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Assessing Information from the Vaccine Adverse Event Reporting System (VAERS)

Marcia L. Buck, Pharm.D., FCCP

The National Childhood Vaccine Injury Act of 1986 mandated post-marketing surveillance of vaccine adverse events through the Department of Health and Human Services. In 1990, the Vaccine Adverse Event Reporting System (VAERS) was established to meet this need. The program is a collaborative effort by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) to provide a system for the collection and analysis of adverse events reported by patients, health care providers, and vaccine manufacturers. After more than a decade of data collection, the VAERS database includes over 120,000 reports and has become a rich source of information for clinicians and researchers.[1-3]

This issue of *Pediatric Pharmacotherapy* will review the VAERS program and highlight the findings from several recent analyses of adverse events taken from the VAERS database. In addition, new strategies for international collaboration, including standardization of case definitions and methods for data collection, will be addressed.

The VAERS Program

The VAERS program is a passive surveillance system. Its success relies on the information provided by health care providers and manufacturers. Its goals are to identify new and/or rare adverse events, determine the rates of adverse event occurrence, and identify patient risk factors. The VAERS program is also charged with identifying vaccine lots associated with an increased number of adverse events. Data from VAERS is particularly valuable to pediatric health care providers: 59% of the reports in the database involve patients under 18 years of age. Forty-nine percent involve children under 6 years of age.[1] The database has been instrumental in identifying rare serious adverse events in children, such as intussusception following administration of rotavirus vaccine.[2,3]

While any adverse event associated with a vaccine may be reported, a listing of reportable events was established with the advent of the VAERS system to define those reactions which must be reported by vaccine manufacturers and prescribers (Table). In addition to these reactions, any event described in the manufacturer's package insert as a contraindication to additional doses of vaccine must be reported.[1] Reports to VAERS may be mailed, faxed, or sent through a secure e-mail site. More information is available on the program website at www.vaers.org

Table. Reportable Events After Immunization

Tetanus alone or in combination vaccines
- Anaphylaxis or anaphylactic shock
- Brachial neuritis

Pertussis alone or in combination vaccines
- Anaphylaxis or anaphylactic shock
- Encephalopathy or encephalitis

Measles, mumps, and rubella in any combination
- Anaphylaxis or anaphylactic shock
- Encephalopathy or encephalitis

Rubella alone or in combination vaccines
- Chronic arthritis

Inactivated polio
- Anaphylaxis or anaphylactic shock

Hepatitis B
- Anaphylaxis or anaphylactic shock

Haemophilus influenzae type b (polysaccharide)
- Early-onset *Haemophilus* disease

Within the last five years, a number of investigators have utilized the VAERS database to examine vaccine adverse events. Some reports have identified vaccines associated with specific

adverse events or administration errors, while others have described the adverse events associated with a particular vaccine.

Hypotonic-Hyporesponsive Episodes

In 2000, Du Vernoy and colleagues, a team of FDA and CDC staff publishing as the VAERS Working Group, used the database to examine the frequency of hypotonic-hyporesponsive episodes (HHE) occurring after vaccine administration.[4] From over 40,000 VAERS reports filed between 1996 and 1998, the authors identified 215 cases of HHE. The median patient age was 4 months, with a median time to onset of symptoms of 3.5 hours after immunization. As anticipated, the majority of the cases reported involved administration of a pertussis-containing vaccine. Sixty-one percent of the children had received the diphtheria, tetanus, whole cell pertussis (DTP) hepatitis B combination product, while 28% had received diphtheria, tetanus, acellular pertussis vaccine (DTaP), and 11% had received the diphtheria, tetanus, whole cell pertussis (DTP) product. A full recovery was reported for all but three cases. In those cases, the reactions were not determined to have been caused by the vaccine. The authors concluded that HHE is generally a mild, self-limiting event that still occurs, but has been reported in fewer patients with the transition to the acellular pertussis vaccine.

Severe Dermatologic Reactions

Ball and colleagues, also publishing as the VAERS Working Group, recently conducted a review of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reported after vaccination.[5] Of the 131 cases identified in the VAERS database, there were 33 reports of SJS, 8 reports of TEN, 58 reports of serious erythema multiforme, and 32 reports of skin necrosis at the site of injection. Of the 35 total evaluable cases, the authors found one definite case and five probable cases of SJS and TEN. Two of the cases involved hepatitis B vaccine, one case involved influenza vaccine, and one case occurred after varicella vaccine administration. In the remaining two cases, multiple vaccines had been administered. One child had received *Haemophilus influenza* type b and measles, mumps, rubella (MMR) vaccines. The other child had received DTP, MMR, and oral polio vaccine. Although causality could not be definitively established or disproven, the authors concluded that SJS and TEN may occur following vaccination, but appear to be rare.

Chronic Arthritis

The VAERS database has also been examined for the occurrence of chronic arthritis after vaccination in adults.[6] Only cases with symptoms persisting for at least one year were included in this study. Using the tetanus booster as a control, the authors found a significantly increased rate of arthritis with both the rubella and hepatitis B vaccines. The reactions were more likely to occur in women, with an average patient age of 45 years for rubella vaccine and 33 years for the hepatitis B vaccine. The average time to onset of symptoms was 10 to 11 days following the rubella vaccine and 16 days after hepatitis B vaccine administration.

Extensive Limb Swelling

In a report published in *Clinical Infectious Diseases* last year, Woo and colleagues evaluated which vaccines have been most frequently associated with extensive limb swelling.[7] Using the VAERS database, 497 cases were identified, involving 504 limbs. Patients ranged from 0.1 to 81 years of age. The majority of reports (84.1%) involved a single vaccine in a single limb. In 80% of the cases, the arm was involved. Swelling was typically limited to the proximal half of the extremity. No cases of death or life-threatening reactions were reported, but 20 patients required hospitalization. The need for hospitalization was more common in younger patients, with 6.3% of the children less than 2 years of age and 7.6% of the children between 2 and 7 years requiring admission.

As expected, the vaccines most commonly associated with limb swelling varied with age. In the patients less than 2 years of age, diphtheria, tetanus, and pertussis vaccine products produced the greatest number of reactions; 26.6% of the reactions involved DTaP, 26% involved DTP, and 23.4% involved the combination DTaP/ *Haemophilus influenzae* type b vaccine. In patients 8 to 17 years of age, the tetanus booster was the most frequent cause of limb swelling, with 55% of the reports. Hepatitis B vaccines accounted for another 30% of the reports in this age group.

Medication Errors

In 2002, Varricchio examined errors in vaccine administration reported through VAERS between 1994 and 2001.[8] A total of 49 reports were identified and grouped into seven categories. Thirty percent of the errors involved administration of the wrong vaccine. Administration of a vaccine at the wrong interval was reported in 10% of the cases. Incorrect route and overdose were each reported in 9% of the cases. Among the adverse effects associated with these errors, the most frequent finding was injection site reaction (24%). One patient death

occurred when pancuronium was inadvertently used as the diluent for vaccine preparation.

Acellular Pertussis Vaccine

The VAERS database has also been used to describe the adverse effects reported with a single vaccine. In 2000, Braun and coworkers from the VAERS Working Group, examined a sampling of reports associated with pertussis vaccines.[9] A time period from January 1995 through June 1998 was selected in order to examine trends during the transition from whole cell to acellular pertussis vaccine use. The authors found a total of 5,770 reports of adverse events within their sample. The number of reports slowly declined during the sample period, with 2071 reports in 1995, 1,894 reports in 1996, 1,314 reports in 1997, and 491 reports in the first half of 1998. Among the reports, the authors noted a significant decrease in the less serious adverse effects (fever, prolonged crying, or injection site reactions) with the use of the acellular product, as reported in clinical trials. The incidence of serious adverse effects was also reduced. The authors concluded that the VAERS reports supported the prelicensure safety data for the acellular pertussis vaccine.

Varicella Vaccine

Also that year, Wise and colleagues reviewed the reports associated with the varicella vaccine. This review incorporated data from 1995, when the vaccine was licensed, to 1998.[10] A total of 6,574 reports were evaluated, providing an overall rate of 67.5 reports per 100,000 doses. The most frequently reported adverse events were rash (55%), possible vaccine failure (19%), and injection site reactions (9%). Four percent of the reports were serious reactions, including pneumonia, encephalitis, ataxia, SJS, arthritis, thrombocytopenia, vasculitis, and hepatitis. There were 30 cases of anaphylaxis. Based on these reports, the authors concluded that most of the reactions reported after administration of the varicella vaccine were minor.

Anthrax Vaccine

Sever and colleagues used the VAERS database to examine the safety of the anthrax vaccine.[11] In the 602 reports reviewed, the most frequent adverse event was an injection site reaction. Six cases were considered serious and causally related to vaccine administration, including two cases of aggravation of spondyloarthropathy, two cases of arthritis, and one report each of an anaphylactoid reaction and bronchiolitis obliterans-organizing pneumonia. The authors concluded that the VAERS reports reflected the expected adverse effect profile of this vaccine.

Typhoid Fever Vaccines

Earlier this year, Beigier and colleagues from the VAERS Working Group, evaluated reports of reactions to typhoid fever vaccines.[12] Although these vaccines are not routinely administered in the United States, they are given prior to international travel and may be useful in the event of a bioterrorism threat. A total of 321 reports involving the parenteral Vi capsular polysaccharide vaccine and 345 reports following administration of the oral attenuated product were gathered between July 1990 and June 2002. Among the reports, 60 (18%) involved children. The most common adverse effects with the Vi product were fever (in 18% of the reports), headache (18%), dizziness (15%), rash or urticaria (15%), myalgia, pain, abdominal pain, and pruritus (each 10%), and injection site reactions (8%). For the attenuated product, fever was the most frequently reported adverse effect (15%), followed by pruritis, vasodilation, headache or injection site hypersensitivity (13% each), rash (12%), myalgia, urticaria, and nausea (10% each), and dizziness (9%). As with the anthrax study, the authors found no unexpected serious adverse events after typhoid fever vaccine use.

Standardized Definitions

In 2002, the VAERS Working Group reported their initial attempts to standardize the terminology used to define cases of acute encephalopathy, encephalitis, and multiple sclerosis.[13] The standardization of case terminology was intended to increase the utility of the VAERS database, allow for a more accurate assessment of causality, and highlight areas requiring supplemental information from the original source. After the case definitions were developed, a panel of four independent neurologists used the new definitions to review a sample of VAERS reports to establish validity.

Since that initial report, the VAERS group has become part of an international effort to standardize case definitions and data collection for vaccine-associated adverse events.[14,15] The Brighton Collaboration is a voluntary group of approximately 300 individuals working together to create case definitions for 50 to 100 of the most commonly reported vaccine adverse events. To date, the group has published case definitions for fever, generalized convulsive seizure, hypotonic-hyporesponsive episode, acute intussusception, nodule at the injection site, and persistent crying in infants and children.[16-21] Work is currently underway to develop case definitions for allergic reactions, chronic fatigue syndrome, idiopathic thrombocytopenia, myalgia, paresthesia, and rash.[15]

Summary

The VAERS database is a valuable tool for the collection of vaccine-associated adverse effects. The ability to review the database on-line and the move towards standardized case definitions have made this system more useful for practitioners as well as investigators. Pediatric health care providers should be familiar with the VAERS system, including methods for reporting and accessing the database.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 4/28/04:

1. Cyclosporine ophthalmic emulsion (Restasis®) was added to both the Inpatient and Outpatient Formularies. This product increases tear production in patients with dry eyes resulting from ocular inflammation.
2. Bupropion immediate release (generic) was deleted from the Inpatient and Outpatient Formularies due to an increased seizure risk associated with the immediate release formulation and lack of use. A request to add bupropion extended release (Wellbutrin XL®) was rejected because of the lack of significant benefit over bupropion SR, a less expensive product currently on Formulary.
3. The quarterly results of the Adverse Drug Reaction Reporting Program were presented. For more information, contact Drug Information Services at 4-8034.

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