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Control of canine distemper

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Abstract

Control of canine distemper can realistically only be achieved by the use of vaccination. The types of vaccine in current use are described, together with some of the problems encountered such as interference by maternal antibodies, and usage in species other than dogs. Modified live viral vaccines, as used for more than thirty years, have proved very effective. Nevertheless there is scope for some improvement in vaccine efficacy and recent developments in genetic recombinant methods are described.

Keywords: Distemper; Dog; Vaccination

1. Introduction

The only practicable and effective measure to control canine distemper is, at present, immunization by vaccination, even if classical hygienic measures can be applied in parallel. In 1966, R. McClelland and J.H. Gillespie wrote: "A great deal could be written about immunization against canine distemper, and much has been said in the past. With our present knowledge and testing procedures, there is less need for words because the approach to successful protection is relatively straightforward and simple" (McClelland and Gillespie, 1966).

Active immunity against canine distemper in dogs can be achieved by the use of various types of vaccines. Active immunization has been practised since Puntoni (1923) described the use of formaldehyde-inactivated canine distemper virus (CDV)-infected dog brain tissue. These early vaccines proved incapable of controlling the disease. Active immunization became very successful after live attenuated vaccines became available: ferret-pas-saged modified vaccine, modified hen egg virus vaccine (Haig, 1956), modified cell culture virus vaccines (Rockborn, 1959), heterotypic measles vaccine, and combined vaccines.

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Purified vaccines (Norrby et al., 1986) and ISCOM vaccines (de Vries et al., 1988) prepared over the past few years remain at an experimental stage.

2. Current vaccination practices

2.1. Usage

At present, modified live virus (MLV) vaccines are used on a large scale: in 1992 approximately $27.5 \times 10^6$ doses of vaccine were used in the U.S.A. for a population of $53 \times 10^6$ dogs, while in France in 1993, $4 \times 10^6$ doses were used for a population of $9.9 \times 10^6$ dogs. Vaccines against distemper are now supplied only in freeze-dried form and are combined with other components such as adenovirus, parvovirus, and parainfluenza type 2 virus, and, sometimes, with rabies virus, coronavirus and Leptospira. The modified live CDV vaccines available today are either of avian egg origin (Onderstepoort strain) or canine cell culture adaptations (Rockbom strain). Both these strains enable the preparation of very effective vaccines.

2.2. Regulatory requirements

From the regulatory viewpoint, it is interesting to compare the requirements of European authorities with those of America. The European Pharmacopoeia (European Council) monograph "Vaccinum morbi carrei vivum cryodesiccatum pro cane" [Freeze-dried Canine Distemper Live Vaccine] mentions the essential criteria: safety of master seed virus, safety of every batch, potency. These specific requirements have been emphasized by the more recent regulations governing the registration of products in the European Union (Anon., 1992). In the United States of America, the Code of Federal Regulations presents two monographs related to canine distemper vaccine, one concerning a ferret avirulent strain (9 CFR 113–306), and the other one concerning a ferret virulent strain (9 CFR 113–307). These monographs are very complete and more precise than the European monograph.

2.3. Vaccine properties

The intrinsic properties of vaccines containing a distemper component are critical for vaccine performance. Although industrial scale culture of the virus on cell systems does not raise any special problems, the storage and the heat-stability of the freeze-dried virus remains delicate. The producer therefore has to find a formula for the stabilizer to obtain the best shelf-life for the product. In combined vaccines, the distemper component is always the least heat-stable (by comparison with adenovirus and parvovirus components).

Both methods of adaptation result in very effective vaccines (CDV Onderstepoort (CDVo), CDV Rockbom (CDVR)) which induce immunity in susceptible dogs that lasts for at least one year. If the routes of vaccination are compared in susceptible dogs immunized with a single dose of MLV-CDVo vaccine ($10^{6.6}$ CCID50/dose), we can observe a better seroneutralizing antibody response at 21 days post-vaccination by the intravenous and intramuscular routes than by the subcutaneous route ($2.6 \log_{10}$ by IV route, $2.2 \log_{10}$ by IM.
Table 1
Comparison of immunogenicity of CDV vaccinal strains by different routes of inoculation

| Vaccine   | Route of vaccination | Mean neutralizing antibody titre \( \log_{10} \) (with standard deviations) |
|-----------|----------------------|----------------------------------|
|           |                      | 21 dpv\(^c\) | 42 dpv | 1 ypV |
| CDV\(_O\) | IM                   | 2.2 (0.26)\(^d\) | 2.0 (0.21) | 1.7 (0.17) |
|           | SC                   | 1.8 (0.10) | 1.9 (0.13) | 1.5 (0.17) |
| CDV\(_R\) | IM                   | 2.6 (0.21) | 2.9 (0.13) |         |
|           | SC                   | 1.7 (0.20) | 2.8 (0.22) |         |

\( ^{a} \)CDV\(_O\) Onderstepoort.
\( ^{b} \)CDV\(_R\) Rockbom.
\( ^{c} \)dpv days post vaccination.
\( ^{d} \) Standard Deviation.

...
rapid-growth breeds “eliminate” their maternally-derived antibodies more quickly and therefore become more rapidly susceptible to the disease and receptive to immunization. Thus maternally-derived antibodies, whilst beneficial for early protection against the infection, disturb the vaccinal immunization. It could be postulated, as has been shown in the case of canine parvovirus (Burtonboy et al., 1991), that vaccines with high titres are likely to be more effective in the presence of residual maternally-derived antibodies. Recent evidence for CDV vaccine supports this (Chalmers and Baxendale, 1994). Because the persistence of maternal antibodies is a well-known cause of vaccine failure, the recommended primary vaccination consists of two consecutive injections. The second should be given to puppies around 12–14 weeks of age, by when a complete disappearance of passive immunity is expected and the vaccine should be completely effective (Chappuis et al., 1974; Terre et al., 1978).

For an active booster effect, it is possible to increase the level of preexisting active antibodies by revaccination. In our experiments a booster effect was observed in dogs with existing seroneutralizing antibody titres up to 1:100. The booster effect is inversely related to the level of previous seroneutralizing antibody titre. In a kennel, booster vaccination can establish a homogeneous immune status among the bitches thus simplifying the vaccination programme for the litters (Michel et al., 1971).

Heterotypic (measles) virus vaccination has been one approach to overcoming neutralization by maternally-derived antibody. Measles virus (MV) is not neutralized by CDV antibodies. MV induces a clinical protection against CDV (Baker, 1970). The use of MV vaccines was originally recommended for puppies aged 2–4 weeks, although it was not very successful in field conditions. Afterwards, a combination of attenuated MV and CDV was applied in puppies aged 6 to 10 weeks. This is acceptable for the first generation; however puppies vaccinated and boosted with this vaccine will produce antibodies against both MV and CDV, and subsequently as bitches will transfer antibodies of both specificities to their litters.

3. Adverse reactions to CDV vaccines

Although CDV vaccines are safe and efficacious, adverse reactions can occur (Tizard, 1990; Brooks, 1991). Adverse reactions are often a complex interaction between the animal,
the vaccine (which contains more and more antigens) and the environment which includes
the veterinarian. In the investigation of any adverse reaction, all three components need to
be examined.
Modified live CDV vaccine multiplies in dogs causing transient immunosuppression and
thrombocytopenia (Straw, 1978). The reversion to virulence of Rockborn strain was dem-
donstrated by Appel (1978) after serial passages in dogs. Encephalitis in dogs with a batch
of CDV vaccine was observed by Cornwell et al. (1988). Interactions between CDV and
adenovirus MLV vaccines can induce the suppression of lymphocytic respondiveness (Phil-
lips et al., 1989). Canine parvovirus infection potentiates canine distemper encephalitis
attributable to modified live virus vaccine (Krakowka et al., 1982). A parallel can be drawn
between the latter observation and epidemiological observations over the last fifteen years.
In fact, before the emergence of canine parvovirus, distemper had largely disappeared from
veterinary practice, whereas since 1980, it has not been exceptional to observe distemper,
sometimes in the form of epidemics, and even in urban dog populations (Blixenkrone-
Møller et al., 1993). This can but lead us to continue promoting vaccination with the existing
vaccines, even if improvements can still be made.

4. Immunization of other species

4.1. Minks and ferrets

The vaccination of mustelids has been widely and successfully used in colonies. The
MLV "ferret avirulent" strains, strain Onderstepoort for instance, are fully effective. The
doses used represent one tenth of the dose for dogs. The routes of administration are
subcutaneous, intramuscular and aerosol-spraying routes. Concerning the latter route, the
adjustment of the dose volume is difficult and generally induces a lesser degree of immu-
nization.

4.2. Wild carnivores

It is recommended to take great care with vaccination of captive wild carnivores (Montali
et al., 1983). In principle, modified live vaccines should be avoided unless they have been
shown to be totally safe for the species involved. If not, the preparation of inactivated
vaccines should be considered. This was carried out by Appel and colleagues to save Mustela
nigripes (black footed ferret) from complete disappearance (Carpenter et al., 1976). An
adjuvanted inactivated ISCOM vaccine was successfully used in seals in 1989. Its immu-
nogenicity was demonstrated against both the PDV₁ and PDV₂ viral strains (Osterhaus et
al., 1989; Visser et al., 1992).

5. Is there a need for a "better" vaccine?

The vaccines used at present have provided an adequate solution for the immunization
of dogs against CDV over more than thirty years. If there is still scope for improving the
epidemiological situation in the canine species by enhancing preventive medicine, then the principal tools used, the vaccines, could also be improved. It has been indicated above that attenuated vaccine strains have certain deficiencies as regards heat stability and specific safety for some immunodeficient puppies and for other wild carnivores. Furthermore, safer routes of administration than injection could be used, the oral route for instance, and more practical and more effective vaccination schedules could be developed, above all for combined vaccinations. One of the most promising approaches is that offered by new technologies, using recombinant vaccines.

A variety of viruses have been used as carriers for heterologous genes inserted by recombinant DNA technology. Vaccinia virus has been most commonly used as a vector for foreign genes (Panicali and Paoletti, 1972). Studies have been undertaken in recent years to evaluate the safety and suitability of vaccinia virus as an eukaryotic expression vector in different mammalian species including dogs (Appel, 1988; Pastoret et al., 1992). Because of its safety, efficacy, and heat-stability, the vaccinia-rabies recombinant offers an excellent alternative to the attenuated strains of rabies virus currently used in the field to achieve the immunization of foxes (Kiény et al., 1984). The potency of the same recombinant (vVRG) was demonstrated in the canine species (Chappuis et al., 1994).

Experimental vaccines prepared from poxvirus recombinants (vaccinia, fowl pox or canary pox) including genes F and H of measles virus and of canine distemper virus have been tested in mice (Wild et al., 1993) but mainly in dogs. Their total safety and excellent immunogenicity were demonstrated during vaccination/challenge trials (Tartaglia et al., 1972). As an example, Table 2 shows recent results obtained in our laboratory using a CDV-Canary pox recombinant. The four vaccinated puppies received 2 injections of recombinant at a 3-week interval (10^7 PFU/dose). Challenged 6 weeks after the first injection, they were totally protected after having developed an antibody response. Out of the seven challenge control puppies, five developed distemper and three died. These results are therefore highly encouraging and support other results obtained with other similar recombinants. This new approach offers the prospect of positive developments and further improvements in the control of canine distemper.

### 6. Conclusion

I would like, as a conclusion, to quote from Max Appel (1987):

“Eradication of CDV, as has been suggested for the related measles virus in man, may be desirable but is not possible. Many species of wild carnivores are susceptible to CDV
and they represent a constant source of infection together with diseased dogs that have not been properly vaccinated."

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