Original Article

Adverse Events Following Yellow Fever Vaccination in Korean Children

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Purpose : Yellow fever, a mosquito-borne viral hemorrhagic fever, is one of the most lethal diseases. Recently there have been an increasing number of Korean children who have travelled to yellow fever endemic zones and were administered yellow fever vaccine (YFV). Therefore, we carried out this study to provide child travelers with safety information of YFV.
Methods : This study was conducted at the International Clinic of National Medical Center in Seoul between April 2007 and June 2008 for the evaluation of adverse events of YFV. One hundred twenty-five children received YFV (17-DD) and were prospectively monitored for adverse events through telephone interviews on day 3, 6, 9, 16, 23 and 30 after vaccination.
Results : Adverse events were observed in 31 (24.8%) of 125 child travelers who received the YFV. The mean age was 12.5±5.0 years. Sixty-six of the child travelers (52.8%) were males. The common adverse events were pain in 11 (8.8%), swelling in 8 (6.4%) and redness in 7 children (5.6%) at the injection site. The systemic adverse events included mild fever in 5 (4.0%), headache in 5 (4.0%), cough in 4 (3.2%), abdominal pain in 3 (2.4%), and vomiting in 2 children (1.6%). Most of the adverse events were detected within 7 days of administration and there were no differences in adverse events by gender or age. All travelers who had complained of symptoms improved spontaneously or following symptomatic treatment.
Conclusion : This study showed that YFV is well-tolerated and there were no reports of severe adverse events. Studies are ongoing to clarify the cause and risk factors for rare adverse events. **(Korean J Pediatr Infect Dis 2009;16:54-60)**

Key Words : Yellow fever, Yellow fever vaccine, Adverse events

Introduction

Yellow fever (YF), a mosquito-borne viral hemorrhagic fever, is one of the most lethal viral diseases of humankind and occurs only in sub-Saharan Africa and South America[1]. In the past 15 years the incidence of YF has steadily increased and the World Health Organization (WHO) estimates that a total of 200,000 cases of YF occur each year[2]. YF has an abrupt onset after an incubation period of 3-6 days and it usually manifests as fever, prostration, headache, photophobia, lumbosacral pain, anorexia and vomiting. The illness might progress to hepatitis, renal failure, hemorrhage, shock, and death with mortality rate of 20-50%[3].

YFV is a live, attenuated virus preparation made from the 17D yellow fever virus strain. Historically, the YFV has been considered to be one the safest and most effective live virus vaccines ever developed. Persons aged ≥9 months who are traveling to or living in areas of South America and Africa where yellow fever infection is officially reported should be vaccinated.

The incidence of YF in South America is lower than that in Africa (Fig. 1), because virus transmission between monkeys and mosquitoes occurs in the canopy of the forest, isolated from human contact, and vaccine

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coverage is high[4].

According to up-to-date reports, 9 million individuals travel to YF-endemic zones annually and also, recently, there are an increasing number of South Korean adults and children who travel to YF-endemic zones (Fig. 2). Therefore, we carried out this study to provide children traveling to YF endemic zones with safety information of YFV through a prospective research for adverse events after YF vaccination.

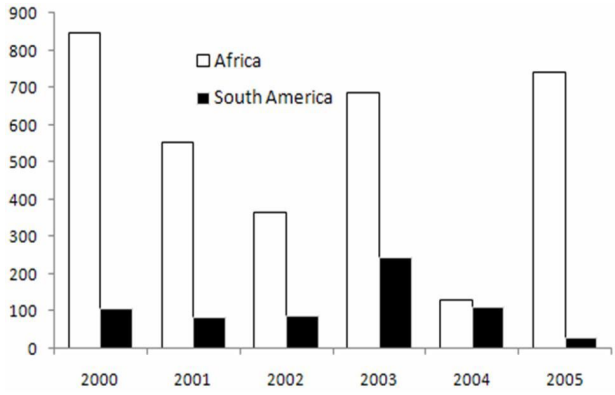

Fig. 1. The number of yellow fever cases reported by endemic area (WHO, 2000-2005).

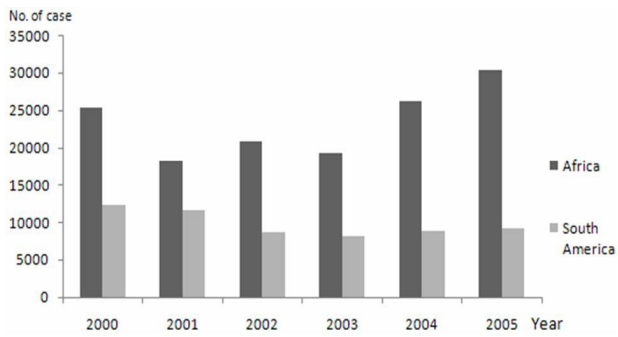

Fig. 2. The number of Koreans who traveled to yellow fever endemic zones (Korea Tourism Organization, 2000-2005).

Materials and methods

1. Objects and Subjects

From April 1, 2007 to June 30, 2008, 125 healthy children aged from 11 months to 19 years who visited the International Clinic at the National Medical Center and had plans to visit to yellow fever endemic areas, were chosen as study subjects. This study was explained to the parents and informed consent was obtained from the parents. They were examined by six telephone interviews on day 3, 6, 9, 16, 23 and 30 after vaccination.

The vaccine for the study was manufactured by Bio-Manguinhos (YFV-17DD), Brazil (Table 1)[5, 6]. A single dose of 0.5 mL of the vaccine was administered to each children by subcutaneous injection before their travelling.

2. Data analysis

For this study the statistical data processing was done with SPSS (ver.12.0K), the frequency analysis was used for the basic data of examples, and the difference of each variable was compared using Fisher's exact test or chi-square verification. In all cases, the differences were considered significant when the probabilities of equality, *P*-value, were <0.05.

Table 1. Manufacturers of Yellow Fever Vaccine*

Country	Manufacturer	Trade name	Qualified by WHO	Comment
U.S.A	Sanofi Pasteur, Swiftwater PA	YF-VAX	No	Principally U.S.A.
Brazil	Bio-Manguinhos, Rio de Janeiro	YFV-17DD	Yes	Only 17DD vaccine
United Kingdom	Chiron/Norvatis Vaccines,Liverpool	Arilvax	Yes	Stopped in 2003
France	Sanofi Pasteur Marcy I Etoile	Stamaril	Yes	
Senegal	Pasteur institute, Dakar		Yes	

*Adapted from the reference 7

Results

One hundred twenty-five assessed children were 66 (52.8%) males and 59 (47.2%) females. The subjects were classified by age in fives. The majority was aged 10-14 years and the mean age was 12.5±5.0 years (Table 2). The destination was Africa and South America (110:15) (Table 3).

Table 2. Characteristics of 125 Children Vaccinated with Yellow Fever Vaccine

Age (Year)	Number of Subjects (%)		
	Male (N=66)	Female (N=59)	Total (N=125)
<5	5 (4.0)	6 (4.8)	11 (8.8)
5-9	9 (7.2)	10 (8.0)	19 (15.2)
10-14	26 (20.8)	23 (18.4)	49 (39.2)
15-19	26 (20.8)	20 (16.0)	46 (36.8)

Table 3. Destination of Travel in 125 Children Vaccinated with Yellow Fever Vaccine

Destination	Number of Subject (%)		
	Male (N=66)	Female (N=59)	Total (N=125)
Africa	57 (45.6)	53 (42.4)	110 (88)
South America	9 (7.2)	6 (4.8)	15 (12)

1. Adverse events after receiving YFV

Of the 125 children in the group that received YFV, 31 (24.8%) participants had adverse events for 3-7 days. They were 16 (12.8%) males and 15 (12.0%) females and 53 adverse event cases were confirmed.

The common local adverse events reported were pain (11), swelling (8), redness (7) on injection site. The most common systemic adverse events reported were fever (5), headache (5), cough (4), abdominal pain (3) and nausea with vomiting (2). In most cases the symptoms were improved spontaneously, or with symptomatic treatment. Serious adverse events, such as jaundice and encephalitis, were not noted or reported within 30 days after immunization. Frequency of adverse events according to age group and gender has no significant difference statistically (P>0.05) (Table 4, 5).

2. Relationship between other vaccinations and and adverse events of YFV

Out of 125 who received YFV, 73 (58.4%) received

Table 4. Correlation between Age and Adverse Events

Adverse event \ Age (yr)	0-4 yr (N=11)	5-9 yr (N=19)	10-14 yr (N=49)	15-19 yr (N=46)	Total (N=125)	P-value
Local event						
Pain	0	1	4	6	11	NS
Swelling	0	3	4	1	8	NS
Redness	0	1	4	2	7	NS
Systemic event						
Fever	1	2	1	1	5	NS
Headache	0	1	2	2	5	NS
Cough/Sputum	0	1	1	2	4	NS
Nausea/Vomiting	0	2	1	0	3	NS
Abdominal pain	0	0	0	3	3	NS
Anorexia	0	0	0	1	1	NS
Diarrhea/constipation	0	1	1	1	3	NS
Dizziness	0	0	0	1	1	NS
Skin rash/Urticaria	1	0	1	0	2	NS
Total	2	12	19	20	53	

Abbreviation : NS, not significant

Table 5. Correlation between Gender and Adverse Events

Adverse event \ Gender	Male (N=66)	Female (N=59)	Total	*P*-value
Local event				
Pain	5	6	11	NS
Swelling	3	5	8	NS
Redness	3	4	7	NS
Systemic event				
Fever	2	3	5	NS
Headache	3	2	5	NS
Cough/Sputum	3	1	4	NS
Nausea/Vomiting	2	1	3	NS
Abd. pain	1	2	3	NS
Anorexia	1	0	1	NS
Diarrhea/constipation	1	2	3	NS
Dizziness	1	0	1	NS
Skin rash/Urticaria	0	2	2	NS
Total	25	28	53	

Abbreviation : NS, not significant

YFV alone and 52 (41.6%) received other vaccinations such as typhoid fever vaccine, hepatitis A vaccine, Td vaccine and malaria prevention.

Although 15 (20.5%) of 73 who received YFV alone and 16 (30.8%) of 52 who received YFV with other vaccinations had adverse events, there were not any meaningful relations between specific vaccinations and adverse events after receiving YFV.

Discussion

Increasing travel to the tropics has amplified exposure to YF. Each year, 9 million tourists from North America, Europe, and Asia travel to countries where YF is endemic[8]. Up to 5,000 cases in Africa and 300 in South America are reported annually, but the true incidence is believed to be 10–50 fold higher than the official reports. Between 1990 and 1999, 11,297 cases and 2,648 deaths in Africa were reported by WHO[9]. Estimation of risk of YF associated with travel is made difficulty by fluctuation of disease by year and season, vaccine coverage of the local population (which makes it more challenging to estimate risk for the unimmunized), and incomplete surveillance data[10].

The clinical disease varies from non-specific to fatal hemorrhagic fever. The incubation period after the bite of an infected mosquito is 3–6 day. Disease onset is typically abrupt, with fever, chills, malaise, headache, lower back pain, generalized myalgia, nausea, and dizziness[10]. Young children may experience febrile convulsions. Between 48 and 72 hours after onset and before the appearance of jaundice, serum transaminase levels may rise. This so-called "period of infection" lasts several days and may be followed by a "period of remission", with the disappearance of fever and symptoms lasting up to 24 hours. In approximately 15–25% of people affected, the illness reappears in a more severe form (the so-called "period of intoxication") with fever, vomiting, epigastric pain, jaundice, renal failure, and a hemorrhagic diathesis[11].

Definitive diagnosis is made by viral culture of blood or tissue specimens or by identification of YF virus antigen or nucleic acid in tissues (including liver) using immunohistochemistry (IHC), enzyme-linked immunosorbent assay (ELISA) antigen capture, or polymerase chain event tests. Although antibodies are not always present during the first week of illness, detection of yellow fever-specific immunoglobulin M (IgM) antibody by capture ELISA with confirmation of ›4-fold rise in neutralizing antibody titers between acute- and convalescent-phase serum samples is also diagnostic[12].

The disease mechanisms are poorly understood and have not been the subject of modern clinical research. Since there is no specific treatment, and management of patients with the disease is extremely problematic, the emphasis is on preventive vaccination. As a

zoonosis, YF cannot be eradicated, but reduction of the human disease burden is achievable through routine childhood vaccination in endemic countries.

Vaccination against YF is important for two reasons. First, the vaccine confers effective immunity against a disease with a high case fatality rate. Second, many countries require proof of vaccination against yellow fever under the International Health Regulations as a condition of entry. Vaccination between 10 days and 10 years before entry at an approved vaccination center is accepted internationally as a proof of vaccination[13].

YFV is a live attenuated vaccine that has been used for over 60 years in approximately 400 million people[14]. Protective levels of neutralizing antibody are found in 90% of vaccinees within 10 days and in 99% within 30 days. Routine use of the vaccine in children in endemic countries has a favorable cost-benefit ratio. Revaccination after 10 years is required under International Health Regulations for a valid travel certificate. The vaccine may be simultaneously administered with most other vaccine, including measles, BCG, inactivated and oral polio, DTaP, meningococcus, hepatitis A, hepatitis B, oral cholera, oral typhoid, and parenteral typhoid vaccines[15].

Derived from the original 17D strain, the live attenuated 17D-204 and 17DD YF vaccines are the most commonly used YF vaccines[16]. They meet the same WHO standards for safety and potency. In addition, their biologic performance is similar with respect to seroconversion rate, quility of the immune response, durability of immunity, safety and tolerability.

There are 10 vaccine manufacturers located in the UK (Arilvax), Germany, France (Stamaril), USA (YF-VAX), Brazil (17DD) and Senegal (Table 1) [17-19]. The vaccine for the study was manufactured by Bio-Manguinhos (YFV-17DD). This company is WHO-prequalified manufacturer linked to the Brazilian Ministry of Health supplies YFV for Brazilian and other countries in South America and Africa[20]. From 2000 to 2004 about 30 million dose of YFV-17DD had been exported to 50 different countries in South and Central America, Africa and Asia[21].

However, several instances of YFV-associated neurotropic disease (YFV-AND) and YFV-associated viscerotropic disease (YFV-AVD) have been reported [22-29]. While YFV-AND has been recognized for 60 years, YFV-AVD is a recently recognized phenomenon. 27 cases of YFV-AND have now been reported with an estimated incidence below 1 in 8 million. Eighteen cases of YFV-AVD have been reported since 1996; approximately half of these cases resulted in death[30]. Vaccination of children at 9 months of age or younger is not recommend, since there is high risk of post-vaccination encephalitis in this age group[31].

In the previous studies, after vaccination with 17D yellow fever vaccine, the most common adverse events were fever, cough, diarrhea and mild events at the inoculation site[32, 33]. But these events are mild and do not interfere with normal activities. In most cases the symptoms were improved spontaneously, or with symptomatic treatment. But adverse events according to sex or age was not statistically significant.

Fortunately, the YF virus has never emerged in Asia, and vaccination for travel is not indicated here. Asia is considered vulnerable to the future introduction of the virus, due to the presence of a large susceptible human population and presence of the urban vector. Demands for the vaccine have increased as it is introduced into routine childhood immunization programmes in endemic countries.

Many travellers receiving YFV had been vaccinated against malaria, typhoid fever, tetanus toxoid and

hepatitis A at the same time, but there was not any meaningful difference between the specific vaccinations and adverse events[34, 35].

Korean children travelers to areas with yellow fever transmission should take precautions against exposure to mosquitoes. Staying in air-conditioned or well-screened quarters and wearing long-sleeved shirts and long pants will help prevent mosquito bites. Vaccinees should receive a completed International Certificate of Vaccination or Prophylaxis, signed and validated with the center's stamp (International Clinic, National Medical Center, Seoul, Korea). This certificate is valid 10 days after vaccination and for a subsequent period of 10 years.

In conclusion, YFV appears to be safe in Korean children, but the additional reaearch on adverse events and effectiveness will be necessary.

한글요약

우리나라 소아에게 황열예방 백신을 투여 후 발생한 부작용에 대한 고찰

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목 적: 황열은 모기에 의해 전염되는 급성 바이러스 출혈열로 중부아프리카와 열대 남아메리카에서 주로 발생한다. 이 연구는 황열 백신을 접종한 소아 및 청소년 여행객에게 이상반응에 대한 임상적 고찰을 시행하여 백신의 안전성 및 이상반응에 대한 정보를 제공하고자 시행하였다.

방 법: 이 연구에서는 2007년 4월 1일-2008년 6월 30일까지 국립의료원 해외여행클리닉을 방문한 소아 및 청소년 125명을 대상으로 하였다. 황열백신 투여 이후 6회의 전화면담을 통해 백신투여와 이상반응과의 관련성에 대하여 평가하였다.

결 과: 황열백신을 투여한 11개월에서 19세 사이의 소아 및 청소년 125명 중 이상반응의 발생은 31명(24.8 %)이었다. 증상으로는 주사부위의 통증(8.8%)이 가장 많았고 뒤를 이어 부종(6.4%), 발적(5.6%), 발열(4.0%), 두통(4.0%)순서였다. 대부분의 이상반응은 백신 투여 후 7일 이내에 발생했으며 성별 및 연령과 이상반응간의 유의한 차이가 없었다. 증상을 호소한 모두 자연적으로 혹은 보존적인 치료에 증상이 호전되었다.

결 론: 이 연구에서 황열백신은 우리나라 소아나 청소년에게 심각한 이상반응 없이 널리 사용될 수 있음을 보여주었다. 그러나 심각한 부작용의 원인이나 위험요소에 대한 연구는 지속적으로 필요할 것이다.

References

1) Thompson MJ. Immunizations for international travel. Prim Care 2002;29:787-814.
2) Mutebi JP, Barrett AD. The epidemiology of yellow fever in Africa. Microbes Infect 2002;4:1459-68.
3) Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. Clin Infect Dis 2002; 34:1369-78.
4) Martin M, Tsai TF, Cropp B, Chang GJ, Holmes DA, Tseng J, et al. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. Lancet 2001;358:98-104.
5) Post PR, de Carvalho R, da Silva Freire M, Galler R. The early use of yellow fever virus strain 17D for vaccine production in Brazil-a Review. Memorias Instituto Oswaldo Cruz 2001;96:849-57.
6) Filippis AM, Nogueira RM, Jabor AV, Schatzmayr HG, Oliveira JC, Dinis SC, et al. Isolation and characterization of wild type yellow fever virus in cases temporally associated with 17DD vaccination during an outbreak of yellow fever in Brazil. Vaccine 2004;22:1073-8.
7) Monath TP. Yellow fever. In: Plotkin SA, Orenstein WA, Paul A, editors. Vaccines. 5th ed. Philadelphia: Elsevier, Inc, 2008:959-1055.
8) Sood SK. Immunization for children traveling abroad. Pediatr Clin North Am 2000;47:435-48.
9) Monath TP. Yellow fever: an update. Lancet Infect Dis 2001;1:11-20.
10) Barnett ED. Yellow fever: epidemiology and prevention.

Clin Infect Dis 2007;44:850-6.
11) Barrett AD, Higgs S. Yellow fever: a disease that has yet to be conquered. Annu Rev Entomol 2007;52:209-29.
12) Centron MS, Marfin AA, Julian KG, Gubler DJ, Sharp DJ, Barwick RS, et al. Yellow fever vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. MMWR Recomm Rep 2002;51:1-11.
13) Spira A. Yellow fever vaccine as a vehicle to better travel medicine. J Travel Med 2005;12:303-5.
14) Fitzner J, Coulibaly D, Kouadio DE, Yavo JC, Loukou YG, Koudou PO, et al. Safety of the yellow fever vaccine during the September 2001 mass vaccination campaign in Abidjan, Ivory Coast. Vaccine 2004;23:156-62.
15) Jong EC, Kaplan KM, Eves KA, Taddeo CA, Lakkis HD, Kuter BJ. An open randomized study of inactivated hepatitis A vaccine administered concomitantly with typhoid fever and yellow fever vaccines. J Travel Med 2002;9:66-70.
16) CDC. Fever, jaundice, and multiple organ system failure associated with 17D-derived yellow fever vaccination, 1996-2001. MMWR Morb Mortal Wkly Rep 2001;50:643-5.
17) Pugachev KV, Guirakhoo F, Monath TP. New developments in flavivirus vaccines with special attention to yellow fever. Curr Opin Infect Dis 2005;18:387-94.
18) Lang J, Zuckerman J, Clarke P, Barrett P, Kirkpatrick C, Blondeau C. Comparison of the immunogenicity and safety of two 17D yellow fever vaccines. Am J Trop Med Hyg 1999;60:1045-50.
19) Collaborative Group for Studies with Yellow Fever Vaccine. Randomized, double-blind, multicenter study of the immunogenicity and reactogenicity of 17DD and WHO 17D-213/77 yellow fever vaccines in children : Implications for the Brazilian National Immunization Program. Vaccine 2007;25:3118-23.
20) Martins MA, Silva ML, Marciano AP, Peruhype-Magalhes V, Eloi-Santos SM, Ribeiro GL, et al. Activation/modulation of adaptive immunity emerges simultaneously after 17DD yellow fever first-time vaccination: is this the key to after 17DD yellow fever first-time vaccination: is this the key to prevent severe adverse events following immunization? Clin Exp Immunol 2007;148:90-100.
21) Camacho LA, Freire Mda S, Leal Mda L, Aguiar SG, Nascimento JP, Iguchi T, et al. Immunogenicity of WHO-17D and Brazilian 17DD yellow fever vaccines: a randomized trial. Rev Saude Publica 2004;38:671-8.
22) Vasconcelos PF, Luna EJ, Galler R, Silva LJ, Coimbra TL, Barros VL, et al. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. Lancet 2001;358:91-7.
23) Chan RC, Penney DJ, Little D, Carter IW, Roberts JA, Rawlinson WD. Hepatitis and death following vaccination with 17D-204 yellow fever vaccine. Lancet 2001;358:121-2.
24) Kitchener S. Viscerotropic and neurotropic disease following vaccination with the 17D yellow fever vaccine, ARILVAX. Vaccine 2004;22:2103-5.
25) Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. Vaccine 2005;23:3256-63.
26) CDC. Adverse events associated with 17D-derived yellow fever vaccination--United States, 2001-2002. MMWR Morb Mortal Wkly Rep 2002;51:989-93.
27) Marfin AA, Eidex RS, Kozarsky PE, Cetron MS. Yellow fever and japanese encephalitis vaccines: indications and complications. Infect Dis Clin North Am 2005;19:151-68.
28) Arya SC. Yellow fever vaccine safety: a reality or a myth? Vaccine 2002;20:3627-8.
29) Monath TP, Cetron MS, McCarthy K, Nichols R, Archambault WT, Weld L, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin 2005;1:207-14.
30) Engel AR, Vasconcelos PF, McArthur MA, Barrett AD. Charaterization of a viscerotropic yellow fever vaccine variant from a patient in Brazil. Vaccine 2006;24:2803-9.
31) McGovern LM, Boyce TG, Fischer PR. Congenital infections associated with international travel during pregnancy. J Travel Med 2007;14:117-28.
32) Osei-Kwasi M, Dunyo SK, Koram KA, Afari EA, Odoom JK, Nkrumah FK. Antibody response to 17D yellow fever vaccine in Ghanaian infants. Bull World Health Organ 2001;79:1056-9.
33) Rabello A, Orsini M, Disch J, Marcial T, Leal Md Mda L, Freire Md Mda S, et al. Low frequency of side effects following an incidental 25 times concentrated does of yellow fever vaccine. Rev Soc Bras Med Trop 2002;35:177-80.
34) Choudri Y, Walop W. Review of adverse events reported following use of fever vaccine-Canada, 1987-2000. Can Commun Dis Rep 2002;28:9-15.
35) Robertson S. Yellow fever: the immunological basis for immunization. Document WHO/EPI/GEN/93. 181993.