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Vaccine 18 (2000) 2963–2969

Vaccine

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Adverse events after Japanese encephalitis vaccination: review of post-marketing surveillance data from Japan and the United States

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Received 29 November 1999; received in revised form 10 March 2000

Abstract

We determined the reporting rates for adverse events following the administration of inactivated mouse-brain derived Japanese encephalitis vaccine (JEV) based on post-marketing surveillance data from Japan and the United States. The rate of total adverse events per 100,000 doses was 2.8 in Japan and 15.0 in the United States. In Japan, 17 neurological disorders were reported from April 1996 to October 1998 for a rate of 0.2 per 100,000 doses. In the United States, no serious neurological adverse events temporally associated with JEV were reported from January 1993 to June 1999. Rates for systemic hypersensitivity reactions were 0.8 and 6.3 per 100,000 doses in Japan and the United States, respectively. Passively collected VAERS surveillance data indicate that characteristic hypersensitivity reactions with a delayed onset continue to occur among JEV recipients and that conservative recommendations limiting its use to travelers at high risk of infection with Japanese encephalitis are appropriate. Published by Elsevier Science Ltd.

Keywords: Japanese encephalitis vaccine; Vaccine adverse events; Post-marketing surveillance

1. Introduction

Japanese encephalitis (JE) is a viral zoonosis spread by *Culex* mosquitoes in most of the countries in Asia, including the Indian subcontinent and the Indonesian and western Pacific (Japan to the Philippines) archipelagoes. Clinically apparent illness has been associated with 5–30% mortality and serious neurological sequelae in one-third of survivors. Before Japanese encephalitis vaccine (JEV) became available, more than 100,000 cases were reported annually and in locations where it is still not widely used JE remains a significant public health problem. Since the development of JEV in the 1950s, an inactivated mouse brain-derived vaccine has been used in many Asian countries while cell culture derived vaccines are used exclusively in the People's Republic of China. The World Health Organization recommends the use of JEV in JE-endemic regions and in Japan, Korea, Thailand and parts of China, its introduction into the routine childhood im-

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0264-410X/00/$ - see front matter Published by Elsevier Science Ltd.
PII: S0264-410X(00)00111-0

munization schedule has reduced the incidence of the disease significantly [1,2]. Because tourism and business activities in JE-endemic areas have been growing, increasing numbers of travelers may be at risk of exposure to JE and are candidates to receive the vaccine. Although the risk of acquiring the disease for short-term travelers is considered to be very small, sporadic cases, including deaths, continue to be reported in tourists travelling to endemic areas [3–5].

Inactivated JEV, derived from infected mouse brain, has been purified so that no myelin basic protein can be detected at the detection threshold of the assay (<2 ng/ml) since 1968. The current vaccine contains <50 mcg of mouse serum protein and 500 mcg of gelatin or 0.02–0.05% by dry weight [6]. All JEV distributed in the Japanese market and for export to the US contain gelatin of either bovine or porcine origin.

Two major groups of adverse events, neurological and allergic, have been associated with JEV. Until recently, the estimated rate of moderate to severe neurological adverse reactions due to JEV from the passive surveillance in Japan was considered to be as low as 1–2.3 per million vaccinations [7]. A recent report from Denmark suggested that the rate for neurological adverse events, including acute disseminated encephalomyelitis (ADEM), could be as high as one per 50,000–75,000 vaccinations, however [8].

Although hypersensitivity reactions to mouse brain derived JEV were not reported as a significant adverse reaction in Asian children despite its widespread use over several decades, numerous cases were noted after its distribution to travelers in Europe, North America and Australia [9–12]. These reactions usually presented as generalized urticaria, often with angioedema, and in some cases were considered life-threatening [13]. A consistent pattern of delayed onset, 1–3 days after vaccination was reported in these cases, complicating the timing of vaccine administration to travelers. Rates for these reactions ranged from 1 to 64 per 10,000 vaccinations, a high incidence that, considering the low risk of disease in travelers, led to recommendations for vaccination of high-risk travelers only [14].

Recently, studies in a small number of children in Japan disclosed two patterns of systemic immediate-type reactions to JEV [15]. One distinct group manifested with cutaneous and respiratory symptoms, the other with cardiovascular symptoms without cutaneous and respiratory signs. Sakaguchi et al. have suggested that the first group of reactions could be caused by gelatin contained in the vaccines [16,17].

In Japan, more than 3 million doses of JEV have been used for routine childhood immunizations annually during the 1990s. Approximately 180,000–200,000 doses of JEV are given in the United States annually, mostly to adult travelers. To obtain an estimate of the reporting rates for these and other adverse events, we reviewed the data from the Japanese and US post-marketing vaccine safety surveillance systems.

2. Materials and methods

2.1. Japan

In Japan, JEV has been used in the childhood immunization program since 1954. Initially it was produced from the Nakayama-NIH strain. Starting in 1989, the vaccine strain was changed to Beijing-1. The primary series consists of two 0.5 ml doses (0.25 ml if the vaccinee is under 3 years old), separated by 1–4 weeks, administered subcutaneously from 9 to 60 months of age. Three booster doses 0.5 ml each are given at the age of 4, 9, and 14 years [18].

The Japanese system for vaccine adverse event surveillance, the National Adverse Reaction Reporting System (NARRS), has been maintained by the Japanese Ministry of Health and Welfare (JMHW) since October, 1994. All immunization providers, school nurses, and parents are required to notify the National Adverse Reaction Reporting System of any vaccine adverse reaction, which meet the reporting criteria (Table 1).

We reviewed all JEV adverse events reported to the NARRS from April 1996 through October 1998. Special attention was paid to physicians' comments on the reporting form, especially for those vaccinees who developed hypersensitivity or neurological disorders. The Japanese Ministry of Health and Welfare collects information on total annual doses of JEV from different manufacturers administered. Through the Japanese National Infectious Disease Surveillance Center, we obtained information on the type and amount of gelatin in JEV produced by each manufacturer.

2.2. USA

In the United States, JEV has been given for investigational use since 1983 (mostly in military personnel and through some travel clinics). Since licensure in December 1992, JEV (Nakayama-NIH strain) has been recommended for travelers to Asia spending a month or longer in endemic areas during the transmission season, especially if travel includes rural areas. Three 1.0 ml doses administered subcutaneously (usually on days 0, 7, and 30) are recommended [19].

The Vaccine Adverse Event Reporting System (VAERS) is the US national passive surveillance system, operated jointly by the Centers for Disease Control and Prevention and the Food and Drug Administration since November 1990. The VAERS encourages voluntary reports from vaccine providers,

Table 1
The National Adverse Reactions Reporting System: criteria for reporting JEV adverse events — Japan

Adverse events	Onset interval after vaccination
Anaphylaxis	24 h
Encephalitis/encephalopathy	7 days
Other Central Nervous System disorders	7 days
Systemic eruption or fever above 39°C	2 days
Miscellaneous abnormal reactions not otherwise seen after routine vaccination	Any time

vaccinees or their parents, but reporting from vaccine manufacturers is mandatory [20,21].

We reviewed all reports received by the VAERS since the licensure of JEV until the end of 1998, including copies of medical records when those were supplied with the report. To calculate the reporting rates of adverse events following administration of the US licensed JEV, US Biologic Surveillance Data were used as the denominator. This system collects voluntary reports from vaccine manufacturers of total net doses of vaccine distributed (personal communication from Robert Snyder, CDC Information Systems-Biologics Surveillance, 1999).

3. Results

3.1. Japan

From April 1996 through October 1998, approximately 9.4 million doses of JEV from seven manufacturers were administered. A total of 263 adverse events (99 in 1996, 88 in 1997, and 76 in April–October of 1998) were reported to the NARRS. The reporting rate for all adverse events was 2.8 per 100,000 vaccinations. Reports included 32 cases of anaphylaxis (reported as shock or cyanosis), 17 neurological disorders, and 71 cases of systemic eruption, urticaria or edema (Table 2). The majority of the reports were from vaccine providers and public health nurses. Lot information was available for all reports: 88 lot numbers from six manufacturers were reported. Ages of reported cases ranged from 1 to 15 years with a distribution similar to that expected based on the recommended age of vaccination; 129 (49%) were males and 134 (51%) females. No information on other vaccines administered concurrently with JEV was available.

Among 17 reports of neurological disorders, 16 cases had meningitis or meningoencephalitis including five probable cases of ADEM (0.2 per 100,000 vaccinations). The median onset interval from vaccination was 1 day (range 1 h–16 days). The only fatal case was in a 3-year old boy who 2 days after receiving JEV, developed fever, became comatose, and died from brain edema 4 days after vaccination. The reporting rates of anaphylactic shock, when analyzed by vaccine gelatin concentrations (0.02% vs 0.01% dry weight volume of bovine gelatin) or by the type of gelatin (bovine vs swine gelatin) did not differ significantly.

3.2. USA

More than 813,000 doses of JEV were distributed in the United States between 1993 and 1998. A total of 122 reports were submitted to the VAERS with vaccination dates during the same interval. In 41 (33.6%) cases, JEV was administered simultaneously with other travel vaccines against cholera, diphtheria, hepatitis A and B, influenza, meningococcal meningitis, poliomyelitis, rabies, tetanus, typhoid and yellow fever. Lot information for JEV was available in 105 reports: 42 different lot numbers were reported. Mean age of vaccinees was 32 years (ranging from 2 to 64). The male to female ratio was 61:59 (in two cases no information on the gender of the vaccinee was available). Twenty-five reports came from military settings (20 males and

Table 2
JEV adverse events from the National Adverse Reaction Reporting System — Japan, 1996–1998

Fiscal year	Doses administered (in millions)	Total number of adverse events reported	Adverse events per 100,000 vaccinations	Reports of systemic eruption, or urticaria/edema	Adverse events per 100,000 vaccinations
1996	3.4	99	2.9	27	0.8
1997	3.8	88	2.3	22	0.6
1998[a]	2.2	76	3.6	22	1.0
Total	9.4	263	2.8	71	0.8

[a] April–October, 1998.

Table 3
Adverse events reported to the Vaccine Adverse Event Reporting System following immunization with inactivated JEV (administered alone or in combination with other vaccines) — United States, 1993–1998

		All adverse events		Reports of urticaria and/or edema	
Year	Doses distributed[a]	Total number	Rate per 100,000 doses distributed	Total number	Rate per 100,000 doses distributed
1993	471,695	17	40.8	9	21.6
1994	174,629	21	12.0	4	2.3
1995	162,925	21	12.9	11	6.8
1996	158,399	20	12.6	7	4.4
1997	174,862	20	11.4	10	5.7
1998	101,312	23	22.7	10	9.9
Total	813,822	122	15.0	51	6.3

[a] Data from US Biologics Surveillance System, Centers for Disease Control and Prevention.

five females). The reporting rate by year has been relatively constant (11.4–22.7/100,000 doses) with the exception of the first year of reporting when the rate was approximately three times higher (Table 3).

In 10 vaccinees, the adverse event resulted in a short-term hospitalization. Although 33 vaccinees required an emergency room visit, none resulted in long term sequelae or a disability. Among the 122 cases, the most frequently reported symptoms were headache, pruritus, rash, fever, nausea, urticaria, vasodilatation and dizziness. These symptoms, alone or in combination, occurred in 84 (69%) patients. The only death reported was in an 8-year old boy with a complex congenital heart condition (double outlet right ventricle with pulmonary stenosis) who had a syncopal episode in conjunction with cardiorespiratory failure 13 days after receiving the second dose of JEV. He died of congestive heart failure, renal failure and acute pneumonia 12 days later. One 55 year old male gradually developed Guillain–Barré syndrome (GBS) on the 17th day after JEV vaccination and 5 weeks after a dose of rabies vaccine. A week before the onset of symptoms he also reported having gastroenteritis. He recovered completely. The other report of neurological illness was in a 22-month old child, who developed a febrile seizure ($t = 40^{\circ}C$) 3 days after the second dose of JEV which was inadvertently administered as an overdose of 1.0 ml instead of 0.5 ml. Symptoms of upper respiratory infection were present at the time of vaccination. He recovered completely after treatment. There were no other reports of neurological adverse events temporarily associated with receipt of JEV, for a total reporting rate of 0.2/100,000 for all neurological adverse events.

Fifty-one vaccinees (42%) had symptoms of systemic urticaria and/or edema after JEV (6.3/100,00 doses). Of these, 18 (37%) had onset on the day of vaccination and 25 (51%) within 1–3 days after vaccination. Forty-two reports provided a detailed history: 23 (55%) developed systemic urticaria and/or angioedema on the first dose, 22 vaccinees (52%) required an emergency room visit, six required hospitalization for 1–2 days. Three vaccinees had bradycardia, cyanosis, or hypotension without urticaria or edema on the day of vaccination; for two of them the reaction occurred after the first dose of JEV.

4. Discussion

Inactivated mouse brain derived JEV is considered to be moderately reactogenic with local and systemic side effects reported by 10–30% of vaccinees [22–25]. Since the development of inactivated JEV, derived from mouse brain substrate, the possibility of neurological complications has been a concern. In the initial field trial of a crude formalin inactivated mouse brain vaccine among US soldiers in Okinawa, eight cases of GBS were observed in 53,000 vaccinees (rate 15.1 per 100,000 doses); however, cases also occurred in non-vaccinated persons in what may have been a coincidental outbreak of acute polyneuritis [26]. In pre-licensure studies in the US (mostly among US military) between 1983 and 1992 one case of Guillain–Barré syndrome temporally related to JEV immunization was reported in 20,000 vaccinees [10]. No other serious neurological complications were reported. The rate of allergic reactions (generalized urticaria and/or angioedema) was 15–18 per 10,000 vaccinees. The number of participants in these US studies totaled approximately 63,000 persons.

An early prospective study of the safety of JEV in Japan, during which 38,384 persons received crude or purified mouse brain derived JEV, found no neurological complications within a month after immunization [7]. However, seven anecdotal ADEM cases temporally related to JE vaccination have been reported recently from Japan, plus four cases from Korea; an additional case followed administration of mouse brain derived JEV with hantaviral vaccine [27–31]. Although these

anecdotal reports do not permit estimation of a rate, the controlled distribution of of JEV in Denmark combined with a sensitive vaccine adverse event reporting system allowed an estimate of severe neurological reactions in 1/50,000–1/75,000 traveler–vaccinees. A passive AE reporting system such as the VAERS would be expected to detect some cases temporally related to JE vaccination. For example, assuming that 813,000 doses of JE vaccine were administered among 300,000 persons (average of 2.7 doses per person) and that the true rate of neurological reactions was 1/75,000, at a 75% sensitivity level, we would expect the VAERS to detect at least three cases of such illnesses post-vaccination. The absence of reported ADEM and other neurological illnesses following JEV in the US between 1993 and 1999 is in contrast with the Danish experience and could reflect a lower rate of such vaccine complications or a lower sensitivity of VAERS to detect them.

The reporting rate for JEV adverse events from Japan was approximately one order of magnitude lower than in the US. There are several possible explanations. First, the Japanese National Adverse Reaction Reporting System has strict predefined reporting criteria for which specific vaccine adverse event should be reported. In contrast, the US VAERS prompts the reporting of any suspected vaccine adverse event. Secondly, the vaccinee populations were quite different; in Japan, children usually receive JEV at 3, 4, 9, 14 years, and in the US vaccinees are nearly exclusively adults. The clinical features and risk of adverse reactions to JEV could vary in different age groups and by vaccination schedule. Furthermore, the threshold for reporting may differ in adults who can report adverse events directly and in children, in whom acute rash illnesses are more common and reporting is indirect, through their parents or guardians. The JEV used in the two countries also are prepared from different viral strains, contain different gelatin concentrations, and differ in their degree of purification. All JE vaccines marketed in Japan are made from the Beijing-1 strain, which is more antigenic, permitting formulation in a smaller volume [32].

Forty-two percent of adverse events reported through VAERS were hypersensitivity reactions. Interestingly, more than a half of the cases had a delayed onset of 1–3 days, similar to previously reported observations. This unusual feature of a delayed onset of urticaria and angioedema appears to be a hallmark of the hypersensitivity reactions associated with mouse-brain derived JEV.

Experience from Denmark suggested a two-fold higher risk of allergic reactions among females. When VAERS reports from military vaccinees were excluded, US cases of hypersensitivity were reported in 54 females and 41 males, or 57 and 43% respectively. However, the sex ratio of vaccinees in the US is unknown and no inference can be made about differences in risk by sex. No significant difference in the sex ratio of cases reported from Japan was noted.

We did not observe a difference in the rates of anaphylactic shock associated with mouse-brain JEV containing either bovine or porcine gelatin. Anecdotal reports linking anaphylaxis to the gelatin content of JEV support the need for further clinical and laboratory studies to confirm this association and to establish the pathogenesis of hypersensitivity reactions to mouse brain derived JEV [15–17].

The only JEV associated fatal case reported from Japan was judged to be related to the vaccine by the Vaccine Compensation Program of JMHW. The case of ADEM occurred in a healthy boy without underlying predisposition and he did not have any other illness, vaccine or medication prior to the onset of illness. The only VAERS report of death temporally associated with JEV was probably not attributable directly to vaccination. In two other instances (pre-licensure cases not reported to VAERS), death occurred in JEV vaccinees who also received typhoid or plague vaccine and the cause of death could not be determined [19,33].

Data from the NARRS and the VAERS are subject to the usual limitations for passive surveillance systems [34]. Reporting sensitivity of a passive surveillance systems depends on the type (previously known/unknown) and severity of the outcome, and can range from $<1\%$ (rash following measles vaccination) to 72% (for vaccine associated paralytic poliomyelitis) [35]. Underreporting of minor vaccine adverse events, including local hypersensitivity reactions can be a problem. In addition, delayed reactions that develop after a vaccinee has embarked on a journey may go unreported. However, most severe neurological events following JE vaccination, including ADEM and GBS, would probably be captured by the surveillance system. The absence of detected cases in contrast to the number reported among Danish vaccinees may reflect other antecedent events or cofactors that underlie the pathogenesis of ADEM, including host genetic factors. But the most likely explanation is the increased sensitivity of surveillance in Denmark due to its mandatory nature [8,9].

Prospective studies of vaccine safety via controlled clinical and field studies before licensure may be limited by sample size and the homogeneity of the study participants, so that rare adverse events are not identified [34]. Post-marketing surveillance (passive or active) may be required as a condition of licensure to monitor the frequency of vaccine adverse events that may have been detected anecdotally pre-licensure or to detect adverse events that occur at a rate too low to have been noted during pre-licensure trials [8,13,19].

Although reports of hypersensitivity reactions through VAERS may have underestimated their true frequency, the observation that an unusually high percent of reported reactions had a delayed onset is consistent with previous observations and suggests that this profile is highly characteristic of inactivated mouse-brain derived JE vaccine.

Reports of acute, potentially life-threatening hypersensitivity reactions in recipients of inactivated mouse-brain derived JEV from over 10 countries prior to the vaccine's licensure in the US influenced the Advisory Committee on Immunization Practices (ACIP) to formulate relatively conservative recommendations for its use in travelers and a requirement for post-marketing surveillance. Results of post-marketing surveillance via VAERS support the limited use of JEV only for selected travelers at high risk, as currently recommended by ACIP [19].

Acknowledgements

We would like to thank Kiyosu Taniguchi, Yasuko Matsunaga, and Sakae Inouye of the National Infectious Disease Surveillance Center, Shinjuku-ku, Tokyo, Japan for providing Japanese data, and Andy Pelletier of the Centers for Disease Control and Prevention, Atlanta, Georgia, USA for his advice.

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