Topical Flunixin Meglumine Effects on Pain Associated Biomarkers after Dehorning

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Summary and Implications

Twenty-four calves were dehorned and treated with either topical flunixin meglumine formulated for systemic absorption or a placebo. Biomarkers associated with pain were evaluated for up to 72 hour after the dehorning procedure. Plasma cortisol concentrations, 90 minutes post-dehorning, and mechanical nociception threshold at the control site were the only tested biomarkers where a significant difference was demonstrated. No other differences of biomarkers between the two dehorned groups were observed for any time points. Although this product is easy to dose and dispense, its effects on pain biomarkers appears to be negligible.

Introduction

Dehorning is a common procedure performed on over 90% of dairy farms. The increasing awareness of animal welfare and pain mitigation have made the use of nonsteroidal anti-inflammatory drugs (NSAIDs) common and desirable at the time of dehorning.

Recently a novel formulation of flunixin meglumine has been developed and approved in the European Union. This novel formulation is designed for topical application and transdermal absorption of the active ingredient. Currently, flunixin meglumine is the only NSAID approved for use in bovine in the United States. However, it is only labeled for intravenous administration for pyrexia associated with bovine respiratory disease and endotoxic mastitis as well as the control of inflammation in endotoxemia. The objective of this research experiment was to determine the analgesic effects of a novel European formulation of flunixin meglumine intended for systemic absorption after topical application.

Materials and Methods

Twenty four weaned male Holstein calves, ages 6 to 8 weeks of age were enrolled into the study. The calves were randomly assigned to one of three treatment groups of: 1) topical flunixin and dehorn (DH-FLU); 2) topical flunixin and sham dehorn (SHAM-FLU); and 3) placebo and dehorn (DH-PLBO). Treated calves had tropical flunixin meglumine applied at the label dose of 3.33 mg/kg concurrently with dehorning. The dehorning procedure consisted of applying an electrocautery dehorner to the horn tissue for 10 seconds. Calves in the sham dehorn group had a cold dehorned applied to the horn tissue for 10 seconds. Biomarker parameters collected and analyzed included: infrared thermography (IRT), mechanical nociception threshold (MNT), plasma cortisol, and Substance P.

Infrared thermography images for maximum temperature were analyzed using commercially available research software (FLIR ExaminIR, Inc., North Billerica, MA). Plasma cortisol and Substance P concentrations were determined by radioimmunoassay in the Pharmacology Analytical Support Team (PhAST) lab.

Results and Discussion

There were no differences in the maximum temperatures (°C) detected for the IRT measurements of the medial canthus of the eye, dehorning site and adjacent skin for the DH groups. Mean control point MNT measurements at 49 hours were 3.14 kgF, 3.46 kgF and 1.43 kgF for the DH-FLU, Sham-FLU and DH-PLBO groups respectively ($P = 0.0001$). No other differences of MNT were detected between groups for the other test sites and time points.

Peak plasma cortisol concentrations were reached at 20 minutes post dehorning for the DH-FLU and DH-PLBO groups and 10 minutes for SHAM-FLU group. Peak plasma cortisol concentrations were 32.0 ng/ml, 12.7 ng/ml, and 28.8 ng/ml for the DH-FLU, SHAM-FLU and DH-PLBO groups respectively. Cortisol concentrations were statistically lower for the DH-FLU group at 90 minutes post dehorning compared to the SHAM-FLU and DH-FLU group ($P = 0.04$). Plasma cortisol concentrations were 6.12 ng/ml, 7.66 ng/ml, and 9.68 ng/ml ($P = 0.4066$) at 2 hours post dehorning for the DH-FLU, SHAM-FLU, and DH-PLBO groups respectively. At 4 hours post dehorning, the concentrations were 6.36 ng/ml, 11.91 ng/ml, and 8.94 ng/ml ($P = 0.1142$) for the DH-FLU, SHAM-FLU, and DH-PLBO groups.

Substance P concentrations at 2 hours post dehorning were 27.16 pg/ml, 26.04 pg/ml, and 33.09 pg/ml for the DH-FLU, SHAM-FLU, and DH-PLBO groups respectively ($P = 0.4577$). Substance P concentrations were 27.81 pg/ml, 27.08 pg/ml, and 30.36 pg/ml for the DH-FLU, SHAM-FLU, and DH-PLBO groups respectively ($P = 0.8496$) at 4 hours post dehorning. No differences in Substance P concentrations between groups were detected for all time points.

The published time to maximum drug concentration (Cmax) is between 2 to 4 hours post application according to published reports and provided drug literature. At the time of Cmax, there are no differences between the groups for both plasma cortisol and substance P. Based on the findings presented here flunixin meglumine, when given as

a topical solution, does not have significant effects on biomarkers associated with pain. Other NSAIDs, like meloxicam, have been tested to be efficacious in this application and may be more appropriate for use.

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