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Anthrax vaccination and joint related adverse reactions in light of biological warfare scenarios

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ABSTRACT

Objectives: *The purpose of this analysis was to evaluate anthrax vaccine (AVA) and joint related adverse reactions based upon analysis of the VAERS database in light of the current possibility of the use of anthrax as a biological warfare agent.*

Methods: *A certified copy of the VAERS database was obtained from the CDC. In this study, we conducted a retrospective analysis using Microsoft Access for all joint attributed adverse reactions reported following anthrax vaccination. The employment of chi-square analysis determined if the elevated incidence rates of associated adverse reactions in anthrax vaccine recipients were statistically significant.*

Results: *Our analysis shows a very large and statistically significant increase in joint symptoms following vaccination with AVA when compared to our control population consisting of adverse joint reactions reported following vaccination with hepatitis A vaccine and Td vaccine.*

Conclusion: *We believe that civilian doctors need to become familiar with the adverse reactions that can be expected to follow the use of AVA. Both civilian and military doctors need to be vigilant in reporting all such reactions to VAERS, so that more information can be gathered about AVA. We also believe that an anthrax vaccine with an improved safety profile is needed if it is to be used in populations, either military or civilian, that are not under imminent threat of attack by biological warfare agents. It should also be kept in mind that the widespread use of anthrax vaccination may cause potential producers of biological weapons and terrorists to seek to produce anthrax strains that are not neutralized by the current vaccine.*

Introduction

The United States'military is currently implementing a policy to have all of its members vaccinated with anthrax vaccine adsorbed (AVA). Specifically, its goal is to have all 2.4 million Active, Guard and Reserve service members inoculated by 2003 (1). The reason for this step by the U.S. military stems from the fact that *Bacillus anthracis*, a spore-forming bacterium that causes the disease anthrax, has been manufactured as a biological warfare agent, and concern exists that it could be used as a biological terrorist weapon. *B. anthracis* is considered one of the most likely biological warfare agents because of the ability of *B. anthracis* spores to be transmitted by the respiratory route, the high mortality of inhalation anthrax and the greater stability of *B. anthracis* spores compared with other potential biological warfare agents (2-5). The World Health Organization has estimated that 50 kg of *B. anthracis* released upwind of a population center of 500,000 people could result in 95,000 deaths and 125,000 hospitalizations (6).

AVA, the only licensed human anthrax vaccine in the United States, is produced by BioPort Corporation in Lansing, Michigan, and is prepared from a cell-free filtrate of *B. anthracis* culture that contains no dead or live bacteria (7). The strain used to prepare the vaccine is a toxigenic, non-encapsulated strain known as V770-Np1-R (8). The filtrate contains a mix of cellular products including protective antigen (PA) and is adsorbed to aluminum hydroxide (Amphogel, Wyeth Laboratories) as an adjuvant (9, 10). The amount of PA and other proteins per 0.6 mL dose is unknown, and all three toxin components produced by *B. anthracis* – lethal factor (LF), edema factor (EF) and PA – are present in the product (9). These toxins act in binary combination to form two exotoxins known as lethal toxin and edema toxin (11-13).

PA and LF form lethal toxin; PA and EF form edema toxin. LF is a protease that inhibits the mitogen-activated protein kinase-kinase interaction (14). EF is an adenylate cyclase that generates cyclic adenosine mono-phosphate in the cytoplasm of eukaryotic cells (15, 16). PA is required for binding and translocating LF and EF into host cells. PA is an 82 kD protein that binds to receptors on mammalian cells and is critical to the ability of *B. anthracis* to cause disease. After binding to the cell membrane, PA is cleaved to a 63 kD fragment that subsequently binds with

LF or EF (17). LF or EF bound to the 63 kD fragment undergoes receptor-mediated internalization, and the LF or EF is translocated into the cytosol upon acidification of the endosome. Lethal toxin and edema toxin, respectively, cause local necrosis and extensive edema, which is a major characteristic of natural anthrax disease. Additionally, these toxins have the potential to cause widespread tissue destruction and organ failure. The potency and safety of the final AVA is confirmed according to U.S. Food and Drug Administration (FDA) regulation (18). Primary vaccination consists of three subcutaneous injections at 0, 2 and 4 weeks, and three booster vaccinations at 6, 12 and 18 months. To maintain immunity, the manufacturer recommends an annual booster injection (19-21).

The purpose of this analysis was to evaluate AVA and joint-related adverse reactions based upon analysis of the vaccine adverse events reporting system (VAERS) database, in light of the current possibility of the use of anthrax as a biological warfare agent.

Methods

A certified copy of the VAERS database was obtained from the Centers for Disease Control and Prevention (CDC). The VAERS is a passive epidemiological database that has been maintained by the CDC in Atlanta, Georgia, since 1990. All adverse reactions after vaccination are to be reported to this database, as mandated by law. A recent publication by the CDC has helped to validate the VAERS as an epidemiological database (22). Our own studies have examined arthritic, immunological and gastrointestinal adverse reactions after hepatitis B vaccination and arthritic reactions after rubella vaccination based upon analysis of the VAERS database (23-27). We have also reported on the reactivity of vaccines administered in the state of Texas based upon our analysis of the VAERS database (28).

In this study, we made a retrospective analysis using Microsoft Access for all joint attributed adverse reactions reported following anthrax vaccination from 15 December 1997 to 12 April 2000. The anthrax vaccine-associated, joint-related adverse reactions analyzed included: arthralgia, arthrosis, arthritis, joint disease, myelitis, vasculitis, myalgia, Guillain Barre syndrome and flu syndrome. The CDC estimates indicate that 1,620,793 doses of anthrax were administered during the study period examined. Additionally, as controls hepatitis A vaccine-associated adverse reactions reported to VAERS from 1997 through 1998 in adults and Td vaccine-associated adverse reactions reported to VAERS from 1991 through 1999 in adults were analyzed. The CDC estimates indicate that 6,038,283 hepatitis A vaccinations were administered from 1997 through 1998 to adults. The CDC estimates indicated that 129,293,354 Td vaccination were administered from 1991 through 1999 to adults. The incidence rates of adult associated adverse reactions in hepatitis A vaccine and Td vaccine recipients provided a background rate to compare against the incidence rates of associated adverse reactions in anthrax vaccine recipients, which has

Table I. Joint related adverse events and anthrax vaccination.

Reaction type	Total number of reports	Female reaction reports	Male reaction reports	Mean age (years)	Mean onset (within 60 days)	Incidence per million anthrax vaccinations
Arthralgia	210	28	178	37.4 ± 9.6	4.0 ± 7.8	130
Arthritis	11	9	2	36.7 ± 8.7	6.4 ± 6.2	6.8
Arthrosis	15	6	9	37.7 ± 10.6	3.5 ± 5.3	9.3
Joint disease	20	5	15	35.3 ± 8.6	5.5 ± 9.9	12
Myelitis	3	2	1	31.5 ± 5.9	4.0 ± 4.0	1.9
Vasculitis	2	1	1	33.1 ± 5.9	5.0 ± 5.0	1.2
Guillain Barre syndrome	5	0	5	36.6 ± 12.1	10.5 ± 10.3	3.1
Myalgia	131	22	103	38.4 ± 9.2	2.1 ± 4.2	81
Flu syndrome	74	12	59	37.3 ± 8.1	1.4 ± 4.3	46

Table II. A comparison between anthrax vaccination and adult hepatitis A vaccination.

Type of adverse reaction	Incidence of associated adverse reactions per million adult hepatitis A vaccinations	Incidence of associated adverse reaction per million anthrax vaccinations	Relative risk of the adverse reaction following anthrax vaccination	Percent association between anthrax vaccination and the associated adverse reaction	Chi-square association between anthrax vaccination and the associated adverse reaction
Arthralgia	2.0	130	65	99	$p < 0.0001$
Arthrosis	0.7	9.3	13	93	$p < 0.01$
Arthritis	0.3	6.8	23	96	$p < 0.001$
Myelitis	0.1	1.9	19	95	$p < 0.02$
Vasculitis	0.3	1.2	4	80	Not significant
Guillain Barre syndrome	0.2	3.1	16	94	$p < 0.02$
Joint disease	0.2	12	60	98	$p < 0.0001$
Myalgia	4.0	81	20	95	$p < 0.0001$
Flu syndrome	0.7	46	66	98	$p < 0.0001$

Table III. A comparison between anthrax vaccination and adult Td vaccination.

Type of adverse Reaction	Incidence of associated adverse reaction per million Td vaccinations	Incidence of associated adverse reaction per million anthrax vaccinations	Relative risk of the adverse reaction following anthrax vaccination	Percent association between anthrax vaccination and the associated adverse reaction	Chi-square association between anthrax vaccination and the associated adverse reaction
Arthralgia	2.7	130	48	98	$p < 0.0001$
Arthrosis	0.39	9.3	24	96	$p < 0.001$
Arthritis	0.24	6.8	28	97	$p < 0.001$
Myelitis	0.09	1.9	21	95	$p < 0.02$
Vasculitis	0.04	1.2	30	97	$p < 0.02$
Guillain Barre syndrome	0.22	3.1	14	93	$p < 0.02$
Joint disease	0.02	12	600	99	$p < 0.0001$
Myalgia	8.1	81	10	91	$p < 0.0001$
Flu syndrome	1.1	46	42	98	$p < 0.0001$

only been licensed for use in adult military populations in the U.S.

The employment of chi-square analysis determined if the elevated incidence rates of associated adverse reactions in anthrax vaccine recipients were statistically significant. The use of vaccine control group associated adverse events reported to VAERS as a background rate has been validated in two of our recent studies. We showed that rubella vaccine has a statistically significant increased association with arthritic reactions following vaccination in comparison to a hepatitis A vaccine control group. We also showed that hepatitis B vaccine has a statistically significant increased association with gastrointestinal reactions following vaccination in comparison to hepatitis A and *rubella* vaccine control groups (26, 27).

Results

Table I summarizes the total number of reports, number of female reports, number of male reports, mean age in years, mean onset in days within 60 days of vaccination and incidence per million anthrax vaccinations of joint attributed adverse reactions. Table II compares the reactivity of anthrax vaccination in comparison to our adult hepatitis A vaccine recipient control group. Table III compares the reactivity of anthrax vaccination in comparison to our adult Td vaccine control group.

Discussion

Our analysis shows a very large and statistically significant increase in joint symptoms following vaccination with AVA when compared to our control population consisting of adverse joint reactions reported following vaccination with hepatitis A vaccine and Td vaccine. Most of the reactions were reported by male vaccine recipients rather than female recipients. Since the vaccine was used exclusively by the military, this male verses female ratio preponderance probably merely reflects that there are far more males than females serving in the U.S. military. Despite this demographic fact, female arthritis adverse reactions outnumbered male arthritis adverse reactions 4.5 to one. Although the number of reports was small, this probably indicates some component of autoimmunity in arthritis reactions. Shoenfeld and Aaron-Maor have previously reported on possible mechanisms involved in the development of joint symptoms following vaccination (29). Additional analysis of the possible mechanisms involved in the development of rheumatoid arthritis have been reported in recent articles (30, 31). The remainder of the reactions could well be viewed as a direct effect of the active toxins contained in AVA on vaccine recipients, although obviously much further work needs to be done on the mechanisms by which AVA causes so many adverse reactions.

We believe that, under the threat of eminent biological warfare attack, it might be deemed reasonable that to members of the military the reactogenicity of the vaccine might be tolerated. The decision of the military to vaccinate all of their personal with AVA, whether they are under immediate threat of attack by anthrax or not, with this crude vaccine is more questionable from a cost-benefit point of view. Unfortunately, under certain circumstances large segments of the civilian population may also be at risk for attack by anthrax as a biological weapon. The extreme reactogenticity of AVA vaccine makes its general use for civilian populations undesirable. Rather, if the widespread use of anthrax vaccination becomes necessary, a purified, toxoided anthrax vaccine should be developed which would have far less reactogeneticy than the current AVA. It should also be kept in mind that the widespread use of anthrax vaccination may cause potential producers of biological weapons and terrorists to seek to produce anthrax strains that are not neutralized by the current vaccine.

As a result of the rapidly widening scope of the use of AVA by the U.S. military, the likelihood of civilian doctors seeing patients with adverse reactions to AVA is increasing. Therefore, civilian doctors need to become familiar with adverse reactions that can be expected to follow the use of AVA. Both civilian and military doctors need to be vigilant in reporting all such reactions to VAERS, so that more information can be gathered about AVA.

References

1. NASS M: Anthrax vaccine. Model of a response to the biological warfare threat. *Infect Dis Clin North Am* 1999; 1: 187-208.
2. PILE JC, MALONE JD, EITZEN EM, FRIEDLANDER AM: Anthrax as a potential biological warfare agent. *Arch Intern Med 1998*; 158: 428-34.

3. INGLESBY TV, HENDERSON DA, BARLETT JG, *et al.*: Anthrax as a biological weapon. *JAMA* 1999; 281: 1735-45.
4. CHRISTOPHER GW, CIESLAK JA, EITZEN EM: Biological warfare: a historical perspective. *JAMA* 1997; 278: 412-17.
5. FRANZ DR, JAHRLING PB, FRIEDLANDER AM, *et al.*: Clinical recognition and management of patients exposed to biological warfare agents. *JAMA* 1997; 278: 399-411.
6. WORLD HEALTH ORGANIZATION: *Health Aspects of Chemical and Biological Weapons: A Report of a WHO Group of Consultants*. Geneva, Switzerland, World Health Organization, 1970.
7. ADVISORY COMMITTEE FOR IMMUNIZATION PRACTICES: *Adult Immunization*. MMWR 1984; 33: 33-4.
8. PUZISS M, MANNING LC, LYNCH JW, BARCLAY E, ABELOW I, WRIGHT GG: Large-scale production of protective antigen of Bacillus anthracis in aerobic cultures. *Appl Microbiol* 1963; 11: 330-4.
9. TURNBULL PCB, BROSTER MJ, CARMAN JA, MANCHEE RJ, MELLING J: Development of antibodies to protective antigen and lethal factor components of anthrax toxin in humans and guinea pigs and their relevance to protective immunity. *Infect Immun* 1986; 52: 356-63.
10. MAHLANDT BG, KLEIN F, LINCOLN RE, HAINES BW, JONES WI, FRIEDMAN RH: Immunologic studies of anthrax: IV. Evaluation of the immunogenicity of three components of anthrax toxin. *J Immunol* 1966; 96: 727-33.
11. FRIEDLANDER AM: *Textbook of Military Medicine:Medical Aspects of Chemical and Biological Warfare.* Washington, DC, Walter Reed Army Medical Center, 467-78.
12. MIKESELL P, IVINS BE, RISTROPH JD, DREIER TM: Evidence for plasmid-mediated toxin production in *Bacillus anthracis. Infect Immun* 1983; 39: 371-6.
13. LINCOLN RE, FISH DC: *Microbial Toxins.* New York, Academic Press Inc., 316-414.
14. DUESBERY NS, WEBB CP, LEPPLA SH, *et al.*: Proteolytic inactivation of MAP-kinase-kinase by anthrax lethal factor. *Science* 1998; 280: 734-5.
15. FARRAR WE: Anthrax: Virulence and vaccines. *Ann Intern Med* 1994; 121: 379.
16. FOX J: Bioterrorism: Microbiology ket to dealing with threats. *ASM News* 1998; 64: 225-7.
17. MILNE JC, FURLONG D, HANNA PC, WALL JS, COLLIER RJ: Anthrax protective antigen forms oligomers during intoxication of mammalian cells. *J Biol Chem* 1994; 267:607-12.
18. 21 CFR 620.23.
19. WRIGHT GG, GREEN TW, KANODE RG: Studies on immunity in anthrax. V. Immunizing activity of alum-precipitated protective antigen. *J Immunol* 1954; 73: 387-91.
20. DARLOW HM, BELTON FC, HENDERSON DW: The use of anthrax antigen to immunize man and monkey. *Lancet* 1956: 476-9.
21. TURNBULL PCB: Anthrax vaccines: Past, present and future. *Vaccine* 1991; 9: 533-9.
22. SINGLETON JA, LLOYD JC, MOOTREY GT, SALIVE ME, CHEN RT: An overview of the vaccine adverse events reporting system (VAERS) as a surveillance system. *Vaccine* 1999; 17: 2908-17.
23. GEIER MR, DA GEIER: Hepatitis B vaccine and gastroenterologic adverse reactions. *Hepatogastroenterology* 2001; 48.
24. GEIER MR, GEIER DA: Immunological reactions and hepatitis B vaccine. *Ann Intern Med* 2001; 134: 1155.
25. GEIER MR, GEIER DA: Arthritic reactions and hepatitis B vaccination:an analysis of the vaccine adverse events reporting system, (VAERS) from 1990 through 1997. *Clin Exp Rheumatol* 2000; 18: 789-90.
26. GEIER DA, GEIER MR: Rubella vaccine and arthritic adverse reactions:An analysis of the vaccine adverse events reporting system (VAERS) database from 1991 through 1998. *Clin Exp Rheumatol* 2001; 19: 724-6.
27. GEIER DA, GEIER MR: Hepatitis B vaccination and adult associated gastrointestinal reactions: A followup analysis. *Hepatogastroenterology* 2001-02 (in press).
28. GEIER DA, GEIER MR: An analysis of the reactivity of vaccines administered in Texas from 1991 through 1999:based upon the vaccine adverse events reporting system (VAERS) database. *Texas Medicine* 2001; 19: 724-6.
29. SHOENFELD Y, AARON-MAOR A: Vaccination and autoimmunity-'vaccinosis': a dangerous liaison? *J Autoimmun* 200; 14: 1-10.
30. ROZMAN B, JEVTIC V: The volume of rheumatoid synovial membrane, determined by magnetic resonance, reflects disease activity and predicts joint destruction. *Clin Exp Rheumatol* 2000; 18: 4-6.
31. MATUCCI-CERINIC M, PIGNONE A, GENERINI S, KORN JH: Can fibroblasts determine the late differing outcome between systemic sclerosis and primary hypertrophic osteoarthropathy (pachydermoperiostosis) ? *Clin Exp Rheumatol* 2000; 18: 1-2.