Special Report

Postmarketing surveillance of rabies vaccines for dogs to evaluate safety and efficacy

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Vaccination of dogs against rabies began with Louis Pasteur and his colleagues in 1884.[1] Mass vaccination of dogs against rabies, however, did not begin until 1919 with a phenol inactivated vaccine developed in Japan.[2] This same product was introduced for use in the United States in 1922.[3] Since then, various types of rabies vaccines for animal use have been licensed by the USDA CVB. These products are an important component of rabies control programs that have resulted in a substantial decline of rabies in dogs throughout the world and the elimination of canine variants of rabies in the United States.[4,5] The number of laboratory-confirmed cases of rabies in dogs in the United States has decreased from > 6,949 in 1947 to 71 in 2006.[5] Currently, 14 rabies vaccines are labeled for use in dogs. These vaccines must meet the standard requirements established in the Title 9 Code of Federal Regulations. This requires that the vaccine provide a protected fraction of ≥ 83% when comparing vaccinated animals versus control animals. Also, all rabies vaccines are evaluated for safety prior to licensure, which includes performance of a field safety trial. Additionally, each serial of rabies vaccine is tested for potency by use of the National Institutes of Health potency test or another test approved by the CVB and is tested for safety in host and laboratory animals.

Although the CVB licenses veterinary biological products for use in the prevention of rabies, state and local authorities govern and administer their respective rabies animal control programs. Some of these programs allow exemptions to the vaccination requirements if medical concerns exist related to potential adverse events.

Postmarketing safety and efficacy information regarding rabies vaccines for dogs from April 1, 2004, through March 31, 2007, is summarized and reported here. The findings represent information collected from spontaneous field reports of adverse events. Data were received from multiple sources by use of nonstandardized methods of collection. This report is intended to provide useful information for veterinarians and program administrators to aid in the implementation of rabies animal control programs.

Abbreviation

CVB	Center for Veterinary Biologics

Safety Review

Before licensure, a product must be shown to be safe through a combination of safety evaluations. The field safety trial is the most comprehensive evaluation and has the objective of assessing the safety of the product in its target population under the conditions of its intended use. However, safety studies before licensure may not detect all safety concerns for a number of reasons, as follows: insufficient number of animals for low-frequency events, insufficient duration of observation, sensitivities of subpopulations (eg, breed, reproductive status, and unintended species), or interactions with concomitantly administered products.

The CVB conducts a postmarketing surveillance program that relies primarily on voluntary reports to the CVB from the public, veterinarians, and pet owners.[6] Adverse events are considered to be any unfavorable or unintended observation in an animal after the use of veterinary biological product, regardless of whether it is considered to be a product-related event. However, receipt of an adverse event report by the CVB does not necessarily imply that the product caused the event or even that a particular event actually occurred. Adverse event reports may be submitted to the CVB via a toll-free phone number (800-752-6255), the CVB Web site,[7] surface mail, or fax. These data are used as an aid in performing product trend analysis and to detect lot-to-lot changes in frequency of adverse events. Reporting of potential adverse events, even those included on product label cautionary statements, is encouraged.

During the 3-year period covered in this report, the CVB received 246 adverse event reports for dogs in which a rabies vaccine was identified as 1 of the products administered. Reports were assessed for causality by use of an algorithm similar to the ABON system.[8] Of these, 217 reports were considered possibly related to ≥ 1 of the vaccines given, 7 were considered unlikely, and 22 were assessed as unknown. Of reports with age information (n = 206), 21.4% of the dogs were ≤ 6 months old, 33.5% were > 6 months old but ≤ 2 years old, and

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45.1% were > 2 years old. Of reports with sex information (n = 209), 54.5% of the dogs were female. Adverse events considered possibly related to vaccination included acute hypersensitivity (59%); local reactions (27%); systemic reactions, which refers to short-term lethargy, fever, general pain, anorexia, or behavioral changes, with or without gastrointestinal disturbances starting within 3 days after vaccination (9%); autoimmune disorders (3%); and other (2%; **Table 1**). In nearly 72% of the dogs of these reports, other vaccine or medicinal products were administered in conjunction with the rabies vaccine. In those instances, it was generally not possible to determine which product or products might be most closely linked to the adverse event. Additionally, in some instances, dogs had > 1 clinical sign, resulting in the coding of several clinical signs in a single report.

For this same period, the CVB requested manufacturers of rabies vaccines to provide adverse event report summaries for their products. During this period, nearly 10,000 adverse event reports (all animal species) were received by manufacturers of rabies vaccines. Because of the large number of reports, individual adverse event reports were not requested and causality assessment was not performed. Approximately 65% of the manufacturers' reports involved dogs. An adverse event report profile could not be produced because of the lack of a standardized coding system among manufacturers. However, the general pattern in the manufacturers' summaries (data not shown) did not appear to differ substantially from patterns associated with vaccines for dogs reported elsewhere.[6,9,10] Reports included focal cutaneous alopecia at sites of rabies vaccine administration, which has been described elsewhere.[11,12] The overall adverse report rate for rabies vaccines was determined to be 8.3 reports/100,000 doses sold. A specific adverse report rate for dogs could not be determined because many products are licensed for multiple species.

Table 1—Clinical terms used to describe possibly related adverse events in dogs vaccinated against rabies and reported to the USDA CVB from April 1, 2004, through March 31, 2007.

Clinical terms used to describe adverse events	No. of dogs (%)*
Vomiting	61 (28.1)
Facial swelling	57 (26.3)
Injection site swelling or lump	42 (19.4)
Lethargy	26 (12.0)
Urticaria	22 (10.1)
Circulatory shock	18 (8.3)
Injection site pain	16 (7.4)
Pruritus	16 (7.4)
Injection site alopecia or hair loss	15 (6.9)
Death	12 (5.5)
Lack of consciousness	12 (5.5)
Diarrhea	10 (4.6)
Hypersensitivity (not specified)	10 (4.6)
Anorexia	9 (4.1)
Fever	9 (4.1)
Anaphylaxis	6 (2.8)
Ataxia	6 (2.8)
Lameness	6 (2.8)
General signs of pain	5 (2.3)
Hyperactivity	5 (2.3)
Injection site scab or crust	5 (2.3)
Muscle tremor	5 (2.3)
Tachycardia	5 (2.3)
Thrombocytopenia	5 (2.3)

*Based on 217 adverse event reports.

Efficacy Review

Specific immunogenicity requirements for rabies vaccines are detailed in the Title 9 Code of Federal Regulations.[13,14] However, no vaccine can be expected to afford 100% protection under all conditions of use. Therefore, manufacturers are expected to notify the CVB immediately if rabies is reported in a vaccinated animal (suspected lack of efficacy). This allows the CVB to take rapid action to ensure that animals vaccinated against rabies are protected to the expected degree afforded by the product.

During the reporting period, the CVB investigated 4 reports of lack of efficacy in dogs where rabies was suspected as a result of a positive test at a state laboratory. Of these, 2 dogs were confirmed as rabid by the CDC and 2 were not. In 1 of the dogs confirmed positive for rabies, the vaccination history indicated that the dog was not vaccinated strictly according to label recommendations in that the second dose was not given until nearly 18 months after the initial dose. Additionally, review of the manufacturer's quality control records and adverse event reports submitted to the manufacturer or the CVB did not suggest an ineffective vaccine serial. The vaccine serial in question had expired by the time the affected dog was reported; potency testing the vaccine after expiration would have been questionable because no potency requirements exist beyond the expiration date.

For the other dog confirmed positive for rabies, the serial vaccine of the last rabies product used was still within the period before the expiration date. Testing indicated that the product no longer met minimum required potency; therefore, the lot of this serial vaccine was subsequently recalled from the market. Letters were sent to veterinarians indicating that animals vaccinated with the serial vaccine in question should immediately receive a booster.

Discussion

Rabies vaccines are the most common group of biological products identified in adverse event reports received by the CVB.[a] Additionally, because of the potential for severe outcomes to animal and human health if a rabies vaccine fails to protect, efficacy concerns are given high priority. We reviewed safety and efficacy reports involving rabies vaccines by focusing on canine-related information during a 3-year period (April 1, 2004, through March 31, 2007). Reports submitted directly to the CVB and summaries of reports submitted from rabies vaccine manufacturers were considered. Adverse event profiling indicated that most of the reports could be categorized as acute hypersensitivity or local or systemic events. These types of events are to be expected, within limits, with most biological products. Although the adverse event report rate for rabies vaccines in this report is somewhat higher than a similar measure reported for all canine vaccines in other national reports,[10,15,16] differences between country reporting practices are to be expected. Addition-

ally, a species-specific adverse report rate for rabies vaccine administration in dogs could not be determined for this report. Results of a study[9] in which a large veterinary medical database in the United States was used revealed that the vaccine-associated adverse event rate for a rabies vaccine given to dogs did not differ significantly from several other canine vaccines when the vaccines were administered alone.

Descriptions of the CVB postmarketing surveillance system and limitations of adverse event reporting have been discussed elsewhere.[17] Adverse event reporting may provide insights into concerns regarding product performance in the postmarketing phase, but it is not a total picture. Adverse events should be reported to the vaccine manufacturer and to the CVB. In particular, events concerning efficacy need to be reported so full investigations can ensue.

In summary, findings within this report do not suggest a high frequency or unexpected pattern of adverse events associated with the use of rabies vaccines in veterinary medicine. Nearly 120 million doses of rabies vaccine were distributed within the United States during the 3-year period. Although species-specific use is unavailable, it can be expected that dogs are the most common species vaccinated against rabies because rabies vaccination is a legal requirement for dogs in nearly all states.[18]

Two dogs with confirmed rabies that were previously vaccinated with a rabies vaccine were reported during this period. Because obtaining outcome data with vaccination and exposure status for all dogs in the United States during this period is not feasible, the actual efficacy of rabies vaccines for dogs cannot be determined. Results of other studies[19,20] have revealed apparently rare rabies vaccination failures in dogs without determining a failure rate. The information presented here provides additional support for the premise that rabies vaccines for dogs are highly efficacious and a vital component of a successful rabies animal control program.

a. Report of the Committee on Biologics and Biotechnology (oral presentation). 108th Annu Meet U S Anim Health Assoc, Greensboro, NC, October 27, 2004.

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