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Severe Side Effects of Vaccines in the Veterinary Setting

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ABSTRACT

Objective: To determine the general clinical presentation and incidence of adverse reactions to vaccinations in domestic animals.

Design: A retrospective study using clinical databases and scientific literature.

Methods: Veterinary hospitals, Universities and private animal clinics participated in a database search for all the domestic animals vaccinated within a 2-year period.

Results: We reported all the adverse events, including local injection site reactions and systemic signs recorded in cats, dogs and ferrets.

Conclusions: Data from this study show that adverse reactions occur frequently, we are not aware of the exact role of the vaccinal components or of the their complex formulation altogether, as definite triggers of post-injection complications, but comparative pathology with exhaustive surveys of animals untoward effects either in the domestic or zoo technique setting will assist us in better deciphering this puzzling issue.

KEYWORDS

Adverse Reaction; Vaccine; Cat; Dog.

INTRODUCTION

Since in the last 5 years, our research activity has involved veterinary Universities, Hospitals and Institutions and private animal clinics, together with human clinicians in comparative studies between human mankind and domestic or wild animals; the aim is to clarify some common physiopathology pathways, and to share diagnostics and therapeutic steps with animal cohorts having a shorter overall survival perspective compared with the human beings; in this way it is possible to accelerate the recognition of investigational drugs outcome. In the paper, we perform a retrospective study about vaccination toxicity in some animal species, mainly cats and dogs.

Although there is no government obligation for veterinarians to report vaccine reactions, cumulative incidence of vaccination adverse events data between dogs and cats are reported to the vaccine manufacturer and/or to the Canadian Centre for Veterinary Biologics (CCVB) by the veterinarian or pet owner in Canada between 2010 and 2014 (Table 1) [1].

Table 1: Suspected adverse reactions for small animals (dogs, cats) vaccines reported to the Canadian Centre for Veterinary Biologics between 2010 and 2014.

	Number of reactions per 10.000 doses sold	
Adverse reactions	**Dogs**	**Cats**
Allergic conditions other than anaphylaxis	2,663	187
Anaphylaxis, circulatory shock	332	29
Dyspnea	155	110
Vomiting	2,511	1,131
Diarrhea	791	402
Loss of consciousness, collapse	141	8
Pain	240	176

Lethargy	1,923	1,473
Fever	132	438
Malaise	17	17
Vasculitis	13	1
Cough	445	16
Other upper respiratory tract disorders	346	85
Injection site reaction other than sarcoma	1,144	689
Injection site sarcoma	2	148
Death	104	161
Suspected lack of efficacy	228	39
Neurological disorders	459	249
Autoimmune disorders	27	8

The most common registered adverse reactions are allergic: 2663 cases per 10.000 vaccinated domestic animals [2, 3]. Indeed, Type III allergic reactions, including cutaneous vasculopathy and Arthus reactions (36 cases) occurred mainly at the rabies vaccination, could be correlated to a genetic predisposition [4, 5]. Transient symptoms, such as fever (570 cases), lethargy (3.396 cases), injection site swelling/tenderness (1833 cases), pain (200 cases), or anorexia (24 cases), prolonged up to 48 h, were observed in several cats and dogs [6-8].

Feline injection site sarcomas are rare (1 to 10 per 10.000 cats), but serious, since involve prolonged or repeated inflammatory processes in genetically predisposed individuals and can occur also in response to injected therapeutics including steroids, non-steroidal anti-inflammatory drugs (NSAIDS), non-absorbable sutures, and a microchip device [9-13].

Neurological symptoms (e.g. head tremor/bobbing, encephalitis, head pressing, convulsion/seizure, rigidity, weakness, altered reflexes) have been reported in animals (1186 cases per 10.000 doses) that are showed an allergic reaction or pronounced inflammatory reaction (Cooper C and Naczynski Z, CFIA CCVB, 2015, personal communication). Type II immune-mediated disorders such as immune-mediated thrombocytopenia and immune-mediated hemolytic anemia are very rare in small animals (62 cases per 10000 doses), but case control studies did not demonstrate a causal relationship between vaccine administration and autoimmune disorders [6, 14-16]. Protective and susceptible gene haplotypes have been identified in dogs, demonstrating genetic predisposition to type II hypersensitivities [17, 18]. As vaccines are designed to stimulate an immune response, it is not surprising that a predisposed individual may react to vaccination due to the production of inflammatory mediators [19, 20].

A retrospective study in nine veterinary hospitals in Sydney recorded, in 705 rabbits, 17 (1.8%) adverse reactions: 13 (76.5%) were local injection site reactions involving alopecia, abrasions and scabbing. Other reactions, including systemic signs of gastrointestinal tract stasis, lethargy and forelimb lameness, were also documented. A significant association between increasing age and decreased incidence of adverse events was demonstrated (p value: 0.038) [21].

Vaccine-Associated Acute Polyneuropathy

Quiroz-Rothe and coworkers [22] described a Guillan-Barrè syndrome in a 3.5 year-old male Rottweiler dog after receiving an inactivated rabies vaccine (Rabdomun, Pfizer) and other inactived tetravalent vaccine (Tetradog, Merial) that did not include rabies virus antigen virus, by a distance of three months. The common clinical signs of this syndrome, defined also acute inflammatory demyelinating polyneuropathy and characterized by transient neurological signs associated with an inflammatory demyelination of peripheral nerves in which myelin is the target of immune attack, are been: severe weakness with reduced segmental reflexes, exaggerated head movements and a waddling gait, symmetrical quadriparesis with reduced spinal reflexes. The immunological test in the serum sample of the dog confirmed the presence of antibodies against the myelin sheaths of peripheral nerves that would determine an immune-mediated process directed against the myelin of peripheral nerves affecting more severely the ventral nerve roots as supported by the lack of sensory deficits. This anti peripheral nerve myelin antibody activity may be triggered by cross-reacting bacterial antigens, e.g. Campylobacter jejuni, or by other viral vaccine antigens [23]. Thus, in this dog, there was an apparent cause-effect relationship between vaccination and onset of clinical signs associated with the presence of antibodies against myelin. The fact that two different vaccines from two different manufacturers were involved, suggests a polyclonal activation induced by the vaccine adjuvants without the participation of myelin as the more probable pathogenesis.

In a controlled experimental study to test the effects of vaccination on the immune system, 15 dogs that were immunized with commercially available rabies and canine distemper vaccines developed a significant increase in the titer of IgG antibodies reactive with 10 autoantigens; while no increase was observed in the non-vaccinated dogs. This response could be due to several mechanisms such as cross-reactivity or a 'bystander activation' of self-reactive lymphocytes; and the variety of auto-antigens found suggests a polyclonal activation or adjuvant reaction [24]. Indeed, Shoenfeld and coworkers showed that this adjuvant effect, associated with the development of a wide range of autoantibodies, was more often observed in the vaccines with higher adjuvant contents concentrations [25]. Actually, the information about the content

and type of adjuvants used in commercially available canine vaccines is not usually provided by the manufacturer, and the vaccine-induced autoimmunity is regarded as rare but not excluded. For instance, Hogenesch et al [24] showed that immunized dogs have significant titers of autoantibodies and it is likely that, a genetically-predisposed dog, could also develop autoimmune disease.

In conclusion, these case report suggests a polyclonal immune response induced by the vaccine immune-adjuvants or by the viral antigens, or both, with the preferable option to use of non-adjuvated vaccines.

Vaccine- Associated Myofasciitis

Garner and coworkers [26] described the myofasciitis in 17 young domestic ferrets (5-24 months) that had received at least 1 dose of a canine distemper vaccine licensed for use in ferrets (Fervac-D) and many (8 ferrets) also had received a rabies vaccine. The main clinical symptoms involved fever (16 cases), lethargy (14 cases), recumbence, ataxia, posterior-paresis, or pain when moving (12 cases), bruxism, anorexia, or difficulty swallowing or drinking (6 cases), and abnormal stools (3 cases). The histological exams evidenced random neutrophilic hepatitis (9 cases), multifocal neutrophilic interstitial pneumonia (7 cases), suppurative mediastinitis (7 cases), suppurative panniculitis (3 cases), myeloid hyperplasia of spleen (15 cases) and bone marrow (6 cases). The immunochemistrial findings showed elevated values of alanine amino-transferase (ALT) in few ferrets, possibly because of hepatic or muscle damage, while the values of creatine kinase (CK) or aspartate amino-transferase (AST), generally considered indicators of muscle damage, were normal [27]. The cause for this is not known, probably depending on the stage of the disease, muscle is mostly displaced by inflammation or atrophied rather than necrotic.

In summary, the only known shared feature among all of the ferrets was the administration of the distemper vaccine that could stimulate adverse reactions, particularly anaphylaxis, in the ferrets [28]. A considerable interval exists between the documented time of vaccine administration and the onset of clinical signs for some of these ferrets, but could it be that the disease exists sub clinically up to a point, then progresses rapidly. It is interesting to note that one of the co-authors described identical clinical symptoms in an experimental study on ferrets submitted to experimental castration vaccine potentiated with aluminum adjuvant [29].

The aluminum is the most used adjuvant used in human vaccines [30]. The adjuvant effect of aluminum implies trapping soluble antigens in the aluminum gel, interacting with dendritic cells enhancing antigen presentation, complement and eosinophil activation, as well as promoting an influx of neutrophils and enhancing the secretion of pro-inflammatory cytokines and chemokines. Aluminum can also induce cellular damage with intracellular DNA and uric acid release, activating NALP3 inflammasome in macrophages with subsequent IL-1b secretion [31, 32].

Vaccine-Associated Neurophatologic Damage

The canine distemper vaccine has been able to induce neuropathologic damage (including progressive partial or complete tetraparesis, vestibular signs, seizures, and dementia) in 4 adult dogs that had been vaccinated yearly. The significative histological findings were: 1) severe, non-purulent inflammation in the leptomeninges, the gray matter and white matter of the cerebrum, cerebellum, brain stem, and cervical spinal cord; and 2) multifocal demyelination associated with multifocal hemorrhages [33]. However, the histopathological diagnosis was viral non-purulent meningoencephalitis with severe demyelination in all dog cases. This diagnosis was confirmed by positive immunohistochemical analysis of sections of CNS, indicating those tissues were positive for canine distemper virus (CDV). In this report, the authors evidenced a CDV encephalitis by vaccine in all the dogs as reported by other authors and supposed that this permanent neuropathologic damage could be attributable to incorrect vaccine protocols or vaccine alteration after improper storage, but also to host factors (immunodeficiency, maternal antibody interference, vaccination during incubation period) or possible mutation of the wild CDV [34, 35]. Also, new CD virus genetic variants may be associated with pathogenesis changes or immune evasion in dogs vaccinated with current vaccines [36].

Vaccine-Associated Cutaneous Neoplasms

Bregman and coworkers described 12 cutaneous epithelial masses (11 neoplasms), which occurred at the site of previous intramuscular inoculation of inactivated canine oral papillomavirus (COP) vaccine in 12 beagle dogs (over 7 years) [37]. Histological examination of tumor sections stained for papillomavirus structural antigens by the peroxidase-antiperoxidase (PAP) technique revealed squamous cell carcinomas in 5 dogs. The pathogenesis of the neoplasms in this report is not explained. The development of the cutaneous proliferative lesions (papillomatous cysts) following intramuscular inoculation of COP vaccine was also observed in calves that had developed cutaneous papilloma virus subcutuaneously, after inoculation with bovine papilloma virus (BPV) [38]. All of these lesions could occur from the basal cells of the stratum germinativum of the epidermis or of the basal cells of the pilary complex that could represent the initial site of infection of COP.

In conclusion, the recognition of COP vaccine as an etiologic agent for skin tumors in dogs may provide a model for future oncogenic investigations of this virus.

Vaccine-Associated Sarcoma

Epidemiologic studies evidenced a significative association between the administration of inactivated feline vaccines (feline leukemia virus and rabies vaccines) and subsequent soft tissue sarcoma development at vaccine sites [39-42]. The increased incidence of fibrosarcomas in cats seems be linked to the introduction and widespread use of two adjuvated vaccines not previously used in the cat (rabies and leukemia vaccines) [43]. Studies have been unable to identify specific brands of rabies or leukemia virus vaccines linked to sarcoma development, but the aluminum has been found in several soft tissue sarcomas [10, 39-41]. These post-vaccinal tumors, including fibrosarcomas, myofibroblastic sarcomas, osteosarcomas, chondrosarcomas, undifferentiated sarcomas, and rhabdomyosarcomas, could occur as a result of proliferation of fibroblasts and myofibroblasts at sites of chronic inflammation induced by the vaccine's adjuvants, its antigens, or both [40, 44, 45]. Vaccine-site tumors are histologically similar to mesenchymal tumors that arise in traumatized eyes of cats, suggesting a common pathogenesis of inflammation and wound healing in the development of tumors in these two syndromes [46-48]. However, aluminum may be only a marker of previous vaccination and other vaccine components may induce inflammation or enhance the inflammatory process that results in tumor production in some cats. In an attempt to identify vaccines most likely to induce local post-vaccine reactions, six inactivated feline vaccines (three rabies vaccines and three leukemia virus vaccines) were recently evaluated for evidence of local adverse reactions 21 days after subcutaneous administration to 36 cats [49]. This study showed that 80-100% of the cats vaccinated with inactivated rabies vaccines, appeared local reactions that were approximately twice the size of the adverse reactions found at vaccine sites in cats receiving any of the three feline leukemia virus vaccines. However, the feline leukemia virus vaccine that contained no adjuvant did not produced measurable local reactions at vaccine sites.

CONCLUSION

Our review highlights the side effects of vaccination in domestic animal species comparatively focusing on some symptoms, namely the CNS and PNS one that have been observed especially after HPV vaccine administration; of great help in some developed countries the reports of active surveillance registries of untoward reactions to veterinary drugs administration but the great majority of world nations are actually lacking of this public service, so our report is largely uncompleted and inhomogeneous.

Amazingly however in the feline cohort, the subcutaneous injection of the vaccine induces sometimes sarcomas in the surrounding tissue, but this unexpected and dramatic complication seems to be unique in the immune stimulation panorama and opens the debate whether immune activation of Langherans and other subcutaneous immune cells is able in the cat to suppress or activate oncogenetics or oncostatic steps in the dermis mesenchimal DNA.

As to the less uncommon neurological damages, we didn't find aspecific fibromyalgia picture overlapping the human one but some other Central Nervous disorders have been reported in some series; on the other hand, the experimental induction on the animal lab of polymorphous- postvaccinations syndromes is useful in a perspective explanation of the common physiopathologic mechanism underlying different species enclosed the human gender that develops similar autoimmune diseases, observed in cats and dogs, after vaccine injection (Table 2).

Conclusively right now, we are not aware of the exact role of the vaccinal components or of the their complex formulation altogether, as definite triggers of post-injection complications, but comparative pathology with exhaustive surveys of animals untoward effects either in the domestic or zoo technique setting will assist us in better deciphering this puzzling issue.

Table 2: Autoimmune Diseases after Vaccine Exposure.

Vaccine type	Post-vaccine disease	Incidence	Time post-vaccination	Ref.
Rabies vaccine	-Guillain Barre ´ syndrome (GBS), -Acute disseminated encephalomyelitis (ADEM)	10 cases; 1 case	2 weeks; 3-6 weeks	[50]; [51]
Yellow fever vaccine	Encephalitis, GBS	1 case; 6 cases	2 weeks; 30 days	[52]; [53]
Measles, mumps, rubella(MMR) vaccine	Transverse myelitis; GBS	1 case 24 cases	1 day 6 weeks	[54] [55]
Hepatitis A virus vaccine	Immune Thrombocytopenic Purpura GBS	32 cases 1 case	1 day 5 days	[56] [57]

Hepatitis B virus vaccine	Dermatomyositis; GBS;	1 case; 1 case	3 weeks; 10 weeks	[58] [59]
Bacillus Calmette-Guèrin vaccine	Osteitis;	222 cases	2 weeks	[60]
Tetanus vaccine	Reactive arthritis; GBS	1 case 3 cases	3 days 6 weeks	[61] [62]
Diphtheria/pertussis/ tetanus vaccine	GBS	1 case	4 days	[63]
Influenza vaccine	GBS; Myositis and myocarditis	8 cases; 5 cases	6 weeks 3 weeks	[64] [65]
Smallpox vaccine	GBS	3 cases	1 week	[66]
Poliomyelitis vaccine	Arthritis,	2 cases	1 day	[67]
Human papilloma virus (HPV) vaccine	ASIA syndrome	25 cases	20 days	[68]
Pandemic Influenzae A (H1N1) vaccine	Polymyositis	3 cases	7 days	[69]
Anthrax vaccine	Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE)	77 cases, 39 cases	90 days, 90 days	[70], [70]

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