

Post-Marketing Surveillance Study of Hepatitis A Vaccine in Korean Population

Jae-Won Choi, M.D. Myoung-Seok Kim, M.D. Sang-Hyuk Ma, M.D.
Jin-Han Kang, M.D.^{*}, Jin-Ju Ok, M.D.[†], Timothy L. Ng, M.D.[†]
Hans L. Bock, M.D.[†] and *Havrix*TM PMS Korean study group[‡]

Department of Pediatrics, Fatima Hospital, Changwon; Department of Pediatrics^{*}, Our Lady of Mercy Hospital, College of Medicine The Catholic University, Incheon;
GlaxoSmithKline Biologicals, Rixensart, Belgium[†]; Group Members Listed at the End of Paper[‡]

Purpose : This post-marketing surveillance (PMS) study was conducted in Korea to assess the safety and reactogenicity of hepatitis A vaccine (GlaxoSmithKlineBiologicals' *Havrix*TM) administered to the Korean population.

Methods : A total of 1,188 healthy subjects with 1,122 subjects <6 years of age were enrolled to receive one dose of the hepatitis A vaccine from April 2005 to January 2006. Diary cards were provided to the subjects or subjects' parents for reporting solicited and unsolicited symptoms during the 4-day and 31-day post-vaccination follow-up period.

Results : The number of subjects who returned diary cards was 568, whereas, 620 subjects did not return diary cards. Among the subjects who returned diary cards, 9.9% and 14.3% reported local and general solicited/unsolicited symptoms. Among the subjects who did not return diary cards, 1.6% and 8.4% reported local and general solicited/unsolicited symptoms. At least one unsolicited symptom was reported by 13.2% of the subjects.

Conclusion : Results indicate that the vaccine was well-tolerated and had an acceptable safety profile. The use of diary cards in such a survey provided a prompt and reliable option for recording symptoms. (**Korean J Pediatr Infect Dis 2008;15:115-120**)

Key Words : Hepatitis A vaccine, Diary cards, Post-marketing surveillance

Introduction

Hepatitis A infection has a worldwide distribution with highest incidence in developing countries of Africa, Asia, Central and South America¹⁾. It is the most common form of viral hepatitis which is responsible for around 1.5 million cases of hepatitis A globally each year^{2, 3)}. The development and introduction of inactivated hepatitis A vaccine has aided in controlling the disease across various countries⁴⁻⁶⁾. After the introduction of Hepatitis A vaccine in the US, the disease incidence has dropped from 20 cases

per 100,000 to 2.6 cases per 100,000 population⁵⁾.

Seroprevalence data from different regions of Korea revealed that >60% of people aged under 19 years had antibodies to hepatitis A virus (HAV) in 1979 due to natural exposure to the virus. This figure has dropped to <10% in 1996⁷⁾ suggesting that historically, more than half of the Korean population was exposed to HAV during childhood. More recently, presumably due to improved sanitation and socioeconomic development, anti-HAV antibody acquisition is negligible in childhood. Indeed in the late 1990s, peak age of exposure to HAV has shifted from childhood (15 years of age) to adolescence (11-15 years of age) or early adulthood (15-20 years of age)⁷⁻⁹⁾ resulting in an increased incidence of hepatitis A infection in adults. Consequently, mor-

책임저자 : 마상혁, 창원파티마병원 소아청소년과
Tel : (055)270-1223, Fax : (055)265-7766
E-mail : msh6517@hanmail.net

bidity and mortality of this disease persist, with the focus now shifted to an older age group. Thus, preventive measures, such as immunization against hepatitis A, especially for the high-risk population (such as children, travellers to endemic regions, food handlers, healthcare workers, patients with chronic liver disease, etc) are of particular interest^(6-8, 10).

In case of vaccines, the post-marketing surveillance (PMS) studies focus on safety and reactogenicity data. Since these PMS studies are observational by nature, the intention is to obtain data reflective of routine clinical practice with minimal intrusion into the normal clinical practices. PMS studies may also identify rare adverse events that were not detected during the pre-licensure studies and recognize signals of possible adverse reactions which may necessitate further studies⁽¹¹⁾.

This PMS study was conducted to assess the safety and reactogenicity of GlaxoSmithKline Biologicals' *Havrix*TM (Hepatitis A vaccine) in Korean population as per Korea Food & Drug Administration (KFDA) regulations.

Materials and Methods

This observational post-marketing study, complying with the KFDA regulations was conducted in Korea from April 2005 to January 2006. A total of 1,188 subjects were enrolled from 39 medical centers (35 pediatric clinics and 4 general hospitals) of which 26 centers were located in Seoul or suburbs and the remaining centers in other regions of the country.

Written informed consent was obtained from all the subjects or subjects' parents before enrolment in the study. One dose of *Havrix*TM vaccine was administered by the clinicians following the Korean Pediatrics Immunization Guidelines⁽¹²⁾, and Package Insert⁽¹³⁾: one vial (0.5 mL in case of subjects aged 1 to 15 years) or two vials (1 mL, in case of subjects aged over 16 years). A booster dose (same dosage as primary vaccination) could be given 6 months from the time of first injection.

In this PMS study, diary cards were used considering that this is somewhat more active and more accurate way to check the occurrence of adverse events (AE) after vaccination compared to the passive listening of subjects or subjects' parents when reporting AE.

The subjects or subjects' parents were given a diary card and instructed to record the occurrence and intensity of any local or general solicited symptoms (known adverse events of *Havrix*TM were listed on the diary card) during the 4-day post-vaccination follow-up period. Unsolicited symptoms (symptoms not mentioned on the diary card) were also to be recorded during the 31-day post-vaccination follow-up period.

Among subjects who did not return their diary cards, data regarding adverse events (solicited/unsolicited) were to be collected retrospectively by phone call at the end of the 31-day post-vaccination follow-up period: the investigator has to call the subjects or subjects' parents and ask about the occurrence of AE listed on the diary card (local symptoms <pain, redness, swelling>, fever and other general symptoms relevant to the age) and also about other symptoms as well (not listed on the diary card) occurred after vaccination.

Subjects or subjects' parents were further instructed to contact the investigator immediately if any serious adverse event (SAE) occurred.

A telephone contact for safety follow-up was scheduled at Month 1 to check if any adverse event occurred within 30 days of vaccination.

A chi-square test was done to evaluate the statistically significant difference between the two groups 'Subjects who returned the diary cards' and 'Subjects who did not return the diary cards' in terms of reporting local and also general symptoms. A *P* value<0.05 was considered statistically significant.

Results

A total of 1,188 subjects with 607 (51.1%) males

were enrolled in the study. The mean (\pm standard deviation) age of the subjects was $1.7 \pm (1.96)$ years (age range from 1 to 39 years). Of the total number of enrolled subjects, 1,122 (94.4%) subjects were aged <6 years. The analysis was done on the total vaccinated cohort (1,188 subjects). A total of 568 subjects returned the diary cards (47.8%), while 620 (52.2%) subjects did not return the diary cards.

A booster dose of the vaccine was not administered to any of the subjects in this study.

Of the subjects who returned their diary cards, 19.5% reported symptoms (local or general, solicited or unsolicited) within the 4-day post-vaccination follow-up period. Local symptoms were reported by 9.9% of the subjects, whereas 14.3% of subjects reported general symptoms (solicited or unsolicited) (Table 1). Among subjects who did not return their diary cards (620), 9.7% of subjects reported symptoms (solicited or unsolicited, local or general) during the 4-day post-vaccination follow-up: 8.4% reported general symptoms while 1.6% reported local symptoms (Table 1).

There was a statistically significant difference between the two groups for both types of symptoms (Table 1).

In subjects who returned their diary cards, redness was the most frequently reported solicited local symptom (7.4%) followed by pain and swelling (Fig.

1). In subjects who did not return their diary cards, the order of frequency was the same but each frequency appeared markedly lower (Fig. 1).

Among subjects (<6 years of age) who returned their diary cards, irritability was the most frequently reported solicited general symptom (6.9%) followed by drowsiness, loss of appetite and fever (Fig. 2). However, fever (1.9%) was the most frequently reported solicited general symptom followed by irritability, loss of appetite and drowsiness among the subjects who did not return their diary cards (Fig. 2).

In subjects aged over 6 years (66 of 1,188 subjects enrolled), solicited general symptoms such as fatigue, headache, gastrointestinal symptoms were each reported in 5.6% of subjects (no cases of fever

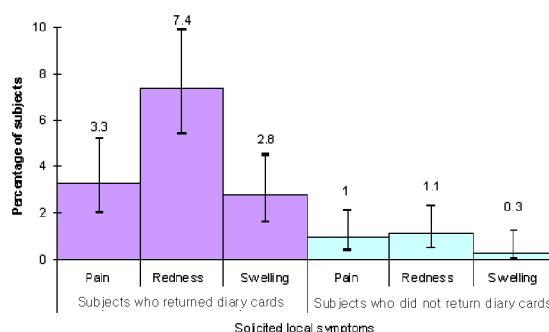


Fig. 1. Frequency of solicited local symptoms within 4 days after vaccination.

Table 1. Frequency of Symptoms Within 4 Days after Vaccination

Symptoms	Diary cards	n	%	95% CI		P-value*
				LL	UL	
Any Symptom	Diary cards returned (N=568)	111	19.5	16.4	23.0	<0.001
	Diary cards not returned (N=620)	60	9.7	7.5	12.3	
General	Diary cards returned (N=568)	81	14.3	11.5	17.4	0.0013
	Diary cards not returned (N=620)	52	8.4	6.3	10.9	
Local	Diary cards returned (N=568)	56	9.9	7.5	12.6	<0.001
	Diary cards not returned (N=620)	10	1.6	0.8	2.9	

P-value based on Chi-square test

*Statistical significance of the difference of the frequency of symptoms reporting between the 2 groups (the group where diary cards were returned and the group where diary cards were not returned), a P value < 0.05 was considered statistically significant

N, Number of subjects who received the vaccine; n, number of subjects presenting at least one type of symptom; %, percentage of subjects presenting at least one type of symptom; 95% CI, exact 95% confidence interval; LL, Lower Limit; UL, Upper Limit

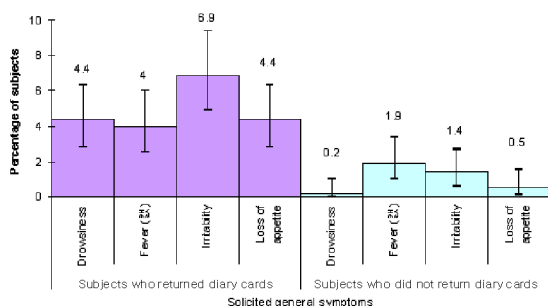


Fig. 2. Frequency of solicited general symptoms within 4 days after vaccination in children less than 6 years of age.

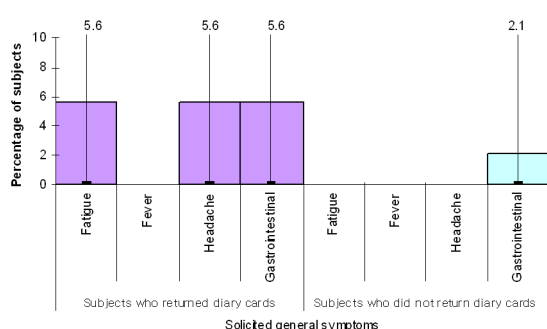


Fig. 3. Incidence of solicited general symptoms within 4 days after vaccination in subjects over 6 years of age.

were reported) when diary cards were returned, whereas, only gastrointestinal symptoms were reported (2.1%) when diary cards were not returned (Fig. 3).

At least one unsolicited symptom was reported by 13.2% of subjects during the 31-day follow-up period; except 7 cases (injection site bruising, dyspepsia, and rash), no other unsolicited symptom was assessed as related to vaccination.

One case of SAE (asthma and acute otitis media) was reported but was assessed by the investigator to be causally unrelated to vaccination.

Discussion

In this PMS study conducted on 1,188 subjects, redness was the most commonly reported solicited local symptom irrespective of whether diary card was returned or not. Irritability (6.9%) in subjects

who returned diary card and fever (1.9%) in subjects who did not return diary card were the commonly reported solicited general symptoms in subjects aged less than 6 years. In subjects aged above 6 years, fatigue, headache and gastrointestinal symptoms were commonly reported (5.6% each) when diary card was returned. However, when diary card was not returned, gastrointestinal symptoms (2.1%) alone were reported.

These results were consistent with the *Havrix*TM product monograph and Prescribing Information^{14, 15)} where the frequency of pain, redness and swelling reports varied between 4% and 7% and the frequency of general solicited symptoms (including headache, malaise, fever, nausea, loss of appetite) between 1% and 13.9%. These frequency of solicited local and general symptoms were also consistent with the previously published data on the safety of *Havrix*^{TM16-19)}.

It is important to note that the subjects who did not return their diary cards reported much less solicited symptoms when they were contacted by phone compared to those who returned diary cards. And, by comparing the groups who returned and who did not return the diary cards, the frequency of adverse events reported by subjects using diary cards was more consistent with the global adverse event information in the *Havrix*TM product monograph¹⁴⁾. It is likely that documentation of AE on a diary card provided a prompt and readily available venue for recording symptoms and thus yielding more reliable incidences than those collected through spontaneous recall at a later point of time, which seemingly resulted in an underestimation of incidences of reactions. So, it appears that in using a diary card, we could get more accurate AE data, and so, we recommend the use of diary card to evaluate the safety of vaccines in future PMS studies.

Finally, this study confirmed that the safety and reactogenicity profile demonstrated by the hepatitis A vaccine under routine Korean clinical environment is consistent with that reported in other regions of

the world^{14, 16-18, 20)} and was also approved by KFDA. In a previously conducted efficacy trial on Asian population, no SAE was reported following the administration of more than 109,000 doses of the hepatitis A vaccine^{16, 21-22)}. The five most frequently reported adverse events during post-marketing surveillance of *Havrix*TM in the last 10 years are fever, rash, nausea, headache and injection site reaction and with the low frequency, severity and the transient character of the events indicates that the vaccine has excellent safety profile consistently with our PMS study's results¹⁶⁾.

In conclusion, this study indicates that *Havrix*TM, administered in a routine clinical practice environment in Korea has a good safety and reactogenicity profile similar to that observed in the global population. No association with any previously not recorded serious adverse events was found. The frequencies of adverse events reported using diary cards are consistent with data collected worldwide during large-scale use of the vaccine with similar methodology applied for recording data for adverse events. On the other hand, the incidences of symptoms recorded are much significantly lower by less stringent means such as delayed phone contact or interview. This study supports the continued use of hepatitis A vaccine to control the disease in Korea.

HavrixTM PMS Study Group

Principal investigator

Sang-Hyuk Ma (Fatima Hospital, Changwon)

Members

Mun-Hye Bang (Bang Pediatrics), Jae-Won Song (Song Jae Won Pediatrics), Yeon-Ho Kim (Kim Yeon Ho Pediatrics), Soon-Jai Lee (Feel Pediatrics), Min-Woo Kim (I-plus Pediatrics), Pill-Jin Shin (Shin Pill Jin Pediatrics), Mi-Na Kang (Chio Cha Hye Pediatrics), Jung-Hoon Lee (Lee Pediatrics), Jung-Hye Kwon (Kangseo-Ms.Medi clinic), Seung-Kyoo Han (Kangseo-Ms.Medi clinic), Mi-Hwa Kim (Chungdam-Koeun-I Pediatrics), Hyung-Seok Oh (Koeunbit Pediatrics), Hee-Kyu Yang (Yonsei-Moa

Pediatrics), Young-Mo Sohn (Navekids Pediatrics), Jong-Wan Kim (Kim Jong Wan Pediatrics), Yoon-Ok Kim (Kim Yoon Ok Pediatrics), Seung-Joon Sung (Grace clinic), Sung-Keun Moon (Moon Sung Keun Pediatrics), Seong-Hang Choi (Jeil Pediatrics), Jae-Hong Yu (Joey Children's Hospital), Seok-Hee Oh (Serim Pediatrics), Joo-Seok Mang (Mang Joo Seok Pediatrics), Byung-Hee Kim (Mirae-A-dong clinic), Sang-Joo Han (Mirr Pediatrics), Jung-Mi Choi (Ilsin-Kidok hospital), Soon-Yeul Hwang (Jamo Pediatrics), Joong-Chul Lee (Green Pediatrics), Hwa-Young Jeon (Motae Pediatrics), Bum-Soo Park (Wooridul Pediatrics), Jeong-Kwon Park (Park Jeong Kwon Pediatrics), Soo-Wae Shin (Teun-Teun Pediatrics), Jung-Soo Park (Park Jung Soo Pediatrics), Hyo-Hee Lim (Medi-Park Pediatrics), Jae-Kook Cha (Rapa Pediatrics), Baek-Gil Lee (Cham Pediatrics), Eun-Ai Rhee (Rhee Eun Ai Pediatrics), Ji-Young Choi (Teun-Teun [Daejeon] Pediatrics), Kyung-Seok Kim (Angel Pediatrics), Jong-Gon Oh (Oh Jong-Gon Pediatrics).

한글 요약

한국에서 A형간염 백신(GlaxoSmithKline Biologicals' *Havrix*TM)의 시판 후 조사

창원파티마병원 소아청소년과, 가톨릭대학교 의과대학 소아청소년과학교실*, GlaxoSmithKline Biologicals[†]
한국 A형간염 백신 시판 후 연구 그룹[‡]

최재원 · 김명석 · 마상혁 · 강진한* · Jin-Ju Ok[†]
Timothy L. Ng[†] · Hans L. Bock[‡]

목 적 : 본 시판 후 조사는 한국인에게 투여한 A형 간염 백신(GlaxoSmithKline Biologicals' *Havrix*TM)의 안전성과 반응원성을 평가하기 위해 한국에서 실시되었다.

방 법 : 6세 미만의 1,122명의 피험자를 포함하는 총 1,188명의 건강한 피험자들이 2005년 4월부터 2006년 1월까지 등록되어 A형 간염 백신 1회를 접종 받았다. 백신 접종 후 4일 동안 명시된 증상 보고와 31일의 추적 기간 동안 명시되거나 되지 않은 증상 보고를 위해 피험자 또는 피험자의 부모에게 증상 기록 카드가 제공되었다.

결 과 : 증상 기록 카드를 돌려준 피험자는 568명이

었고, 반면에 620명의 피험자는 증상 기록 카드를 돌려주지 않았다. 증상 기록 카드를 돌려준 피험자들 중에 9.9%가 국소 증상을 보고하였고, 14.3%가 전신 증상을 보고하였다. 증상 기록 카드를 돌려주지 않은 피험자들 가운데 1.6%가 국소 증상을 보고하였으며 8.4%가 전신 증상을 보고하였다. 이 두 군 사이에는 국소 증상과 전신 증상 보고의 빈도에서는 통계적으로 유의한 차이가 있었다. 명시되지 않은 증상은 13.2%의 피험자에서 최소한 한 번 이상 보고 되었다.

결론 : A형 간염백신(*HavrixTM*)은 접종 후 내약성과 안전성이 있다고 사료된다. 백신 접종 후 증상 기록 카드를 제공함으로써 신뢰할 수 있는 백신 접종 후 이상 반응의 정보를 알 수 있었다.

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