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Influenza vaccination and Guillain Barre syndrome☆

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Abstract

Acute and severe Guillain Barre Syndrome (GBS) cases reported following influenza vaccine to the Vaccine Adverse Events Reporting System (VAERS) database from 1991 through 1999 were examined. Endotoxin concentrations were measured using the *Limulus* amebocyte lysate assay in influenza vaccines. There were a total of 382 cases of GBS reported to the VAERS database following influenza vaccination (male/female ratio, 1.2). The median onset of GBS following influenza vaccine was 12 days (interquartile range, 7 days to 21 days). There was an increased risk of acute GBS (relative risk, 4.3; 95% confidence interval, 3.0 to 6.4) and severe GBS (relative risk, 8.5; 95% confidence interval, 3.7 to 18.9) in comparison to an adult tetanus–diphtheria (Td) vaccine control group. There were maximums in the incidence of GBS following influenza vaccine that occurred approximately every third year (1993, 1996, and 1998) and statistically significant variation in the incidence of GBS among different influenza manufacturers. Influenza vaccines contained from a 125- to a 1250-fold increase in endotoxin concentrations in comparison to an adult Td vaccine control and endotoxin concentrations varied up to 10-fold among different lots and manufacturers of influenza vaccine. The biologic mechanism for GBS following influenza vaccine may involve the synergistic effects of endotoxin and vaccine-induced autoimmunity. There were minimal potential reporting biases in the data reported to the VAERS database in this study. Patients should make an informed consent decision on whether to take this optional vaccine based upon its safety and efficacy and physicians should vigilantly report GBS following influenza vaccination to the VAERS in the United States so that continued evaluation of the safety of influenza vaccine may be undertaken.

Keywords: Autoimmunity; Endotoxin; Guillain Barre Syndrome; LAL assay; VAERS

Introduction

Influenza vaccine is administered annually during the fall season in areas having a temperate climate. The composition of the subvirion influenza vaccine includes two type A antigens and one type B antigen of influenza virus. Because antigenic drift variants are responsible for annual epidemics that occur during the interpandemic periods, distinct, antigenic variant strains of influenza A and B emerge and become predominant over a period of approximately 2 to 5 years, only to be replaced by the next predominant antigenic variants [1,2]. Currently, influenza vaccine is recommended for persons 65 years and older, children and teenagers, pregnant women, those at high risk, such as healthcare workers, and persons who want to reduce the likelihood of contracting influenza [3].

One goal of this study was to determine whether influenza vaccination and Guillain Barre Syndrome (GBS) are temporally related, whether differences in the incidence rates of GBS following influenza vaccination occur annually, and whether there are differences in the incidence rates of GBS following influenza vaccination manufactured by different manufacturers.

It has been previously been reported that A/New Jersey swine influenza vaccine was notable for relative risks of GBS ranging from 4.0 to 7.6 for 6- or 8-week periods after

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vaccination [4–8]. Subsequent studies of GBS have found low relative risks of 1.4 in 1978–1979, 0.6 to 1.4 in 1979–1980 and 1980–1981, and 1.1 in 1980–1988; these relative risks were not significantly different from 1 [9–11]. For the 1990–1991 influenza season an elevated risk was found among vaccinated person 18 to 64 years of age (relative risk, 3.5; 95% confidence interval, 1.5 to 6.3) [12].

Another goal is to offer an etiology for the demyelination of the peripheral nervous system in persons who were injected with influenza vaccine prior to the onset of GBS. Demyelination of the peripheral nerves in GBS is believed to be immune-mediated, resulting in a slowing of nerve conduction due to segmental demyelination and infiltration by mononuclear cells.

The final goal of this study was to measure the endotoxin concentrations present in commercially available influenza vaccines using the *Limulus* amebocyte lysate (LAL) assay. Several studies have used the LAL assay to measure the endotoxin concentrations present in commercial vaccines [13–15]. The authors of these studies concluded that the monitoring and reporting of endotoxins and other contaminants in vaccines might be useful in understanding some of the side effects observed in vaccine recipients. They also concluded that the selection of vaccines with the lowest endotoxin levels might help to avoid some of the adverse effects of vaccinations.

Materials and methods

In this study the Vaccine Adverse Events Reporting System (VAERS) database was analyzed to determine the incidence of GBS. The VAERS database is an epidemiological compilation maintained by the Centers for Disease Control and Prevention (CDC) since 1990. Adverse events following vaccination are required to be reported to this database as mandated by United States law. The protocol for reporting serious events to VAERS requires written and telephonic confirmation by the CDC. The CDC follows-up on serious events 1 year after they occur to determine whether the patients had fully recovered. The Food and Drug Administration (FDA) inquires into deaths reported to the VAERS database by contacting the patient's healthcare provider and physician. The FDA also continually monitors reports to the VAERS database to determine whether any vaccine or vaccine lot has a higher than expected incidence rate of events. The VAERS Working Group of the CDC, the FDA, and ourselves analyze and publish epidemiologic studies based upon analyses of the VAERS database. A recent study by the VAERS Working Group of the CDC stated that VAERS is simple to use, flexible by design, and the data are available in a timely fashion [16]. Our principal aim here is to compare GBS following influenza vaccination with an adult tetanus–diphtheria (Td) vaccine control group based upon analysis of the VAERS database, a massive database otherwise unattainable. The reason for choosing Td as an adult vaccine control group is that the Institute of Medicine (IOM) of the U.S. National Academy of Sciences has concluded that the evidence favors a causal relationship between Td vaccine and GBS [17].

We examined information reported to the VAERS database for the period 1991 through 1999 using Microsoft Access. The Biological Surveillance Summary Reports of the CDC were used to determine the incidence of adverse reactions following vaccination. The Biological Surveillance Summaries noted that 401,201,061 influenza vaccinations were administered from 1991 through 1999. The incidence of GBS reported to the VAERS database following adult Td vaccination served as an adult vaccine control group, providing a maximal estimate of the background rate of GBS reported to the VAERS database. The Biological Surveillance Summaries noted that 129,293,354 Td vaccinations were administered to adults from 1991 through 1999. We also examined the incidence of severe cases of GBS reported to the VAERS database following influenza vaccination in comparison to Td vaccination. A severe case of GBS was defined as a case of GBS in which there was only partial recovery and significant residual disability 1 year later.

We also examined the incidence of GBS reported following influenza vaccine manufactured by Wyeth, Parke-Davis, Lederle, Connaught-Aventis Pasteur, and Evans Medical International. We used denominators obtained from the Biologic Surveillance Summaries of the CDC for the number of doses of each vaccine administered during their respective time periods. The CDC regulations require that the identities of the manufacturers remain unknown, because they claim this information is confidential and proprietary between themselves and the manufacturers [18]. Therefore, we have encoded the manufacturers we examined by assigning each an encoding letter.

Central to our study is the premise that in a similarly aged population an unbiased search for the incidence rate of a specific adverse reaction to a particular vaccine would yield similar data to the incidence rate following another vaccine. This premise is founded on the understanding that the inherent limitations in the accuracy of reported adverse reactions in the VAERS database may be expected to equally affect the reports originating from both vaccines under study. Likewise, the number of administered doses of a particular vaccine, based on the Biological Surveillance Summaries of the CDC, should be unbiased since any inherent limitations of the Biological Surveillance Summaries should equally apply to each vaccine under study. In performing the statistical analyses, the premise of equal reactogenicity between vaccines forms the basis of our null hypothesis. The statistical method used is a 2×2 contingency table which posits that the total number of adverse reactions following a control vaccine and the number of doses administered (based upon the Biological Surveillance Summaries for the period examined) are the expected values, and the total number of adverse reactions following the

Table 1
A yearly comparison between Td and influenza vaccination for associated Guillain Barre Syndrome (GBS) adverse reactions reported to VAERS among those residing in the United States from 1991 through 1999

Year	Incidence of GBS per 10 million Td vaccinations	Incidence of GBS per 10 million influenza vaccinations	Relative risk	Attributable risk	Percentage of association	Statistical significance	95% Relative risk confidence interval
1991	0.0	6.7	—	—	100	$P < 0.0001$	—
1992	1.5	7.4	4.9	3.9	83	$P < 0.05$	1.2 to 20.2
1993	1.3	16.3	12.5	11.5	93	$P < 0.0001$	3.0 to 50.4
1994	1.2	7.7	6.4	5.4	86	$P < 0.005$	1.6 to 27.0
1995	2.8	13.4	4.8	3.8	83	$P < 0.002$	1.7 to 12.9
1996	5.5	18.2	3.3	2.3	77	$P = 0.0020$	1.5 to 7.2
1997	2.0	6.8	3.4	2.4	77	$P < 0.05$	1.1 to 11.4
1998	3.8	7.5	2.0	1.0	67	Not significant	0.84 to 4.7
1999	1.2	5.0	4.2	3.2	81	Not significant	0.81 to 14.3

vaccine under study and the number of doses administered (based upon the Biological Surveillance Summaries for the period examined) are the observed values. In this analysis, the statistical package contained in Corel's Quattro Pro is used and a P value of 0.05 is accepted as statistically significant.

The incidence rate of adverse reactions following the vaccine under study in comparison to the incidence rate of adverse reactions following the control vaccine group is used to determine the relative risk, attributable risk and the percentage of association of the adverse reactions of the vaccine under study. Relative risk is obtained by dividing the incidence rate of the adverse reactions following the vaccine under study by the incidence rate of the adverse reactions following the vaccine control group. The attributable risk is obtained by subtracting 1 from the relative risk. The percentage of association value is determined by dividing the relative risk value by the relative risk value plus 1 and multiplying this computed value by 100.

Limulus E-Toxate kits were purchased from Sigma Chemical Company (St. Louis, MO). They contained individual test tubes of lyophilized LAL, an endotoxin-free distilled water negative control, and a 2-μg endotoxin standard positive control. One-hundred-microliter samples of vaccine were withdrawn sterilely by endotoxin-free syringes and needles and injected directly into the test vials containing lysate. After mixing and 1 h of incubation at 37°C in a water bath, the tubes were gently inverted. Formation of a firm gel was designated a positive result. A weak gel which could broken was scored $\pm$, whereas a watery fluid result was considered a negative. When it was necessary to dilute the sample because of high levels of endotoxin, dilutions were made with the negative control solution as diluent. Samples of the negative control were run through an identical mock dilution procedure to rule out contamination due to our manipulations. Also, assay sensitivity experiments were run using the positive controls provided. The assay sensitivity for a positive result was determined to be 0.38 endotoxin units, (EU)/ml and a $\pm$ result was determined to be 0.304 EU/ml. Although the LAL is a qualitative not quantitative test, it was made quantitative by this method. Commercially available vaccines produced in the 1970s that were analyzed in this way are summarized in Table 3.

Results

We found that a total of 382 cases of GBS were reported to the VAERS database following influenza vaccine administered from 1991 through 1999. There were 172 reports of GBS classified as occurring in female influenza vaccine recipients, 200 reports of GBS classified as occurring in male influenza vaccine recipients, and 10 reports of GBS in influenza vaccine recipients that did not specify a sex (male/female ratio, 1.2). The median onset of GBS following influenza vaccine was 12 days (interquartile range, 7 to 21 days).

A wide range of reactogenicity following influenza vaccination was noted in our year by year analysis. A statistical increase in the incidence of GBS following influenza vaccination, in comparison to the Td vaccine control group, for the years 1991 through 1997 was noted and is summarized in Table 1. The relative risk of GBS following influenza vaccination, in comparison to adult Td vaccination, remained $\geq$2.0, the attributable risk remained $\geq$1.0, and the percentage of association between influenza vaccination and Guillain Barre Syndrome in comparison to our Td vaccine control group remained $\geq$67% for each year examined. We found that maximums in the incidence of GBS following influenza vaccine occurred approximately every third year (1993, 1996, and 1998). Furthermore, we observed that the yearly incidence of GBS following influenza vaccination varied statistically significantly when examining the maximum incidence years in comparison to the minimum incidence years.

The overall mean incidence of GBS following influenza vaccination was 9.5 per 10 million influenza vaccinations in

Table 2
A statistical comparison between manufacturers for the incidence of GBS following influenza vaccination

Manufacturer type (incidence of GBS per million vaccines)	Statistical significance vs A (relative risk)	Statistical significance vs B (relative risk)	Statistical significance vs C (relative risk)	Statistical significance vs D (relative risk)	Statistical significance vs E (relative risk)
A (0.58)	—	Not significant (0.63)	Not significant (1.2)	Not significant (0.67)	$P < 0.0001$ (0.45)
B (0.92)	Not significant (1.6)	—	$P < 0.05$ (2.0)	Not significant (1.1)	Not significant (0.71)
C (0.47)	Not significant (0.81)	$P < 0.05$ (0.51)	—	$P < 0.05$ (0.55)	$P < 0.0001$ (0.36)
D (0.86)	Not significant (1.5)	Not significant (0.93)	$P < 0.05$ (1.8)	—	$P < 0.05$ (0.66)
E (1.3)	$P < 0.0001$ (2.2)	Not significant (1.4)	$P < 0.0001$ (2.8)	$P < 0.05$ (1.5)	—

comparison to 2.2 per 10 million Td vaccinations. The incidence rate of GBS following influenza vaccine was statistically increased in comparison to the adult Td vaccine control group (relative risk, 4.3; attributable risk, 3.3, percentage of association, 81%; $P < 0.0001$; 95% relative risk confidence interval, 3.0 to 6.4). The incidence of severe GBS was elevated following influenza vaccination in comparison to the adult Td vaccine control group. The overall mean incidence of severe GBS was 3.9 per 10 million influenza vaccinations in comparison to 0.46 per 10 million adult Td vaccinations. The incidence rate of severe GBS following influenza vaccination was statistically increased in comparison to the adult Td vaccine control group (relative risk, 8.5; attributable risk, 7.5; percentage of association, 89%; $P < 0.0001$; 95% relative risk confidence interval, 3.7 to 18.9).

In Table 2, we determined that there were statistically significant differences in the incidence of GBS when comparing the different manufacturers of influenza vaccine. We determined that manufacturer E had the highest incidence of GBS and it had a statistically significantly higher incidence of GBS in comparison to manufacturers A, C, and D. We also determined that manufacturers B and D had statistically significant increases in the incidence of GBS in comparison to manufacturer C.

In Table 3, we determined the endotoxin concentrations present in various lots of commercial influenza vaccines and a Td vaccine control. We found that influenza vaccines contained from a 125- to a 1250-fold increase in the concentration of endotoxin in comparison to the Td vaccine control. We also found that there was up to a 10-fold variation among different lots and manufacturers of influenza vaccine.

Discussion

The results of our analysis showed that both acute and severe cases of GBS following influenza were statistically elevated in comparison to the adult Td vaccine control group. This is particularly remarkable considering that the IOM has reported that evidence favors a causal relationship between Td vaccine and GBS [17].

Lasky et al. have examined GBS within 6 weeks following influenza vaccines by retrospective period cross-sectional examination [19]. They interviewed a population of 180 adults with GBS and found that 19 patients had confirmed influenza vaccination in the 6 weeks before the onset of GBS. They determined that overall there was a 2.4 statistically significant ($P < 0.001$) increased relative risk of GBS within 6 weeks following influenza vaccine in comparison to their control population and that when age, season, and sex were controlled for there was a 1.7 statistically significant ($P < 0.05$) increased relative risk of GBS within 6 weeks following influenza vaccine. They observed that the background incidence of GBS in their adult control populations was 1.45 cases per 10 million persons per week (8.7 cases per 10 million persons per 6-week period), where as during the 6 weeks following influenza vaccination the incidence of GBS was 14.79 cases per 10 million vaccina-

Table 3
Measured concentration of endotoxin present in each lot of vaccine analyzed

Manufacturer	Lot	Type of vaccine	Concentration of endotoxin (EU/ML)
Connaught	1494FK	Influenza	380
Connaught	1505FK	Influenza	380
Connaught	1527FK	Influenza	304
Connaught	1489FK	Influenza	38
Merck Sharp & Dohme	4840G	Influenza	304
Merck Sharp & Dohme	4871G	Influenza	38
Parke–Davis & Co.	913362A	Influenza	38
Parke–Davis & Co.	909515A	Influenza	304
Eli Lilly & Co.	9PB83A	Influenza	38
Lederle	466-340	Td	0.304

tions. They found that the peak incidence of GBS occurred during the second week following influenza vaccination. They also found a male/female ratio of 1.2 for GBS following influenza vaccination.

The results of our analysis are very similar those of Lasky et al. We both observed that there was a statistically significant increase in the incidence of GBS following influenza vaccination in comparison to our background populations and both of our overall relative risks were similar (2.4 vs 4.3). We observed based upon our interquartile range of the incidence of GBS from 7 to 21 days (4.75 cases per 10 million vaccinations) that there was an increased relative risk of 1.6 in comparison to the background rate (2.90 cases per 10 million persons per 2-week period) of GBS determined by Lasky et al. and that this was a similar relative risk value determined by Lasky et al. We both observed that the peak incidence of GBS following influenza occurred in the second week following vaccination and a male/female ratio of 1.2 was observed by both of us for GBS following influenza vaccination. In light of the similarities in the data we observed and those of Lasky et al., this tends to mutually validate both sets of observations and show that there may be minimal potential reporting biases present in the VAERS database.

We hypothesize that the GBS observed in this study following influenza vaccine may arise by either molecular mimicry or nonspecific activation of the immune system. We believe there may be chicken P2 protein present in influenza vaccines (influenza vaccines prepared from the allantoic fluid of chicken embryos), despite some previous studies to the contrary that may have lacked appropriate controls [20–23] and that P2 protein may be the target for a humoral or cell-mediated immune reaction observed in patients developing GBS following influenza vaccination. The concept of vaccine-induced autoimmunity has been analyzed in a recent review by Shoenfeld and Aron-Maor [24]. They report that influenza vaccine may increase the risk of inducing GBS and suggest that genetic predisposition of the patient presents a very important factor in the development of autoimmune disorders following vaccination.

The results of our endotoxin analysis indicated that influenza vaccines contain considerably more endotoxin then the Td vaccine control employed. In addition, the concentrations of endotoxin present in influenza vaccine varies from one manufacturer to another and in different lots of influenza vaccine. Since influenza vaccines are prepared in embryonated chicken eggs, *Salmonella* contamination may influence the concentration of endotoxin present in the different influenza vaccines examined [13].

The presence of endotoxin in influenza vaccines is a serious cause for concern because it has been shown to elevate antibody production to unrelated antigens. The injection of only microgram quantities of endotoxin together with a group of antigens into various species has been shown to result in a pronounced increase in antibody titer. In addition, it has been shown that endotoxin may increase the permeability of the blood–brain barrier to allow circulating colloids normally excluded from the brain to enter it [25]. The presence of endotoxin in influenza vaccine, because of its ability to increase the permeability of the blood–brain barrier, may allow proteins that may have deleterious neurogenic properties to enter into the nervous system and, because of its activity in elevating antibody production, may contribute to the autoimmune conditions observed in GBS. Therefore, the synergistic effects of endotoxin and vaccine-induced autoimmunity may contribute to the GBS observed in this study following influenza vaccination.

Although influenza vaccine is routinely given during the fall and early winter seasons in regions with a temperate climate, the efficacy of this vaccine in any given year cannot be determined prospectively because the vaccine is not tested against the current year's influenza strains. Retrospective assessment of influenza vaccination in past years reveals efficacy values that range from poor to good [26,27]. In recognition of some of the problems with the current inactivated influenza vaccine, many efforts are currently being aimed at improving its efficacy and providing longer lasting immunogenicity [28–30]. It is noteworthy that there are medications effective in the prevention and treatment of influenza, including Amantadine hydrochloride (Endo Laboratories), Tamiflu (Roche Laboratories), indicated for the treatment of early infection by influenza A and B viruses, and Flumadine (Forest Laboratories), for the prophylaxis and treatment of various strains of influenza A infection in children and adults.

As an optional vaccine for high-risk patients in a rapidly enlarging population, influenza vaccination should only be given with informed consent. Patients need to understand the potential benefits, limitations, and risks involved with influenza vaccination. In years when there is poor antigenic match between the influenza vaccine in use and the influenza strains infecting the population, the manufacturers and/or the FDA and CDC should release such information to physicians and patients so that informed consent decisions may be realized. Such information is not currently made available to physicians and patients on a timely basis. The elderly need to be informed of the markedly reduced efficacy of influenza vaccine in comparison with that in other age groups.

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