A one year followup of chronic arthritis following rubella and hepatitis B vaccination based upon analysis of the Vaccine Adverse Events Reporting System (VAERS) database

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Abstract

Objectives

This analysis examined the incidence rate of chronic arthritis adverse reactions reported following adult rubella and hepatitis B vaccinations. In this analysis, etiologic mechanisms for chronic arthritis following adult rubella and hepatitis B vaccines were also explored.

Methods

The Vaccine Adverse Events Reporting System (VAERS) database was analyzed for the incidence rate of reported cases of chronic arthritis in comparison to Tetanus-diphtheria (Td) and tetanus toxoid adult vaccine control groups.

Results

Chronic arthritis adverse reactions following adult rubella vaccination were primarily reported in females (female/male ratio = 3.0), at about 45 years-old, and at a mean onset time of 10-11 days following vaccination. Chronic arthritis adverse reactions following adult hepatitis B vaccination were also primarily reported in females(female/male ratio = 3.5), at about 33 years-old, and with a mean onset time of 16 days following vaccination. The incidence rates of chronic arthritis following adult rubella and adult hepatitis B vaccinations were statistically significantly increased, by $\chi 2$ analysis, in comparison to the adult vaccine control groups. The attributable risk of chronic arthritis following adult rubella vaccine ranged from 32 to 53 and from 5.1 to 9.0 following adult hepatitis B vaccine in comparison to the adult vaccine control groups.

Conclusion

This study revealed that adult rubella and adult hepatitis B vaccines were statistically associated with chronic arthritis which persisted for at least one year. The etiology for these adverse reactions may involve autoimmune mechanisms. Furthermore, potential biases in the reporting rates of adverse reactions to VAERS were not observed.

Key words

Adult, autoimmune, hepatitis B, rubella, rheumatoid arthritis, vaccine, VAERS.

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Introduction

We have previously reported on arthritic conditions in *Clinical and Experimental Rheumatology* following adult rubella vaccination administration from 1991 through 1998 and following adult hepatitis B vaccination from July 1990 through August 1999 (1, 2). We found that arthritic reactions reported following adult rubella vaccination were as follows: 78 per million adult rubella vaccinations for arthralgia, 24 per million adult rubella vaccinations for arthrosis, 19 per million adult rubella vaccinations for arthritis and 5.0 per million adult rubella vaccinations for joint disease and that the incidence of arthritic reactions following adult rubella vaccination were statistically significantly increased, by $\chi 2$ analysis, in comparison to an adult hepatitis A vaccine control group. Arthritic reactions reported following adult hepatitis B vaccination were as follows: 27 per million adult hepatitis B vaccinations for arthralgia, 5.0 per million adult hepatitis B vaccinations for arthritis, 2.4 per million adult hepatitis B vaccinations for joint disease and 4.7 per million adult hepatitis B vaccinations for arthrosis and that the incidence of arthritic reactions following adult hepatitis B vaccination were statistically significantly increased, by $\chi 2$ analysis, in comparison to an adult Td vaccine control group. However, it should be noted that there is the potential that some of the cases of arthritic reactions we analyzed following adult rubella vaccination and adult hepatitis B vaccination may have been, acute self-limited reactions that did not lead to chronic serious problems.

The purpose of this analysis was to examine chronic arthritic adverse reactions reported to the Vaccine Adverse Events Reporting System (VAERS) database following adult rubella vaccination and adult hepatitis B vaccination. The VAERS database has been maintained by the Centers for Disease Control and Prevention (CDC) since 1990 as mandated by US law. All suspected adverse reactions to vaccines are to be reported to the VAERS database (required by US law). The protocol for reporting serious reactions to VAERS requires written and telephonic confirmation by the CDC. The CDC also follows up serious reactions one year after they occur to determine whether or not the patients had fully recovered. It was our aim in this study that by examining the VAERS database we would gain a broad perspective of the effects of adult rubella vaccination and adult hepatitis B vaccination in the United States population based upon many millions of doses of vaccine that is virtually unattainable by any other methods of analyses.

Another goal was to offer an etiology for chronic arthritis in adults who were vaccinated with hepatitis B vaccine or rubella vaccine. The etiology for chronic arthritis following both vaccines, may involve autoimmunity. The suggested role of autoimmunity in vaccine reactions has been described in a recent review (3).

Methods

We retrospectively examined the adverse reactions reported to the VAERS database from 1991 through 1999 following adult rubella vaccination and from 1997 through 1999 following adult hepatitis B vaccination using Microsoft Access. We focused on arthritis adverse reaction reports where patients were considered not to have recovered after a one year followup. Descriptions of adverse reactions relied upon those reporting them and were defined by the reporting fields contained in the VAERS database. The calculated incidence rates were obtained from the estimates of the Biological Surveillance Summaries received from the CDC.

The CDC estimated that 2,752,883 adult rubella vaccinations and 16,204,207 adult hepatitis B vaccinations were administered during their respective study periods. Tetanus-diphtheria (Td) vaccine and tetnaus toxoid vaccine chronic arthritis adverse reactions reported to VAERS from 1991 through 1999 in adults were analyzed to maximize the background of adverse reactions reported to the VAERS database and thereby, increase the power of statistical calculations undertaken in this study. The CDC estimated that

129,293,354 adult Td vaccinations and 22,774,922 tetanus toxoid vaccinations were administered from 1991 through 1999. The incidence rates of adult adverse reactions in the Td and tetanus toxiod vaccine recipients provided a background rate to compare against the incidence rates of adverse reactions in adult rubella vaccine recipients and adult hepatitis B vaccine recipients.

We have introduced the use of reactions to certain vaccines as baseline control groups with which to compare the relative reactivity of different types of vaccines (4, 5).An unbiased search of the incidence rate of a specific adverse reaction to one vaccine would be expected to be similar to the incidence rate following another vaccine administered to a similarly aged population because whatever the inherent limitations in the accuracy of reported adverse reactions to the VAERS database, they would be expected to equally affect the reports of both vaccines under study. Similarly, the number of doses of a type of vaccine administered, based on the Biological Surveillance Summaries of the CDC should be unbiased, because whatever the inherent limitations of the Biological Surveillance Summaries, they should apply equally to each vaccine under study. In performing the statistical analyses, the assumption of equal reactogencity between vaccines forms the basis of our null hypothesis. A 2 x 2 $\chi 2$ contingency table was employed, where we assume that the total number of adverse reactions following the control vaccine, and the number of doses administered based upon the Biological Surveillance Summaries for the time period examined are the expected values. The total number of adverse reactions following the vaccine under study, and the number of doses administered based upon the Biological Surveillance Summaries for the time period examined are the observed values.

The incidence rate of an adverse reaction following the vaccine under study in comparison to the incidence rate of an adverse reaction following the control vaccine group determines the relative risk, attributable risk and the percent association of the adverse reaction for the vaccine under study. The relative risk value is obtained by dividing the incidence rate of the adverse reaction following the vaccine under study by the incidence rate of the adverse reaction following the vaccine control group. The attributable risk value is determined by subtracting one from the relative risk. The percent association value is calculated by dividing the relative risk value by the relative risk value plus one and multiplying this computed value by 100.

We used the statistical package contained in Corel's Quattro Pro and accepted a p value of 0.05 as statistically significant.

Results

Table I summarizes the reports of chronic arthritis reported to the VAERS database following adult rubella vaccination and adult hepatitis B vaccination. The vaccine type, number of male and female reaction reports, mean and standard deviation of the age in years, mean and standard deviation of the onset time in days following vaccination and the incidence per million vaccinations for cases of chronic arthritis are summarized in Table I. Chronic arthritis adverse reactions following adult rubella vaccination were primarily reported in females(female/male ratio = 3.0), at about 45 years-old, and at a mean onset time of 10-11 days following vaccination. Chronic arthritis adverse reactions following adult hepatitis B vaccination were also primarily reported in females (female/male ratio = 3.5), at about 33 years-old, and with a mean onset time of 16.1 days following vaccination. Table II summarizes the relative risk, percent association and statistical significance of chronic arthritis adverse reactions reported following adult rubella vaccination and adult hepatitis B vaccination in comparison to those reported following adult Td and tetanus toxoid vaccinations. Similarly, there were 0.054 cases of chronic arthritis reported per million adult Td vaccinations and 0.088 cases of chronic arthritis reported per million adult tetanus toxoid vaccinations (not statistically significantly different). Both adult rubella vaccination and adult hepatitis B vaccination had statistically significant increases in the incidence of chronic arthritis in comparison to adult Td and adult tetanus toxoid vaccinations.

Table I. Chronic arthritis following adult rubella vaccination and adult hepatitis B vaccination

Type of vaccine	Number of female reports	Number of male reports	Mean age (years)	Mean onset (days)	Incidence per million vaccinations
Adult rubella vaccine	6	2	45.5 ± 7.8	10.5 ± 8.7	2.9
Adult hepatitis B vaccine	7	2	33.2 ± 11.0	16.1 ± 18.6	0.56

Table II. Chronic arthritis following adult rubella vaccination and adult hepatitis B vaccination in comparison to adult vaccine control groups.

Vaccines compared	Relative risk	Attributable risk	Percent association	Statistical significance
Adult rubella vaccine vs adult Td vaccine	54	53	98	$p < 0.0001$
Adult rubella vaccine vs adult tetanus toxoid vaccine	33	32	97	$p < 0.0001$
Adult hepatitis B vaccine vs adult Td vaccine	10	9.0	91	$p < 0.0001$
Adult hepatitis B vaccine vs adult tetanus toxoid vaccine	6.1	5.1	84	$p < 0.05$

Discussion

The results of this analysis confirm a statistically significant relationship between chronic arthritis developing following adult rubella and adult hepatitis B vaccination in comparison to vaccine control groups. The two vaccine control groups employed had very similar incidence rates for chronic arthritis that were not statistically significantly different. This helps to suggest that the two vaccine control groups used in this study may indeed reflect the background reporting rate of chronic arthritis to the VAERS database and also show that adverse reaction reports are not randomly reported to the VAERS database. It would be expected that Td vaccine and tetanus toxoid vaccine administered to adults should have similar incidence rates of chronic arthritis based upon similarities in the molecular design of each vaccine.

The Institute of Medicine (IOM) of the National Academy of Sciences (USA) reported a causal relationship between the currently used rubella vaccine and chronic arthritis in adult women and recommended prospective, double-masked, controlled trials where subjects would be followed for at least 12 months to confirm a biological relationship between rubella vaccination and chronic arthritis (6). This study helps to fulfill the IOM mandate by providing a controlled examination of chronic arthritis in subjects immunized with rubella vaccine for one year following vaccination.

The results here are in agreement with previous analyses by Tingle *et al*. who reported two cases of chronic arthritis in women following rubella immunization with the current strain of rubella vaccine (7, 8). The arthritis in these cases persisted for 2 and 3.5 years. They reported that two additional young women had recurrent arthritis or arthralgia (not otherwise specified) for 18 to 24 months after receipt of the current strain of rubella vaccine. Tingle *et al.*, have also conducted a randomized double-blind placebo-controlled study on the adverse effects of rubella immunization in seronegative women (9). They found a statistically significant increase in the incidence of acute and chronic arthritis in those vaccinated with the currently used rubella vaccine. In line with a proposed antigenic stimulus that results in chronic arthritis, Tingle *et al.*, have isolated rubella virus from peripheral blood mononuclear leukocytes of several patients with persistent post-rubella vaccine arthritis (10). We suggest that further studies should be done to isolate rubella virus from the synovial fluid of affected-joints in cases of chronic arthritis, with molecular analysis performed to determine whether the isolated strain corresponds to the one injected. We hypothesize that the live-attenuated rubella vaccine goes onto attack the joints by the virus exhibiting molecular mimicry of self, resulting in an inflammatory response in a susceptible patient.

The finding of statistically significant chronic arthritis following adult hepatitis B vaccination was surprising because this genetically engineered, single antigen vaccine was predicted to be well-tolerated by the vaccine recipients. The CDC has determined that rheumatoid arthritis following hepatitis B vaccination has not been confirmed (11).

Pope *et al*., have reported 11 cases of arthritis following adult hepatitis B vaccination (12). Ten of the 11 patients fulfilled the revised criteria of the American College of Rheumatology for rheumatoid arthritis which persisted for more than six months; and at a 48-month follow-up 9 of the patients still had inflammatory arthritis. The authors note a personal communication received from the CDC's adverse events report study confirming that rheumatoid arthritis occurred ten times more frequently in 15-45 year-old adults after vaccination with hepatitis B than with influenza or pneumomococcal vaccine.

Furthermore, Pope *et al.*, found that many persons experiencing arthritis following hepatitis B vaccination share common HLA haplotypes (Drβ-0101, 0301, 0401, 0404) that possess the predicted binding anchor for peptides 96-104 and 161-169 within the hepatitis B surface antigen (HBsAg) sequence. It has been shown previously that different immunodominant epitopes of HBsAg were found to stimulate CD4+ lymphocytes *in vitro* in recombinant hepatitis B vaccine recipients (13). One of four immunodominant peptides used in, namely the 165-172 peptide sequence, shares the first five amino acids (WASVRFSWA) with the last five amino acids (YLWEWASVR) of the 161-169 pepitde sequence desribed by Pope *et al*., as a candidate rheumatoid epitope. Additionally, the 96-104 sequence described by Pope *et al.*, as a potential binding region to the rheumatoid haplotype, shares the first three amino acids (VLL) with the final 80-98 peptide sequence of HBsAg. This 80-98 sequence, which exhibits an α-helix conformation, identifies a T helper (CD4+) epitope. It is has also been shown that even if both peptides 165-172 and 80-98 do not completely overlap with the sequences proposed by Pope *et al*., as the rheumatoid epitope, they share one anchor (alanine and valine, respectively) with the Major Histocompatibility Complex, Class II (MHC II) binding pocket (14). The 161-172 sequence of the HBsAg has been preferentially found to stimulate Th0 or Th2 CD4+ lymphocytes *in vitro*, resulting in the secretion of interleukin 2, IL-4, and IL-5 (13). We hypothesize that HBsAg sequence exhibits molecular mimicry of self, resulting in an inflammatory response signal that is further compounded by the effects of the aluminum adjuvant and the thimerosal perservative, in a sensitive patient, within a fairly close temporal relationship to vaccination.

We have recently published how to design vaccines that may be accompanied by fewer serious adverse reactions (5). We suggested that vaccines should be single antigen, highly purified and checked to determine if any of the epitopes they contain are cross-reactive with human lymphocytes. They should come in single dose sealed vials,so that preservatives are not necessary, and should contain enough antigenic material, so that adjuvants are not needed.

Overall, this study demonstrates the usefulness of the VAERS database to determine the reactogenicity profile of vaccines. The VAERS Working Group of the CDC states that VAERS is sim-

ple for reporters to use, flexible by design and that its data are available in a timely fashion (15). The potential for biases in the reporting rates of adverse reactions to VAERS because of alerts within scientific publications and publicity in the media when a vaccine is marketed, in consequence whereof, adverse reactions, whether vaccine-related or not, may be much more likely to be reported following one vaccine comparted to another, were not borne out. This study succinctly showed that adult rubella and adult hepatitis B vaccines are statistically associated with acute arthritic symptoms and that some of these patients go on to have chronic arthritis which persists for at least one year following vaccination.

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