RESEARCH ABSTRACT

ANIMAL WELFARE

Title: The Plasma And Tissue Pharmacokinetics And Pharmacodynamics Of Nonsteroidal Anti-Inflammatory Drugs In Neonatal Piglets – NPB #16-091

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SCIENTIFIC ABSTRACT

Pain medications, predominately nonsteroidal anti-inflammatory drugs (NSAIDs), are used in the EU and Canada to decrease pain associated with castration and tail docking and to improve piglet welfare. However, in piglets, the efficacy and required dose of these NSAIDs is unknown.

Forty 4-day old male Yorkshire x Landrace piglets were removed from the sow and IV catheters, interstitial probes and activity monitors were placed. At 6 days-of-age the piglets were randomly assigned to one of five treatment groups (saline sham [SAL SHAM], 0.1 mL saline and no processing; saline castration [SAL CAST], 0.1 mL saline and processed; Meloxicam treatment [MLX], 0.4 mg/kg meloxicam and processed; Flunixin treatment [FLU], 2.2 mg/kg flunixin meglumine and processed; or Ketoprofen treatment [KETO], 3 mg/kg ketoprofen and processed. Two hours post-dose, all all piglets underwent routine castration and tail docking (with the exception of the SAL SHAM piglets, which were not castrated or tail docked, but handled for a similar length of time and in a similar manner).

Behavior (pain) scores, grimace scores, and activity counts were obtained at multiple time points before, and after processing. Blood samples and interstitial fluid samples were obtained at similar time points as the pain data. Plasma concentrations of meloxicam and ketoprofen were obtained by HPLC with fluorescence (KETO) or UV detection (MLX); plasma and interstitial fluid flunixin concentrations, and interstitial fluid meloxicam and ketoprofen were obtained with UPLC-MS/MS detection. Prostaglandin E2 concentrations in interstitial fluid were obtained with ELISA. Plasma cortisol concentrations were determined via RIA. All data was analyzed using ANOVA.

The time to maximum concentrations (Tmax) of meloxicam, flunixin and (S-)-ketoprofen in plasma were 1.21, 0.85 and 0.59 h, respectively. Plasma half lives ($T_{1/2}$) were 4.39, 7.69 and 3.50 h, respectively. The Tmax in ISF were 2.81 and 3.64 h for meloxicam and flunixin, and tissue half lives were 11.3 and 16.3 hours, respectively.

SAL CAST cortisol levels were significantly ($p=0.0031$) higher than that of SAL SHAM at the time of processing (2 h post-dose). This suggests that it is the procedure, rather than the handling of the animals that greatly increases cortisol and is indicative of stress. Cortisol concentrations were also significantly ($p=0.0488$) lower in the FLU group compared to the SAL CAST group at the time of processing.

All the NSAIDs decreased prostaglandin E2 levels in interstitial fluid when compared to the SAL CAST group, however only flunixin was able to maintain that inhibition beyond 24 h post-dose.

Overall, meloxicam was the least effective NSAID when examining the behavior and grimace scores beyond 6 h post-dose. At the time of processing, all the NSAID treated groups had increased pain behaviors and increased pain scores. This may have been noted because the piglets were more active, making the active pain-related behaviors more obvious to the observers (e.g. scratching at castration site), compared to the SAL CAST group which showed more inactive behaviors (e.g. laying still and protecting the castrated site). Activity levels, obtained via Actical® monitoring, were also decreased in the SAL CAST and MLX piglets following processing. This was likely related to the reduced number of active pain-related behaviors.

In conclusion, this study found that the administration of NSAIDs 2 hours prior to castration and tail docking had a positive impact on pain alleviation in piglets, with flunixin demonstrating superiority compared with ketoprofen and meloxicam, and meloxicam being the least efficacious at the doses and routes used. Management strategies that include the administration of flunixin to reduce pain associated with processing will improve piglet health and welfare in the United States.