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Epidemiological approaches to safety investigations

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Abstract

This paper considers the different approaches to post-authorisation safety monitoring of veterinary medicinal products that is essential to ensure confidence in their safety.

Most safety testing is undertaken prior to granting of a marketing authorisation and is generally on a small scale. Field trials are usually much larger, but still involve relatively low numbers of animals compared to the number to which authorised products are administered. Safety testing is generally aimed at detecting common events; the numbers of animals used in the tests are too small for detection of all but the most common reactions. The efficiency of the tests depends on the frequency and severity of the adverse reaction and the ability to associate the adverse event with the product. The latter is affected by the period of time between administration and the event, as well as by its underlying frequency.

Adverse reaction surveillance is critical in monitoring the safety of a marketed product. Most is entirely passive and so reporting rates are likely to underestimate true incidence. It is relatively efficient for rare, serious adverse effects and for those with a low underlying frequency in the population, but it is less useful when there is long period between administration and the event, or where the event has a relatively high underlying frequency. Greater emphasis should be placed on active surveillance after production registration.

Detailed epidemiological investigations, including cohort, case control and cross-sectional designs, offer the only approaches that provide more information on the association between a product and events that have a high underlying frequency in the population or where there is a long period between administration and the adverse event. The relative merits of different approaches are discussed, with particular reference to our recently published study of the temporal association between canine vaccination and non-specific signs of ill health and plans to undertake studies of associations with feline injection site sarcoma. Emphasis is placed on the need for clearly stated hypotheses and the consideration of equivalence, rather than significance testing when considering safety studies.

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1. Introduction

Safety testing and surveillance of adverse reactions to administration of all medicinal products is critical to

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ensure continued consumer and professional confidence in their use.

There are many ways that the safety of vaccines is ensured and then evaluated. This paper considers, in the context of the testing that has been undertaken prior to authorisation, the different post-authorisation approaches to safety monitoring essential to ensure safety of medicinal products. Manufacturing processes that ensure product purity throughout its production for the years after initial authorisation, although essential, are not considered.

Generally, formal safety testing of veterinary medicinal products and field trials of the same are undertaken on a much smaller scale than that of the final target market. Most products are associated with occasional adverse reactions and it is thus inevitable that safety testing will fail to detect some rare reactions that are subsequently observed during commercial use of the products.

Adverse reaction surveillance is thus critical in monitoring the safety of a marketed product. Most adverse reaction surveillance is entirely passive and so reporting rates are likely to underestimate true incidence rates. While it is likely to be relatively efficient for rare, serious adverse effects and for those with a low underlying frequency in the population, it is less efficient when there is long period between administration and the event, or where the event has a relatively high underlying frequency.

Pharmacovigilance is the term often used to describe surveillance of adverse reactions to marketed products. There is a requirement under European law for companies and authorising bodies to undertake pharmacovigilance for all authorised medicinal products. Surveillance is generally defined as a three tier process which involves the routine collection of disease data, its collation and interpretation, and, finally, its dissemination to all those who need to know. Unusually for surveillance schemes, for pharmacovigilance data, there appears to be no requirement under European law for dissemination to those who provide the raw data (the practitioners) of collated and interpreted results. The reports, be they periodic safety update reports (PSUR) or more immediate reports of individual serious adverse reactions, are interpreted and acted on by companies and licensing authorities. Thus, practitioners rely on sporadic reports from companies or authorities concerning the occurrence of adverse reactions. The situation has been rather better in the UK, with the Veterinary Medicines Directorate providing annual reports, published and available online, broken down by species and product types, of adverse reaction reports that they have received. However, except for what are defined as ''serious'' adverse reactions, there is no requirement for companies to report adverse reactions other than in PSURs, which are only required every 5 years for products licensed more than a few years. Thus, these annual reports can provide misleading information on the occurrence of less serious adverse reactions. Furthermore, there is no specific requirement under European legislation for specific statistical analysis of batch to batch variation in reports of adverse reactions. Such a requirement could provide particular benefits for consumers in the case of biological products manufactured using processes that are hard to standardise on a large scale, such as the growing of antigen for vaccines in embryonated eggs.

More emphasis, as described in Eudralex (2004, vol. 9), should also be placed on active surveillance after production registration. Detailed and carefully planned epidemiological investigations provide the best means of undertaking active surveillance and are the only approach that provides more information on the association between a product and events that have a high underlying frequency in the population or where there is a long period between administration and the adverse event. The strengths and weaknesses of different approaches are discussed, with particular reference to our recently published study of the temporal association between canine vaccination and non-specific signs of ill health and our plans to study the associations of vaccines with feline injection site sarcoma.

2. Available active epidemiological approaches

Standard epidemiological study designs, including cross-sectional, case control and cohort studies, can be used to study safety of vaccine usage in the field. The most appropriate study design will depend on the type of adverse reaction being studied, its approximate frequency, the expected period between product administration and the development of clinical signs

and critically, on the experimental question being tested by the study. In every instance, there needs to be an unambiguous case definition and a clear statement of the specific hypothesis being tested.

Cohort study designs are often heralded as the gold standard of epidemiological study design, as they are less prone to bias than others. However, their nature dictates that they are often massive, expensive and require years to undertake. Usually, a cohort of individuals from the population of interest is recruited and then followed over an extended period of time and the association between the outcome and exposure(s) of interest is estimated. The recruitment of large numbers of individuals prior to the development of the disease generally ensures that cases and controls are derived from equivalent populations. The measurement and recording of exposures of interest prior to the development of disease reduces the possibility of the systematic misclassification of exposure. However, final statistical analysis of cohort studies of rare diseases makes inefficient use of much of the data collected, particularly from individuals without the disease.

Recently, the UK Veterinary Products Committee (VPC) recommended that a cohort study of the association between feline infections site sarcoma (FISS) and vaccination be undertaken (DEFRA, 2003). Using reasonable estimates of the possible strength of association between vaccination and FISS and published estimates of its frequency, we estimated that it would be necessary to recruit around 50% of all the cats in the UK into such a study if it were undertaken over a minimum 5-year period (Adams and others, unpublished observations) and concluded that a case control study was more feasible and appropriate.

Case control study design is often the most efficient when the disease or condition being studied is rare, particularly when there are reasonable pre-existing records of the exposure of interest (Schlesselman, 1982). Great care needs to be taken to ensure that results are not confounded or biased by uncontrolled or unmeasured exposures, or by systematic bias in the classification of exposure, or by inadequate case definitions leading to misclassification of outcome. Case control studies should be designed, in particular when considering the ratio of cases to controls, to make maximally efficient use of information from both cases and controls.

Cross sectional studies will only rarely be of use in studies of medicinal product safety, although they can be invaluable in situations where the condition of interest is common in the population. They can be undertaken efficiently, although the simultaneous classification of outcome and exposure, in contrast to cohort studies, means that care similar to that in case control studies needs to be taken to ensure that results are minimally affected by bias and confounding.

Whatever the general study design chosen, care needs to be taken to ensure that the sample size is appropriate to test the chosen experimental question. In some cases, studies will be designed to test a positive hypothesis (e.g. that FISS is associated with administration of specific injectable products). If designed appropriately and undertaken without significant problems, such studies should provide definitive answers to hypothesis tests. In studies of safety however, the overall objective is often to demonstrate that the occurrence of the disease or outcome of interest is not higher than in the population not receiving the product in question. Such studies should be designed and analysed to demonstrate ''equivalence'', usually within certain confidence limits (Christley and Reid, 2003). Equivalence studies, depending on the width of the predetermined confidence limits, often need to be rather larger than studies designed to test hypotheses.

It is not sufficient to demonstrate that any association between administration and outcome is not statistically significant, as such results could be based on either an inadequate sample size or the lack of any association. Inadequate sample size was identified as being a critical barrier to drawing accurate inferences from statistically non-significant results more than 150 years ago (Balfour, 1854), but this error remains disappointingly commonplace in veterinary and medical practice.

3. Is canine vaccination associated with signs of ill health in dogs?

Concerns were raised in Britain over a period of several years in the 1990's regarding the safety of canine vaccines by an anti-vaccination campaign group, the Canine Health Census (later renamed to Canine Health Concern, CHC). Based on a magazine- and then

web-based survey in which dog owners were requested to contact them if they had observed health problems in their dogs following vaccination, CHC concluded that around a third of dogs were made ill by vaccination. These claims received widespread attention in the media, echoing to an extent the public concern over the possible links between the use of MMR vaccination and autism. The veterinary profession and the pharmaceutical industry, while not accepting the results, had no direct evidence base with which to counter the claims. We therefore conducted an epidemiological investigation to evaluate the evidence for a temporal association between vaccination and ill health in dogs (Edwards et al., 2004).

There were no baseline disease incidence data around which to base the study hypotheses. Given the claims of CHC about the common frequency of illness following vaccination, it was felt that a cross-sectional study was the most efficient study design. The owners of a randomly selected population of 9055 dogs registered with a random sample of 37 British veterinary practices were sent postal questionnaires and 4040 were returned. The questionnaire asked for information on ill health in the preceding 2 weeks. Not only was no temporal association found between vaccination and ill health in dogs after adjusting for potential confounders, such as age, but the frequency of illness in varying times following vaccination was found to be equivalent to that prior to vaccination. In detail, the results demonstrated that recent vaccination (<3 months) was not associated with an increase in signs of ill health of more than 0.5% and might actually have been associated with a decrease of as much as 5%.

The study's strengths were that the results demonstrated equivalence in the frequency of signs of disease between those dogs recently vaccinated and not vaccinated and that baseline frequency data on signs of ill health in British dogs were produced. The weaknesses were that the study was not specifically designed to demonstrate equivalence (although it was large enough to do so) and that health in an unvaccinated dog population was not compared to that in a recently vaccinated population. However, it was not possible to gain access to equivalent populations of vaccinated and unvaccinated dogs, which is why the approach of studying disease associated with recent vaccination was taken, this was also appropriate given what CHC had claimed. The study concluded generally that all future studies of product safety should attempt to demonstrate equivalence rather than non-significant differences.

4. Does vaccination cause feline injection site sarcoma?

An apparent increase in the frequency of poorly differentiated sarcomas in the inter-scapular space was reported a number of years ago in North America (Esplin et al., 1993; Hendrick et al., 1992; Coyne et al., 1997). Results from a number of case control studies of what were termed vaccine associated sarcomas subsequently undertaken (Kass et al., 1993, 2003) suggested an association with the use of some specific vaccine types, although important questions concerning unmeasured confounding from the use of other injectable products remained unanswered. A similar increase in what appeared to be the same condition in the UK (DEFRA, 2003) was also reported. As discussed above, evidence concerning the condition was reviewed by the VPC, who, as previously noted, recommended that a detailed epidemiological study be conducted to determine any association between the use of different products and the occurrence of FISS.

One of us (VA) recently gained funding to conduct a large scale case control study of factors associated with FISS, including the administration of vaccines and other injectable products. The funded project is entitled 'Incidence of, risk factors for, histological features of and protein expression patterns in injection site sarcomas in cats'. The primary hypothesis of this study is that vaccination or drug administration is associated with the occurrence of feline injection site fibrosarcomas (FISS). The aims of the 3-year project are to: (a) identify risk factors related to the occurrence of FISS in a case-control study, (b) estimate the incidence of FISS in the UK, (c) create an expert consensus of opinion on the histological characteristics of this tumour type that can be used as consistent diagnostic criteria and (d) classify FISS using a proteomics based approach to characterise differences in protein expression between injection site sarcomas and sarcomas arising at non-injection sites.

5. Conclusions

This paper has reviewed some of the factors that should be considered in the epidemiological surveillance or evaluation of the safety of marketed veterinary medicinal products. It has not considered the controls in the manufacturing processes nor the relatively small scale pre-authorisation safety testing undertaken. Greater openness is needed in reporting rates of adverse, or suspected adverse reactions to marketed products. Epidemiological studies need to be designed carefully and specifically for each particular situation, in particular being large enough to demonstrate equivalence in health before and after product administration whenever appropriate.

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