Preventive Veterinary Medicine 91 (2009) 73–84

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed

Review

Systematic review and meta-analyses of the effects of halofuginone against calf cryptosporidiosis

Charlotte Silverlås *, Camilla Björkman, Agneta Egenvall

Department of Clinical Sciences, Division of Ruminant Medicine and Veterinary Epidemiology, Swedish University of Agricultural Sciences, P.O. Box 7054, SE-750 07 Uppsala, Sweden

ARTICLE INFO

Article history:
Received 23 July 2008
Received in revised form 1 May 2009
Accepted 7 May 2009

Keywords:
Cryptosporidium
Diarrhoea
Prophylaxis
Therapy
Halofuginone

ABSTRACT

Halofuginone seems to reduce diarrhoea and oocyst shedding in calves with cryptosporidiosis, but provides no complete cure. To develop more precise estimates of the effects of halofuginone on calf cryptosporidosis, meta-analyses were performed, including studies on prophylactic and therapeutic treatment. Meta-analysis increases statistical power because several trials are evaluated together, increasing the effective sample size and possibility of detecting true effects. In total, 20 cohort or clinical studies (in 16 publications) investigating halofuginone treatment in calves were identified. One study was excluded because treated calves and control calves were not investigated in parallel. Four studies (three publications) were excluded because only abstracts were available. Thus, 15 studies from 12 publications, with 10–311 calves were included for data extraction. Of these, five studies from three publications could not be used for meta-analysis because they did not report the data needed.

Effects on infection prevalence, diarrhoeal prevalence and mortality were investigated. For prophylactic treatment, halofuginone had an effect on infection and diarrhoeal prevalence on study days 4 and 7, but the control group had significantly lower infection prevalence than the halofuginone treated group on study day 21. Heterogeneity was detected on study days 14 and 21 and publication bias was detected on study days 7 and 14. Mortality was not affected. For therapeutic treatment, a shortage of studies in combination with heterogeneity made interpretations uncertain, and we could not determine if halofuginone treatment benefits calves.

Contents

* Corresponding author. Tel.: +46 018 67 19 26; fax: +46 018 67 35 45.
E-mail address: charlotte.silverlas@kv.slu.se (C. Silverlås).

0167-5877/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.prevetmed.2009.05.003

1. Introduction

Cryptosporidiosis is a diarrhoeal disease of calves, caused by the protozoan parasite *Cryptosporidium parvum* (*C. parvum*). In some infected herds, disease and mortality rates are high (Cannas da Silva et al., 2000). Co-infection with other enteric pathogens are probably common in fatal cases, but mono-infection with *C. parvum* can cause death (Sanford and Josephson, 1982; Moore and Zeman, 1991).

C. parvum oocysts can survive a long time in the environment and disinfectants have little or no effect (Fayer et al., 1997). Moreover, a low infective dose (Moore et al., 2003) and high oocyst outputs during infection facilitate spread of the parasite. Any measures able to reduce infection pressure from shedding calves and from environmental contamination are therefore important.

Several substances have been tested for anti-cryptosporidial effects. Among those showing at least some effect is halofuginone, which reduces oocyst shedding, diarrhoeal prevalence and time to recovery in calves (EMEA/V/C/040, Revision 4, 2007). In vitro studies did not reach full cryptosporidicidal effect although high doses were used (McDonald et al., 1990; Castro-Hermida et al., 2004; Linder et al., 2007). Also, the therapeutic interval of halofuginone is narrow and signs of intoxication appear already at twice the recommended dose. Signs include diarrhoea, inappetence and weakness, which are also associated with cryptosporidiosis. Halofuginone lactate (Halocur®, Intervet International BV, Boxmeer, the Netherlands) is approved in Europe for use against calf cryptosporidiosis. Indications for use are: prophylactic treatment in infected herds and therapeutic treatment of acute diarrhoea in calves diagnosed with cryptosporidiosis (EMEA/V/C/040, Revision 4, 2007). Halofuginone hydrobromide (Stenorol^{NV}, Huvepharma, Sofia, Bulgaria) is used against poultry coccidiosis, and has been tested against calf cryptosporidiosis (Lallemond et al., 2006).

Studies have been conducted to test the effect of halofuginone on calf cryptosporidiosis but these usually include few study objects (here calves), for example Villacorta et al. (1991) ($n = 25$), Naciri et al. (1993) ($n = 10$), Jarvie et al. (2004) ($n = 31$), Lallemond et al. (2006) ($n = 60$). Few study objects (animals) reduces power, which increases the risk of not detecting true effects (that is false negatives). It also increases the risk of conflicting results, that is some studies find and some do not find an effect of the investigated drug. Data from studies examining the same factors can be compared statistically by meta-analysis to overcome these problems and increase the chance of detecting true effects (Egger et al., 2001; Dohoo et al., 2003a).

The aim of this study was to investigate the effects of halofuginone on infection prevalence, diarrhoeal prevalence, mean oocyst output, mortality, dehydration, inappetence and weight gain when used as prophylactic or therapeutic treatment against calf cryptosporidiosis. This was done by performing a systematic review and meta-analysis of available data.

2. Methods

2.1. Literature search

The first author (CS) searched the electronic databases PubMed, Scirus, Web of Science, Agricola, and IVIS on 15 September 2006 and again on 28 May 2007. Search terms were 'cryptosporid* AND halofuginone' for PubMed, Scirus, Web of Science and Agricola, and for IVIS, 'cryptosporidium halofuginone' was used. The library catalogue (LUKAS, http://dk-elib-srv-07.elibdrift.dk/lukas.html) of the Swedish University of Agricultural Sciences was searched using the terms 'cryptosporidios*', 'parvum' and 'halofuginone'.

Searches were not limited to parts of documents such as title or abstract. However, because Web of Science demands a definition of where to search (such as author, title) and whole documents cannot be searched, 'title' was searched in this database. The Scirus search was limited to publications concerning agricultural and biological sciences. A monthly automatic search using search terms cryptosp* AND (treat* OR inhibit* OR elimin* OR prevent*) was also undertaken through PubMed from October 2006 to October 2007. A "*" is a truncation, telling the database to search for publications containing words with this stem. No language limits were used in any of the searches.

Although Scirus, Web of Science and IVIS can identify studies that have not been published in peer reviewed journals (for example conference abstracts or patents), some documents might still not be identified by the search criteria. Thus, CS conducted a further search as follows. The European Medicines Agency web site (http://www.emea.europa.eu/) was visited, since this is the agency that approves drugs for market use in Europe. Documents concerning the approval of Halocur® were read in search for references to trials done prior to approval (EMEA/V/C/040, Revision 4, 2007). A brochure about Halocur®, collected at an Intervet stand during the Cattle Consultancy Days in Denmark, August 2006, was explored for references. The XXIV World Buiatrics