were collected from all subjects before and 42±7 days after the vaccination and stored at -20℃ until analysis.

3. Safety assessment methods

Symptom logs were given to the parents for recording of body temperature, local adverse events such as pain, redness, or swelling of the injection site, and general adverse events such as fever, drowsiness, irritability, or loss of appetite for 4 days after the vaccination. Furthermore,

the subjects were monitored for fever, skin rash, swelling in the parotid or salivary gland, and symptoms of meningitis (vomiting, neck stiffness, or photophobia) for 42 days after the vaccination. If any of these were observed, related information was recorded in the symptom log. When febrile convulsions or neurological symptoms or signs of meningitis were observed, neurological examination was conducted. Swelling of the injection site was recorded in millimeters, with measurements of 20 mm or larger defined as severe. Body temperature was measured in Centigrade, with measurements of 39.0℃ or higher defined as severe. Moreover, adverse events interrupting normal daily activities were defined as severe. All adverse events observed within 42 days after the vaccination were recorded in the CRFs regardless of their severity or relationship with the vaccine. In addition, the investigator explained each adverse event and judged its relationship with the study drug.

4. Efficacy assessment methods

The blood samples collected before and 42±7 days after the vaccination were stored at -20℃ until analysis. The levels of serum antibody against measles, mumps, and rubella were assessed using IgG ELISA assays at GlaxoSmithKline Biologicals in Belgium. Antibody levels of 150 mIU/mL or higher in the case of the measles, 231 U/mL or higher in the case of the mumps, and 4 IU/mL or higher in the case of the rubella were defined as positive. Seroconversion was defined as the detection of antibodies above these cutoffs in previously seronegative samples. Geometric mean antibody levels were calculated for all seropositive samples.

5. Statistical analysis methods

The major safety variable of this study was the rate of known or unexpected local or systemic reactions observed after the vaccination. 95% confidence intervals for each rate were calculated. In the efficacy assessment, seroconversion rates against measles, mumps, and rubella calculated 42 days after the vaccination and geometric mean antibody titers and their 95% confidence intervals were presented by age.

Results

1. Subject distribution

A total of 252 subjects were enrolled in this clinical study and 199 of them, including 103 aged 12-15 months, and 96 aged 4-6 years, were selected for the final assessment (Table 1).

2. Safety assessment

1) Anaphylaxis after the vaccination

No anaphylactic episodes occurred among any subjects during observation in the hospital for at least 30 minutes after the vaccination.

2) Injection site reactions reported within 4 days after the vaccination

Reviewed by age, 8 subjects (7.8%) from the 12-15 months group reported 10 cases of local reactions including 8 (7.8%) cases of redness and 2 (1.9%) cases of swelling. In addition, 12 subjects (12.5%) from the 4-6 years group reported 17 cases of local reactions including 3 cases (3.1%) of pain, 3 cases (3.1%) of swelling, and 11 cases (11.5%) of redness. None of these reactions was severe except one case of redness that interrupted normal daily activities and persisted for 4 days. In general, a total of 20 (10.1%) out of 199 subjects reported 27 cases of local reactions including 3 cases (1.5%) of pain, 19 cases (9.6%) of redness, and 5 cases (2.5%) of swelling. One subject in the 4-6 years group reported severe redness, but it resolved within the 4 days of observation (Table 2).

3) Systemic reactions reported within 4 days after the vaccination

Reviewed by age, 27 subjects (26.2%) from the 12-15

Table 1. Demographic Data of Subjects

	12-15 months group n=103 (51.8%)	4-6 years group n=96 (48.2%)	Total N=199
Sex			
Male (%)	58 (56.3)	56 (58.3)	114 (57.3)
Female (%)	45 (43.7)	40 (41.7)	85 (42.7)
Age			
12 months (%)	50 (48.5)	0	50 (25.1)
13 months (%)	33 (32.0)	0	33 (16.6)
14 months (%)	11 (10.7)	0	11 (5.5)
15 months (%)	9 (8.7)	0	9 (4.5)
4 years (%)	0	71 (74.0)	71 (35.7)
5 years (%)	0	25 (26.0)	25 (12.6)
6 years (%)	0	0	0
Mean±SD (months)	12.8±1.0	55.0±6.4	33.1±21.6
Height (cm) (Mean±SD)	77.9±4.0	110.0±11.3	93.4±18.1
Weight (kg) (Mean±SD)	10.5±1.2	18.1±2.5	14.2±4.3
BMI* (Mean±SD)	17.4±2.1	15.2±2.5	16.3±2.5

*BMI = Weight (kg)/Height $(m)^2$

months group reported 52 cases of systemic reactions including 9 cases (8.7%) of fever, 11 cases (10.7%) of drowsiness, 18 cases (17.5%) of irritability, and 14 cases (13.6%) of appetite loss. None of them, however, was severe except 2 cases of irritability that interrupted normal daily activities but had no relationship with the study drug. One of them resolved 4 days, and the other 5 days, after vaccination. A total of 14 subjects (12.9%) from the 4-6 years group reported 18 cases of systemic reactions including 3 cases (3.1 %) of fever, 8 cases (8.3%) of drowsiness, 4 cases (4.2%) of irritability, and 3 cases (3.1%) of appetite loss. In general, 41 (20.6%) out of 199 subjects reported 70 cases of systemic reactions including 12 cases (6.0%) of fever, 19 cases (9.6%) of drowsiness, 22 cases (11.1%) of irritability, and 17 cases (8.5%) of appetite loss. Two cases of severe irritability were reported from the 12-15 months group. One of them resolved 4 days, and the other 5 days, after the vaccination. Both of them, however, had no relationship with the study drug (Table 3).

4) Local and systemic reactions reported within 42 ±7 days after the vaccination (Table 4)

The occurrence of local reactions related to the study drug was 10.1%, with 7.8% in the 12-15 months group and 12.5% in the 4-6 years group. The occurrence of systemic reactions was 6.5% with 8.7% in the 12-15 months group and 4.2% in the 4-6 years group. The occurrence of local and systemic reactions was 14.6% in the 12-15 months group and 15.6% in the 4-6 years group (Table 4). During the study, 1 subject reported fecal impaction which subsequently resolved as a serious adverse event, but it had no relationship with the study.

Table 2. Incidence of Local Adverse Events for 4 Days Postvaccination

	12-15 months group (n=103)	4-6 years group (n=96)	Total (N=199)
Number of subjects	8	12	20
Incidence [95% C.I.]	7.8 [2.60, 12.94]	12.5 [5.88, 19.12]	10.1 [5.87, 14.23]
Pain	0	3	3
Incidence [95% C.I.]		3.1 [0.00, 6.61]	1.5 [0.00, 3.20]
Redness	8	11	19
Incidence [95% C.I.]	7.8 [2.60, 12.94]	11.5 [5.09, 17.83]	9.6 [5.46, 13.63]
Swelling	2	3	5
Incidence [95% C.I.]	1.9 [0.00, 4.61]	3.1 [0.00, 6.61]	2.5 [0.34, 4.69]
Severe adverse events (redness)	0	1	1

95% C.I.=95% Confidence intervals

Table 3. Incidence of Systemic Adverse Events for 4 Days Postvaccination

	12-15 months group (n=103)	4-6 years group (n=96)	Total (N=199)
Number of subjects	27	14	41
Incidence [95% C.I.]	26.2 [17.72, 34.71]	14.6 [7.52, 21.64]	20.6 [14.98, 26.22]
Associated with vaccination	8	4	12
Incidence [95% C.I.]	7.8 [2.60, 12.94]	4.2 [0.17, 8.16]	6.0 [2.72, 9.34]
Fever	9	3	12
Incidence [95% C.I.]	8.7 [3.28, 14.19]	3.1 [0.00, 6.61]	6.0 [2.72, 9.34]
Drowsiness	11	8	19
Incidence [95% C.I.]	10.7 [4.71, 16.64]	8.3 [2.80, 13.86]	9.6 [5.46, 13.63]
Irritability	18	4	22
Incidence [95% C.I.]	17.5 [10.14, 24.81]	4.2 [0.17, 8.16]	11.1 [6.70, 15.41]
Loss of appetite	14	3	17
Incidence [95% C.I.]	13.6 [6.97, 20.21]	3.1 [0.00, 6.61]	8.5 [4.66, 12.43]
Severe adverse events (Irritability)	2	0	2
Association with vaccination			
Yes (%)	12 (23.1)	4 (22.2)	16 (22.9)
No (%)	40 (76.9)	14 (77.8)	54 (77.1)

95% C.I.=95% Confidence intervals

3. Efficacy assessment

The existence of antibody was assessed at the baseline (Table 5) and the efficacy was evaluated by this factor.

1) Seronegative subjects

Subjects who were seronegative against each disease at baseline were evaluated for seroconversion after the vaccination, and the geometric mean antibody titers of subjects with seroconversion were calculated. Reviewing seroconversion by age, in the case of the 12-15 months group, 99%, 91%, and 100% of subjects demonstrated seroconversion against measles, mumps, and rubella respectively. In the 4-6 years group, 100% of subjects showed seroconversion against measles, mumps, and rubella. In addition, in the 12-15 months group, the geometric mean antibody titers of those who seroconverted were 3,838.6 mIU/mL for measles, 956.3 U/mL for mumps, and 94.5 IU/mL for rubella. In the 4-6 years group, they were 1,886.2 mIU/mL for measles, 2,473.8 U/mL for mumps, and 168.9 IU/mL for rubella (Table 6).

Table 4. Incidence of Systemic Adverse Events for 4 Days Postvaccination

	12-15 months group (n=103)	4-6 years group (n=96)	Total (N=199)
Local symptoms			
associated with vaccination	8	12	20
Incidence [95% C.I.]	7.8 [2.60, 12.94]	12.5 [5.88, 19.12]	10.1 [5.87, 14.23]
General symptoms			
associated with vaccination	9	4	13
Incidence [95% C.I.]	8.7 [3.28, 14.19]	4.2 [0.17, 8.16]	6.5 [3.10, 9.97]
Symptoms			
associated with vaccination	15	15	30
Incidence [95% C.I.]	14.6 [7.75, 21.38]	15.6 [8.36, 22.89]	15.1 [10.41, 20.82]

95% C.I.=95% Confidence intervals

Table 5. Antibody Presence before Vaccination

	12-15 months group (n=103)			4-6 years group (n=96)			Total (N=199)		
	Negative (%)	Positive (%)	N/A* (%)	Negative (%)	Positive (%)	N/A* (%)	Negative (%)	Positive (%)	N/A* (%)
Antimeasles	94 (91.3)	9 (8.7)	-	6 (6.3)	90 (93.8)	-	100 (50.3)	99 (49.8)	-
Antimumps	94 (91.3)	8 (7.8)	1 (1.0)	19 (19.8)	69 (71.9)	8 (8.3)	113 (56.8)	77 (38.7)	9 (4.5)
Antirubella	94 (91.3)	9 (8.7)	-	7 (7.3)	89 (92.7)	-	101 (50.8)	98 (49.3)	-

Positive antibody titers mean that antibody titers for measles, mumps and rubella were more than 150 mIU/mL, 231 U/mL and 4 IU/mL

*N/A = Non-available (cannot detect antibody titers)

Table 6. Seroconversion Rate and Geometric Mean Antibody Titers in Initially Seronegative Subjects

		12-15 months group (n=94)	4-6 years group (n=6)	Total (N=100)
Antimeasles (mIU/mL)	Seroconversion rate	0.99 (93/94)	1.00 (6/6)	0.99 (99/100)
	[95% C.I.]	[0.94, 1.00]	[0.54, 1.00]	[0.95, 1.00]
	GMT	3,838.6	1,886.2	3,676.8
	[95% C.I.]	[3,304.47, 4,458.91]	[825.83, 4,308.26]	[3,168.08, 4,267.10]
Antimumps (U/mL)	Seroconversion rate	0.91 (84/92)	1.00 (19/19)	0.93 (103/111)
	[95% C.I.]	[0.84, 0.96]	[0.82, 1.00]	[0.86, 0.97]
	GMT	956.3	2,473.8	1,139.5
	[95% C.I.]	[821.81, 1,112.71]	[1,518.94, 4,028.92]	[965.98, 1,344.24]
Antirubella (IU/mL)	Seroconversion rate	1.00 (94/94)	1.00 (7/7)	1.00 (101/101)
	[95% C.I.]	[0.96, 1.00]	[0.59, 1.00]	[0.96, 1.00]
	GMT	94.5	168.9	98.4
	[95% C.I.]	[79.56, 112.28]	[108.96, 261.90]	[83.48, 115.98]

*GMT = Geometric mean antibody titers for measles, mumps, rubella in seroconverted subjects

Table 7. Seropositivity Rate and Antibody Titers ≥4-Fold in Initially Seropositive Subjects

		12-15 months group (n=9)	4-6 years group (n=90)	Total (N=99)
Antimeasles (mIU/mL)	Seropositivity rate	1.00 (9/9)	1.00 (90/90)	1.00 (99/99)
	[95% C.I.]	[0.66, 1.00]	[0.96, 1.00]	[0.96, 1.00]
	Antibody Titers 4-Fold (%)	44.4 (4/9)	7.8 (7/90)	11.1 (11/99)
	[95% C.I.]	[13.70, 78.80]	[3.18, 15.37]	[5.68, 19.01]
	GMT	3,142.6	2,834.3	2,861.0
	[95% C.I.]	[2,288.06, 4,316.26]	[2,436.03, 3,297.69]	[2,488.40, 3,289.46]
Antimumps (U/mL)	Seropositivity rate	1.00 (8/8)	1.00 (68/68)	1.00 (76/76)
	[95% C.I.]	[0.63, 1.00]	[0.95, 1.00]	[0.95, 1.00]
	Antibody Titers 4-Fold (%)	12.5 (1/8)	30.9 (21/68)	29.0 (22/76)
	[95% C.I.]	[0.32, 52.65]	[20.24, 43.26]	[19.11, 40.49]
	GMT	1,683.9	3,816.9	3,501.9
	[95% C.I.]	[933.82, 3,036.56]	[3,256.21, 4,474.22]	[2,981.72, 4,112.86]
Antirubella (IU/mL)	Seropositivity rate	1.00 (9/9)	1.00 (89/89)	1.00 (98/98)
	[95% C.I.]	[0.66, 1.00]	[0.96, 1.00]	[0.96, 1.00]
	Antibody Titers 4-Fold (%)	0.0 (0/9)	25.8 (23/89)	23.5 (23/98)
	[95% C.I.]	-	[17.14, 36.21]	[15.50, 33.11]
	GMT	118.4	164.7	159.8
	[95% C.I.]	[90.96, 154.22]	[148.79, 182.26]	[145.15, 175.86]

*GMT = Geometric mean antibody titers for measles, mumps, rubella in seropositive subjects

2) Seropositive subjects

For subjects who were seropositive at baseline, seroconversion rates against each disease after vaccination were obtained. The rates of immune response, defined as a 4 times or more increase in geometric mean antibody titers, were also obtained. In the 12-15 months group, seroconversion was 100% against all 3 diseases, and the percentage of subjects whose antibody level increased by 4 times or more was 44.4% for measles and 12.5% for mumps. Furthermore, the geometric mean antibody titers were 3,142.6 mIU/mL, 1,683.9 U/mL, and 118.4 IU/mL for measles, mumps, and rubella, respectively. In the 4-6 years group, seroconversion was 100% against all 3 diseases, and the percentage of subjects whose antibody level increased by 4 times or more after vaccination was 7.8%, 30.9%, 25.8 % against measles, mumps, and rubella, respectively. The geometric mean antibody titers after vaccination were 2,834.3 mIU/mL, 3,816.9 U/mL, and 164.7 IU/mL for measles, mumps, and rubella, respectively (Table 7).

Discussion

In Korea, vaccination against measles was initiated from 1965, against mumps from 1974, and against rubella from 1979. In 1982, combination MMR vaccination was introduced and it was recommended that this vaccine be first administered at the age of 12-15 months and re-administered at the age of 4-6 years. The timing of vaccination varies slightly among countries but the second vaccination is commonly recommended[12]. The first vaccination is not sufficient for the prevention of measles, mumps, and rubella. The second vaccination may cover those who were not vaccinated or experienced no effect from the first vaccination, increasing the coverage of vaccination and improving herd immunity. As a result, the occurrence of these diseases has decreased[13-15].

The WHO judges universal mass vaccination against measles to be the best way to lower the occurrence of the disease. In 1999, WHO had set the target of reducing the death rate from measles by 50% by the year 2005, through a worldwide measles-prevention program[16]. WHO also recommends that all infants aged 12-15 months be vaccinated against mumps using combination vaccines. If 70-80% of children at this age are not vaccinated against mumps, the disease will be prevalent among many adults who do not acquire immunity against it[17, 18]. In the case of rubella, its prevalence differs among countries, and worldwide vaccination against it is not a requisite. In order to prevent the congenital rubella syndrome, however, vaccination against rubella is strongly recommended[19].

Until 1992, M-M-R II from Merck & Co. and Pluserix from GlaxoSmithKline were widely used as MMR vaccines. M-M-R II contains Enders Edmonston measles strains, Jeryl Lynn mumps strain, and RA 27/3 rubella strain, and

Pluserix contains the Schwarz measles strain, Urabe Am 9 mumps strain, and Wistar RA 27/3 rubella strain. However, it was reported that the Urabe strain contained in Pluserix increased the risk of abacterial cerebral meningitis, and as a result, the vaccine has gradually disappeared from the market[20]. In 1997, GlaxoSmithKline developed Priorix™ as a new MMR vaccine. Priorix™ includes RIT 4385 mumps strain derived from the Jeryl Lynn strain[8]. Berna-MMR is another widely used MMR vaccine. It contains Edmonston-Zagreb measles strain, Rubini mumps strain, and Wistar RA 27/3 rubella strain[8].

Since the occurrence of abacterial cerebral meningitis due to an MMR vaccine containing the Urabe strain, safety considerations have become very important in the development of MMR vaccines. Since the development of the RIT 4385 strain, many studies on the prevention of abacterial cerebral meningitis have been conducted[8, 9]. Febrile convulsions and multiple flushing in the 15-35 days after vaccination were regarded as criteria for suspecting abacterial cerebral meningitis. In this study, no febrile convulsion or multiple flushing in the 15-35 days after vaccination was observed. Fever was reported only within 2 weeks after the vaccination and judged as related to the vaccine against measles[21-24].

Among the adverse events, only 10.1% of local reactions and 6.5% of systemic reactions were related to the study drug. Moreover, dreaded adverse events such as abacterial cerebral meningitis or febrile convulsion were not observed. No serious adverse events associated with the study drug were reported, and all adverse events resolved.

The frequency of local adverse reactions with the study drug was similar to that of Berna-MMR vaccine and much lower than with Merck-MMR vaccine. In terms of systemic adverse events, the frequency with the study drug was similar to Merck-MMR vaccine but much higher than Berna-MMR vaccine[25, 26].

In terms of immunogenicity, the study drug was similar to GSK-MMR vaccine and Merck-MMR vaccine, with almost the same seroconversion rates and geometric mean antibody titers. In the case of mumps, the study drug showed a higher seroconversion rate and higher geometric mean antibody levels compared with Berna-MMR vaccine, proving its superior immunogenecity[25, 26].

Reviewing seroconversion by age among subjects who were seronegative at baseline, 99%, 91%, and 100% of the 12-15 months group showed seroconversion against measles, mumps, and rubella respectively, and 100% of the 4-6 years group showed seroconversion against all 3 diseases. The geometric mean antibody titers of those who showed seroconversion were 3,838.6 mIU/mL, 956.3 U/mL, and 94.5 IU/mL for measles, mumps, and rubella respectively in the 12-15 months group, and in the 4-6 years group, they were 1,886.2 mIU/mL, 2,473.8 U/mL, and 168.9 IU/mL respectively (Table 6).

The seroconversion rate after vaccination was obtained from subjects who were seropositive at baseline. In addition, for the subjects who showed seroconversion, the percentage whose geometric mean antibody titers and antibody levels increased by 4 times or more illustrating immunogenicity was calculated. In this efficacy analysis, the 12-15 months group showed 100% seropoconversion against measles, mumps, and rubella. In addition, 44.4%, 12.5%, and 0% of this group showed a 4 times or more increase in antibody titers after vaccination for measles, mumps, and rubella respectively. The geometric mean antibody titers after vaccination were 3,142.6 mIU/mL, 1,683.9 U/mL, and 118.4 IU/mL for measles, mumps, and rubella respectively. The 4-6 years group also showed 100% seroconversion against measles, mumps, and rubella. In addition, 7.8%, 30.9%, and 25.8% of this group showed a 4 times or more increase in antibody titers after vaccination. The geometric mean antibody titers after vaccination were 2,834.3 mIU/mL, 3,816.9 U/mL and 164.7 IU/mL for measles, mumps, and rubella respectively (Table 7).

In conclusion, Priorix™ injection may be safely administered to healthy Korean children aged 12-15 months or 4-6 years. Adverse events reported from the vaccination were common ones also observed with other vaccines. Moreover, Priorix™ injection showed very high seroconversion rate and geometric mean antibody titers proving its excellent immunogenicity.

한 글 요 약

MMR(Measles-Mumps-Rubella) 약독화 생백신인 프리오릭스주를 접종한 후 안전성과 유효성의 평가에 관한 연구

한일병원 소아과, 경희대학교 의과대학 소아과학교실*,
가톨릭대학교 성바오로병원 소아과†,
고려대학교 의과대학 안산병원 소아과‡

안승인 · 정민국 · 유정석 · 정혜전
허재균† · 신영규‡ · 장진근 · 차성호*

목 적 : 본 연구는 한국인 소아를 대상으로 MMR 약독화 생백신인 프리오릭스주를 단독 접종한 후 공개, 다 기관, 비비교 시험으로 프리오릭스주의 안전성과 면역성 평가를 목적으로 수행되었다.

방 법 : 2002년 7월부터 2003년 2월까지 한일병원, 경희대학교 부속병원, 가톨릭대학교 성바오로병원, 고려대의과대학부속 안산병원 등 4개의 병원에 예방 접종을 위해 내원한 12-15개월 또는 4-6세의 건강한 남녀 소아 252명을 대상으로 하였으며, 이 중에서 임상시험계획서의 모든 기준을 충족하는 피험자를 최종 분석대상군에 포함시켰다. 접종 후 이상 반응 및 중대한 이상 반응에 대하여 42일간의 추적관찰을 통하여 증례기록서의 이상 반응란에 기록하였다. 각 피험자들은 시험백신 투여 직전과 투여 후 42일 후 혈액검체를 채취하여 벨기에 GlaxoSmithKline Biologicals 실험실에서 면역분석법을 통하여 항체가를 측정하였다.

결 과 : 등록된 피험자 총 252명 중 최종적으로 12-15개월군에서 103명, 4-6세군에서 96명으로 총 199명이 분석대상으로 선정되었다. 본 임상시험 기간 동안 발생한 이상반응 중 시험약물과 관련 있는 국소 반응은 10.1% 전신 반응은 6.5%에 불과하였으며, 우려하였던 이상 반응, 예를 들면 무균성 뇌막염, 열성 경련 등은 발생하지 않았으며, 시험백신과 관련된 중대한 이상 반응은 없었다. 유효성 분석에서, 항체 음성인 피험자들의 혈청전환율은 홍역인 경우 99%, 유행성 이하선염인 경우 93%, 풍진인 경우 100%이었다. 시험백신 투여 전 항체 음성인 피험자군의 혈청전환시 항체가의 기하평균은, 홍역의 경우 12-15개월에 속하는 피험자군에서는 383±8.6 mIU/mL, 4-6세에 속하는 피험자군에서는 188±6.2 mIU/mL, 유행성 이하선염의 경우 12-15개월에 속하는 피험자군에서는 95±6.3 U/mL, 4-6세에 속하는 피험자군에서는 247±3.8 U/mL, 풍진의 경우 12-15개월에 속하는 피험자군에서는 94.5 IU/m±, 4-6세에 속하는 피험자군에서는 16±8.9 IU/mL을 보였다.

결 론 : 12-15개월 또는 4-6세의 건강한 소아를 대상으로 프리오릭스주를 접종하였을 때, 이와 관련된 이상 반응은 대부분의 백신 접종 후 나타날 수 있는 일반 반응에 한정된 것으로 나타나 한국인 소아에게서도 안전하게 사용될 수 있으며 또한 매우 높은 항체양전율 및 항체가의 기하평균치를 보여 우수한 면역효과를 기대할 수 있는 백신으로 사료된다.

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