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VACCINE ADVERSE EVENTS

Adverse events diagnosed within three days of vaccine administration in dogs

Although vaccines are designed to be immunogens and must have potency, safety, and efficacy before licensing, no vaccine is completely free of adverse reactions or totally effective. While pre-marketing safety trials by manufacturers help ensure that vaccine-associated adverse events (VAAEs) occur infrequently, their potential has generated public and professional concern regarding overvaccination of humans and animals.

A published retrospective cohort study of over 1.25 million dogs vaccinated at 360 veterinary hospitals permitted accurate estimation of the incidence rate of practitioner-diagnosed acute VAAEs occurring within 3 d of vaccine administration. Specific clinical signs and treatments were reviewed in a random sample of 400 affected dogs. The association between potential risk factors and a VAAE was estimated by use of multivariate logistic regression.

There were 4,678 adverse events (38.2/10,000 dogs vaccinated) associated with administration of 3,439,576 doses of vaccine to 1,226,159 dogs. The VAAE rate decreased significantly as body weight increased. Risk was 27-38% greater for neutered versus sexually intact dogs and 35-64% greater for dogs approximately 1-3 yr old versus 2-9 mo old. The risk of a VAAE significantly increased as the number of vaccine doses administered per office visit increased; each additional vaccine significantly increased risk of an adverse event by 27% in dogs = or < 10 kg (22 lb) and 12% in dogs > 10 kg.

The risk of a VAAE in this study population was inversely related to a dog's weight. This weight - response relationship had been suggested previously in a study where toy breed dogs had significantly more suspected vaccine reactions than other dogs. [Vaccines, in contrast to nearly all veterinary pharmaceuticals, are prescribed on a 1-dose-fits-all basis, rather than by body weight.] A genetic predisposition to VAAEs has been documented for some dog breeds, and the relatively low VAAE rate observed in mixed-breed dogs suggests that laboratory safety trials using mixed breeds may underestimate the VAAE rates that would occur in purebreds. This is important because purebred dogs comprise at least two thirds of the US dog population. Further, the risk of allergic reaction has been reported to increase after the 3rd or 4th vaccination.

In the present study, VAAE risk increased for dogs up to 2 yr of age and then declined thereafter. The decline after 2 yr of age may have been attributable to allergen desensitization, initiation of an alternative vaccination protocol in predisposed dogs, or owner refusal to revaccinate dogs that previously had a VAAE. Neutering appeared to increase the risk of a VAAE more than sex. Females are believed to mount stronger immune responses after vaccination or infection than males because of a dimorphic enhancing effect of estrogens and a protective effect of androgens.

Research is still required to characterize the primary allergenic components of different licensed veterinary vaccines, and it remains to be determined whether vaccine allergenicity and volume can be reduced while immunologic protection is maintained, particularly for smaller dogs.

Premarketing safety studies, when fiscally or logistically limited in size, will remain limited in power to detect rare adverse events that may be more common among animals with particular risk factors.

Conclusions and Clinical Relevance—Young adult small-breed neutered dogs that received multiple vaccines per office visit were at greatest risk of a VAAE within 72 hr after vaccination. These factors should be considered in risk assessment and risk communication with clients regarding vaccination.

Adverse events after vaccine administration in cats: 2,560 cases (2002–2005)

A recently published retrospective cohort study of nearly 500,000 cats vaccinated at 329 hospitals analyzed VAAEs that occurred 30 d after vaccine administration classified by practitioners as nonspecific vaccine reaction, allergic reaction, urticaria, shock, or anaphylaxis. Clinical signs and treatments were reviewed, and the

association between potential risk factors and a VAAE occurrence was estimated via multivariate logistic regression.

There were 2,560 VAAEs associated with administration of 1,258,712 doses of vaccine to 496,189 cats (51.6 VAAEs/10,000 cats vaccinated). The risk of a VAAE significantly increased as the number of vaccines administered per office visit increased. Risk was greatest for cats approximately 1 yr old; overall risk was greater for neutered versus sexually intact cats. Lethargy with or without fever was the most commonly diagnosed VAAE. No localized reactions recorded in the 30-d period in these particular cats were subsequently found to be neoplastic when followed for 1-2 yr.

Most VAAEs were diagnosed within the first 3 d of vaccination, and significant risk factors included age, sex, neuter status, weight, and number of vaccines concurrently administered. The VAAE rate within 3 d of vaccine administration in cats (0.48%) was approximately 25% greater than the VAAE rate (0.38%) in dogs reported by the study described above.

In multivariate analysis, the factor associated with the greatest increase in VAAE risk was the number of concurrently administered vaccines or the total vaccine volume administered during the office visit. The increase in risk associated with each additional vaccination (27.5%) in cats was equivalent to the risk recently reported for dogs that weighed < 10kg (< 4.5 lb). When multiple vaccines are simultaneously administered to an animal, the ratio of total volume received per pound of body weight per animal increases, indicating an antigenic dose-response relationship.

Nonspecific systemic reactions with clinical signs of anorexia, lethargy, fever, or soreness were the most common VAAEs observed in cats in the present study. These findings are consistent with results of feline vaccine safety studies, although rates for such reactions may exceed 1%. The causes of these nonspecific reactions may include vaccine organism replication of modified-live vaccines, exposure to endotoxins, adjuvant toxicity, or immune system responsiveness. Clinical signs potentially attributable to immediate-type hypersensitivity reactions and mast-cell degranulation (e.g., vomiting, facial edema, and pruritus) were less common VAAEs in this cat population than reported in dogs. Specific causes of vaccine-induced immediate-type hypersensitivity reactions have not been investigated in cats, but heterologous proteins (e.g., bovine serum albumin) have been implicated as a cause in dogs.

The observed dose-response relationship between the VAAE rate and number of concurrently administered vaccines, as well as the inverse relationship observed between VAAE rate and increasing weight in mature cats, has also been reported in dogs, suggesting that manufacturers may need to reformulate vaccines to reduce protein and excipient concentrations in vaccines for cats and dogs. This will become increasingly important as new vaccines are introduced for disease prevention and veterinarians must consider additional biologics in vaccination protocols. Veterinarians should still limit vaccinations to those needed on the basis of individual risk assessments and should limit the number of concurrently administered vaccinations.

Conclusions and Clinical Relevance—Although overall VAAE rates were low, young adult neutered cats that received multiple vaccines per office visit were at the greatest risk of a VAAE within 30 d after vaccination. Veterinarians should incorporate these findings into risk communications and limit the number of vaccinations administered concurrently to cats.

References: Moore et al, J Am Vet Med Assoc 227:1102–1108, 2005; ibid, J Am Vet Med Assoc 231:94-100. 2007.

Journal Resource

Gallbladder disease in Shetland Sheepdogs: 38 cases (1995–2005)

Risk, clinical features, and treatment responses were determined in a retrospective case-control study of gallbladder disorders in Shetland Sheepdogs. The medical records of 38 affected dogs were reviewed for signalment, history, physical findings, laboratory results, imaging features, coexistent illnesses, histologic findings, treatments, and survival rates.

Results showed that mature dogs with gastrointestinal signs were predisposed (odds ratio, 7.2) to gallbladder disorders. Gallbladder mucocele was confirmed in 25 dogs. Concurrent problems included pancreatitis, hyperlipidemia, corticosteroid excess, hypothyroidism, protein-losing nephropathy, diabetes mellitus, cholelithiasis, and gallbladder dysmotility. Mortality rate was 68% with and 32% without bile peritonitis. Non-survivors had high WBC and neutrophil count and low potassium concentration. Although preprandial hypercholesterolemia, hypertriglyceridemia, and high serum liver enzyme activities were common, gallbladder disease was serendipitously discovered in 11 of 38 dogs. Histologic examination (n = 20 dogs) revealed gallbladder cystic mucosal hyperplasia in 20 dogs, cholecystitis in 16, periportal hepatitis in 9, and vacuolar hepatopathy in 7. Surgery included cholecystectomy (n = 17) and cholecystoenterostomy (4). In 1 hyperlipidemic dog without clinical signs, gallbladder mucocele resolved 6 months after beginning use of a fat-restricted diet and ursodeoxycholic acid.

Conclusions and Clinical Relevance—Shetland Sheepdogs are predisposed to gallbladder disorders, with mucoceles and concurrent dyslipidemia or dysmotility in many affected dogs. Most dogs were without clinical signs during mucocele development. Low survival rate after cholecystectomy in clinically affected dogs suggested that preemptive surgical interventions may be a more appropriate treatment strategy.

Reference: Aguirre et al, J Am Vet Med Assoc 231:79-88, 2007.