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Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ADVISORY NOTICE TO VETERINARY SURGEONS REGARDING THE DEVELOPMENT OF FIBROSARCOMAS AT SITES OF INJECTION OF VETERINARY MEDICINAL PRODUCTS IN CATS

Summary

In response to increasing concern, the Committee for Veterinary Medicinal Products (CVMP) has produced this advisory notice for veterinary surgeons on the development in cats of fibrosarcomas at sites of administration of veterinary medicinal products. The advice relates principally, but not exclusively, to the subcutaneous injection of vaccines. The issue is of relevance only to cats and no extrapolation should be made to other species or to man. At the current state of knowledge, it is not possible to provide specific advice on the risk that any product, or any type of product, might represent in terms of inducing a fibrosarcoma at the site of administration. However, following the precautionary principle, the CVMP considers that information on this issue should be made available to veterinary surgeons in order that they can have an informed discussion with owners of the benefits and risks of therapeutic interventions in cats, particularly in relation to vaccination and re-vaccination. The CVMP wishes to emphasise that modern vaccines continue to represent the only safe and effective means of protecting cats against serious infectious diseases and this should be taken fully into account in any discussion between veterinary surgeons and owners of cats.

Introduction

This advisory notice is issued by the Committee for Veterinary Medicinal Products (CVMP) in recognition of growing concern about an apparent increase in the number of fibrosarcomas being diagnosed in cats in the EU at anatomical locations commonly used as sites of administration of veterinary medicinal products, principally the interscapular region or "scruff". Concern has mainly, but not exclusively, been focussed on the link between subcutaneous injection of vaccines in this region and the subsequent development of fibrosarcomas[1]. The notice summarises some of the key information available at the present time and recommends that veterinary surgeons should take this information into account when discussing vaccination of cats with owners. In addition, the notice indicates those areas where further data are required in order to improve the quality of information provided to veterinary surgeons and owners in relation to this issue.

The CVMP considers that modern vaccines are a safe and effective means of protecting cats against infectious diseases. The risk to individual animals of contracting an infectious disease can be considerably reduced by vaccination and the prevalence of infectious diseases is reduced in a population by widespread uptake of vaccination. The CVMP is therefore concerned to ensure that these proven benefits of vaccination are taken fully into account when veterinary surgeons discuss with each owner the relative risks and benefits of vaccinating their individual cat.

All data available to date suggest that this issue relates only to cats and no extrapolation should be made to any other species, including man. The phenomenon appears to be related to the particular nature of the reaction of cats to substances, particularly when administered at subcutaneous sites.

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Fibrosarcomas at sites of administration of veterinary medicinal products

History and incidence
Reports of epidemiological studies have been published since the early 1990's demonstrating a statistical association between the administration to cats of veterinary medicinal products, in particular inactivated, adjuvanted vaccines, and the subsequent development of fibrosarcomas at the site of administration. These studies have been largely retrospective and based on surveys of biopsy specimens submitted to diagnostic pathology laboratories. There are no accurate estimates of the incidence of the development of fibrosarcomas following vaccination in the EU. A recent retrospective analysis of pharmacovigilance data in the UK found an incidence of 0.021 fibrosarcomas for every 10,000 doses of cat vaccines sold in the period 1995-1999[2]. In contrast, in the USA, where vaccines and vaccination practices differ from the EU, an incidence was estimated of between 1 to10 cases per 10,000 doses of FeLV (Feline Leukaemia Virus) or rabies vaccine used. These figures must be viewed with caution due to the large amount of uncertainty that is inherent in retrospective epidemiological surveys, such as the number of previous vaccinations, the nature of the product administered, the interval between administration and the development of a tumour, the exact nature of the tumour and its pathological classification etc. On their own, these studies suggest an association between the two events of vaccination and the development of a fibrosarcoma but do not indicate that the two are causally related.

Aetiology
Studies have been conducted to ascertain if certain vaccine components, or other factors, are involved in the pathogenesis of fibrosarcomas in cats but, to date, the aetiology of the condition remains obscure. Contradictory results have been obtained in studies examining the role in fibrosarcoma development of rabies vaccines, FeLV vaccines, aluminium adjuvants, other adjuvants, live viral components, mono- versus multi-valent vaccines and other medicinal products. Epidemiological studies have thus far failed to identify specific brands of vaccines that may represent an increased risk for the development of fibrosarcomas.

At the present time, the most accepted hypothesis is that the pathogenesis of vaccine site associated fibrosarcomas is in some way associated with the induction of a chronic inflammatory response at the site of administration[3]. In this model, any material that induces local inflammation at the site of injection may be associated with the subsequent development of fibrosarcomas in susceptible cats, including live and inactivated vaccines (with or without adjuvants) and other non-immunological veterinary medicinal products. There may be as yet undetermined genetic factors that result in increased susceptibility or resistance to the development of the condition. Concerning the route of administration, tumours have been reported following administration by either the intramuscular or the subcutaneous routes, but the majority of studies published to date relate to vaccines administered subcutaneously.

Recommendations

General
The CVMP is not in a position to provide specific advice in relation to the risk that any particular product, or any type of product, might represent in terms of inducing the development of a fibrosarcoma at the site of administration. Nevertheless, the CVMP considers that veterinary surgeons should be made aware that any product that is administered subcutaneously or intramuscularly to cats that subsequently results in the induction of inflammation at the site of injection may be associated with an increased risk of fibrosarcoma development at that site.

Informed discussion of risk:benefit
Vaccination continues to represent the only safe and effective way of protecting cats against the major infectious diseases of cats. Nevertheless, following the precautionary principle, a risk/benefit assessment on the need for administration of the product should be carried out by the veterinary surgeon in consultation with the cat's owner. Vaccination protocols should be individualised to the patient with consideration given to the medical importance and zoonotic potential of the infectious agent, the patient's risk of exposure and the legal requirements relating to vaccination (e.g. for rabies).

Sites and routes of administration
Veterinary surgeons should consider carefully the site of administration of the vaccine taking into account the authorised routes of administration for the product concerned and the fact that sarcomas in the interscapular region are more difficult to treat than sarcomas in other regions. Some experts advise administering monovalent vaccines distally in separate limbs, on the basis that this facilitates amputation in the event of the development of a fibrosarcoma. However, the Committee is not currently in a position to endorse this advice due to the practical difficulties associated with this regime and the lack of supporting data.

Booster vaccinations
In order to reduce any risk that vaccination might represent, owners may request advice from the their veterinary surgeon on the need for booster vaccinations at regular intervals, usually each year. At the present time, there is insufficient data for CVMP to recommend re-vaccination intervals different from those specified in the product literature for the vaccine concerned. Owners should therefore be made aware that protection against the disease concerned can only reliably be maintained when vaccines are used according to the terms of their authorisation. Nevertheless, veterinary surgeons should note that the duration of immunity claimed by the manufacturer is the minimum duration of immunity that is supported by the data available at the time of authorisation and this should be taken into account when discussing protocols for re-vaccination with the owner.

Requirements for the future

The CVMP considers that a better understanding of the epidemiology and aetiology of fibrosarcomas associated with the administration of veterinary medicinal products is required. This information may enable more specific advice to be given as to the risk that administration of particular products, or particular types of products, might represent in terms of inducing a fibrosarcoma. The CVMP is aware that research projects are underway, both in the EU and elsewhere, to improve understanding of this complex issue.

Continued vigilance by veterinary surgeons represents the best means of surveillance to detect fibrosarcomas that might be associated with veterinary medicinal products. Veterinary surgeons are therefore encouraged to report all such fibrosarcomas to the relevant Competent Authority that is responsible for pharmacovigilance (i.e. for monitoring adverse drug reactions). They are also encouraged to support manufacturers in their investigations into the possible relationship between the administration of their veterinary medicinal products and the subsequent development of fibrosarcomas.

The CVMP, and national competent authorities, will continue to monitor the situation and will provide additional advice to veterinary surgeons and animal owners as it becomes available.

Selected references

[1] Doddy, F.D., Glickman, L.T., Glickman, N.W. and Janowitz, E.B. (1996) Feline fibrosarcomas at vaccination and non-vaccination sites. Journal of Comparative Pathology 114, 165-174

[2] Gaskell, R., Gettinby, G., Graham, S., Skilton, D. (2002) Veterinary Products Committee Report on Feline and Canine Vaccination. Final Report. Defra Publications, UK; ISBN:0-95311234-5-6. (A summary of this document was published in the Veterinary Record (2002), February 2, pages 126-134 and the whole report containing an up-to-date review of the literature on the subject is available at http://www.vpc.gov.uk)

[3] Macy, D.W. (1999) Current understanding of vaccination site-associated sarcomas in the cat. Journal of Feline Medicine and Surgery 1, 15-21

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