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ScienceDirect
Veterinary Microbiology 128 (2008) 65–71
veterinary microbiology
www.elsevier.com/locate/vetmic

Cedivac-FMD can be used according to a marker vaccine principle

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Received 4 April 2007; received in revised form 4 October 2007; accepted 10 October 2007

Abstract

In this study, we investigated whether Cedivac-FMD, an emergency vaccine against foot-and-mouth disease (FMD), is suitable for use conjointly with a screening program intended to confirm freedom from disease in vaccinated herds based on evidence of virus replication in vaccinates. Different sets of sera were tested using the Ceditest® FMDV-NS ELISA for the detection of antibodies against non-structural proteins (NSPs) of FMD virus. During a vaccine safety study, serum samples were collected from 10 calves, 10 lambs and 10 piglets following administration of a double dose and a repeat dose of high payload trivalent Cedivac-FMD vaccine. All serum samples collected both 2 weeks following the administration of a double dose as well as those collected 2 weeks after the single dose booster (given 2 weeks after the double dose) were negative in the Ceditest® FMDV-NS ELISA. In a series of vaccine potency experiments, serum samples were collected from 70 vaccinated cattle prior to and following exposure to infectious, homologous FMD virus. When testing cattle sera collected 4 weeks after vaccination with a regular dose of monovalent >6 PD_{50} vaccines, 1 of 70 animals tested positive in the NSP antibody ELISA. After infection with FMD virus, antibodies to NSP were detected in 59 of 70 vaccinated cattle and 27 of 28 non-vaccinated control animals within 7 days. Cedivac-FMD vaccines do not induce NSP antibodies in cattle, pigs or sheep following administration of a double dose or a repeat dose. FMD-exposed animals can be detected in a vaccinated group within 7–14 days. Because Cedivac-FMD does not induce NSP antibodies, the principle of 'marker vaccine' applies.

Keywords: FMD; Marker vaccine; Emergency vaccination; Non-structural proteins

1. Introduction

In the aftermath of the 2001 FMD outbreaks, European Council directive 2003/85/EC was drafted. This directive retrospectively concludes that when control strategies were implemented in 2001, too much importance was attached to trade aspects and insufficient consideration was given to the possibility offered by the use of emergency vaccination and subsequent tests to detect infected animals in a vaccinated population. Directive 2003/85/EC makes provision for emergency vaccination and reducing

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doi:10.1016/j.vetmic.2007.10.003

significantly subsequent killing of the vaccinated animals following appropriate testing to substantiate the absence of infection. It has been well documented that exposure of susceptible animals to infectious FMD virus elicits the production of antibodies directed against structural as well as non-structural proteins (NSP). Non-structural proteins, which are coded for in the FMD virus genome, are a group of enzymes and other proteins required in the different steps of the virus replication process including the assembly of the virus capsid structure. Previous studies have identified a number of antigenic non-structural proteins of which 3ABC appears to be the most reliable marker of FMD virus replication (Mackay et al., 1998; Sørensen et al., 1998). ELISAs for the detection of antibodies against non-structural proteins will likely play an essential role in the serological survey of livestock herds in future post-outbreak situations. Commercially available ELISA kits, and particularly the Ceditest® FMDV-NS ELISA, have been shown to have a high diagnostic sensitivity and specificity (Brocchi et al., 2006). It should be obvious that the use of such an ELISA in FMD surveillance programs following vaccination is only useful if the vaccine itself does not elicit an antibody response to NSP. The down-stream processing applied in the antigen manufacturing process of Cedivac-FMD vaccines results in a concentrated, purified intermediate product. The purification steps incorporated in the downstream processing separate whole FMD virus particle from proteins that have a significantly different molecular mass. Non-structural proteins are significantly smaller than whole FMD virus particle. Vaccines manufactured using antigen purified in this manner are therefore not expected to contain the amount of NSP necessary to induce an NSP antibody response in vaccinates. The quality requirements of information presented to support this claim in an application for a marketing authorisation in the EU are stated in the Position Paper on Requirements for Vaccines Against Foot-and-Mouth Disease (EMEA/CVMP/775/02-final) which was drafted by the European Medicines Agency (EMEA) and came into effect in late 2004 (Anon., 2004). This guideline provides important information to both FMD vaccine manufacturers as well as competent authorities on the requirements that FMD vaccines should meet before a marketing authorisation can be granted in the EU. Guidance is also specifically provided on how to obtain information to support that a vaccine does not induce antibodies to NSP. This information is also important for policy makers in that it gives guidance on how to evaluate if a given vaccine might interfere with the identification of infected animals in combination with an appropriate diagnostic test in a post-outbreak surveillance program. The EMEA position paper recommends generating data using an immunisation schedule consisting of three administrations of a double dose of vaccine containing the maximum antigen payload at intervals of 2–4 weeks to at least 10 animals of one or more species. Annex XIV of Directive 2003/85/EC, however, lays down an immunisation schedule consisting of one initial and one subsequent booster vaccination. However, it is important to realise that the measure of assurance that vaccination will not interfere with the subsequent identification of infected animals is directly related to the administration regime of the vaccine in question. FMD vaccines which require multiple or frequent injections to achieve and maintain immunity are justifiably subject to stringent data requirements to support that the vaccine does not induce antibodies to NSP. Since a single dose of Cedivac-FMD vaccine confers a duration of immunity of at least 6 months (Selman et al., 2006), repeat administration is not required to achieve immunity that will last probably until well after the post-outbreak surveillance has been completed. Therefore, if no NSP antibody response has been induced following one initial and one subsequent booster vaccination, it can be assumed that future use of the vaccine in an outbreak situation would not interfere with the subsequent identification of animals exposed to wild virus.

This report investigates the assumption that Cedivac-FMD vaccine does not induce an NSP antibody response by evaluating NS-ELISA results from sera collected in safety studies involving repeat vaccination and sera collected in vaccination-challenge experiments.

2. Materials and methods

2.1. Vaccines

All vaccines administered were manufactured by Animal Sciences Group, Lelystad, The Netherlands, and contained inactivated, purified FMD virus