Journal of Equine Veterinary Science 35 (2015) 475–480

Contents lists available at ScienceDirect

Journal of Equine Veterinary Science

journal homepage: www.j-evs.com

Review Article

Anti-inflammatory Drugs in Equine Neonatal Medicine. Part I: Nonsteroidal Anti-inflammatory Drugs

Carolina Castagnetti, Jole Mariella*

Department of Veterinary Medical Sciences, University of Bologna, Ozzano dell'Emilia, Bologna, Italy

ARTICLE INFO

Article history:
Received 18 November 2014
Received in revised form 6 February 2015
Accepted 20 February 2015
Available online 25 February 2015

Keywords:
Foal
NSAID
Side effect
Dosage

ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the class of drugs most commonly used in equine medicine. This article reviews the literature on the different NSAIDs used in equine neonatology: flunixin meglumine, phenylbutazone, ibuprofen, ketoprofen, meloxicam, and firocoxib. These drugs are routinely used in equine adults, but in neonatal foals, the risk of side effects should be carefully evaluated. Many of the studies on NSAID pharmacokinetics in neonatal foals have been performed on healthy animals, and more information is needed to determine the appropriate dosage in the compromised equine neonate. The review highlights the lack of specific NSAID dosages for compromised foals and emphasizes the risk of side effects in the neonate.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically heterogeneous group of compounds able to inhibit the cyclooxygenases (COX), enzymes occurring in two isoenzymatic forms (COX-1 and COX-2), and consequently the conversion of arachidonic acid into prostaglandins, thromboxane, and prostacyclin [1]. Blocking the production of prostaglandins has anti-inflammatory, analgesic, antipyretic, antiendotoxic, and antithrombotic effects. The anti-inflammatory effect of NSAIDs is usually the result of COX-2 inhibition, whereas the unwanted effects of these drugs are primarily due to COX-1 inhibition. Meloxicam and the newest NSAIDs (coxibs) exhibit selectivity for COX-2 and have fewer adverse effects than the other molecules [2]. Irrespective of prostaglandin synthesis, NSAIDs have additional mechanisms of actions such as decreasing oxidants [3,4], scavenging oxygen-derived free radicals [5], and chelating iron [4,6]. Common NSAID characteristics are rapid gastrointestinal absorption because food does not change their bioavailability, high protein binding, usually with albumin, and renal excretion, although some NSAIDs and their metabolites undergo enterohepatic circulation [2]. The side effects associated with the use of NSAIDs are related to COX-1 inhibition, the most common being gastric ulcers and renal failure. Gastric ulceration is related to depressed mucosal production of PGE_2, the prostaglandin responsible for inhibiting acid secretion, enhancing mucosal blood flow, and promoting the secretion of gastric mucus. In 1996, Appleyard et al [7] found tumor necrosis factor α (TNF-α) was released into plasma within 30 minutes of NSAID administration in rats and implicated TNF-α in the pathogenesis of NSAID-induced gastric injury. Previous studies had revealed a direct adverse effect of TNF-α on the gastrointestinal mucosa, whereas TNF-α infusion in rats caused significant gastric and small intestinal mucosal injury at necropsy [8,9]. A study on the mucosal messenger RNA cytokine profile of the gastric wall in neonatal foals found that foals with evidence of gastritis or gastric ulceration were more likely to express TNF-α and that TNF-α was not expressed in foals without evidence of gastritis or gastric ulceration [10].

* Corresponding author at: Jole Mariella, Department of Veterinary Medical Sciences, University of Bologna, Via Tolara di Sopra 50, 40064 Ozzano dell'Emilia, Bologna, Italy.
E-mail address: jole.mariella2@unibo.it (J. Mariella).

0737-0806/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jevs.2015.02.008

Acute renal failure during NSAID therapy develops after inhibition of renal PGE_2 biosynthesis, resulting in renal vasoconstriction and increased water reabsorption [2]. In the kidney, COX-1 functions mainly in the control of renal hemodynamics and the glomerular filtration rate (GFR), whereas COX-2 primarily affects salt and water excretion [11]. Blockade of either or both of these enzymes will therefore have different effects on renal function such as an increase in serum creatinine, hyperkalemia, interstitial nephritis, proteinuria, and acute renal dysfunction. Nonsteroidal anti-inflammatory drugs reduce the production of PGE_2 and PGI_2, involved in renal blood circulation, thereby decreasing the GFR. This is particularly detrimental in patients with impaired renal function, which results in water retention [12].

Based on structure, NSAIDs can be divided into two different classes: carboxylic acid and enolic acid derivatives. The main subgroups of enolic acids are the pyrazolones (phenylbutazone [PBZ]) and the oxicams (meloxicam and piroxicam). The carboxylic acid subgroup includes salicylates (aspirin), propionic acids (ibuprofen, naproxen, carprofen, ketoprofen, and vedaprofen), anthranilic acids (tolfenamic and meclofenamic acids), phenylacetic acids (acetaminophen), and aminonicotinic acids (flunixin). The newest coxib class of selective COX-2 inhibitors studied in adult horses includes deracoxib [13], celecoxib [14], etoricoxib [15], firocoxib [16,17], and robenacoxib [18]. To date, only six NSAIDs have been specifically evaluated in neonate and older foals: flunixin meglumine (FXM) [19–22], PBZ [23,24], ketoprofen [25], ibuprofen [26], meloxicam [27], and firocoxib [28].

The aim of this review was to highlight the lack of specific NSAID dosages for compromised foals and to emphasize the risk of side effects in the neonate. For every drug, studies performed on adult horses or on older foals will be presented first, focusing on the few studies performed on neonatal foals at the end of each section.

2. Flunixin Meglumine

Flunixin meglumine is widely used as an analgesic, antipyretic, anti-inflammatory, and antiendotoxic agent [29,30]. Few studies have addressed the side effects of FXM in older foals. In 1988, Traub-Dargatz et al [19] studied the effects on gastric mucosa of a therapeutic dose of FXM (1.1 mg/kg) administered for 30 days to thirteen 4- to 6-month-old foals. PO administration resulted in oral and gastric ulceration and erosions of the glandular stomach mucosa, whereas intramuscular administration resulted in erosions of the glandular stomach mucosa. No renal lesions were observed.

In neonatal foals, Carrick et al [20] reported the effects of daily IV administration of FXM at dosages of 0.55, 1.1, 2.2, and 6.6 mg/kg for 5 days. The major clinical abnormality was diarrhea, but the incidence was not dose related. All foals were euthanized after 6 days, necropsied, and examined for lesions. The primary gross pathologic lesions consisted of ulceration of the glandular stomach, petechiation or congestion of the cecum, and petechiation, congestion, or edema of the colon. The most common site of cecal petechiation was the cecocolic junction. The foals in the saline-treated control group of this study had the same lesions. The authors concluded that the treatment of healthy neonatal foals with the recommended dosage of FXM caused no clinical, clinicopathologic, or pathologic differences compared with treatment with physiological saline, but treatment with 6.6 mg/kg/d increased total gastrointestinal ulceration, gastric ulceration, and cecal petechiation.

In 1993, Semrad et al [21] studied FXM pharmacokinetics in foals during the first month of life, finding that drug disposition was longer and its clearance was lower at 24–28 hours of life than at 10–11 days or 27–28 days. Crisman et al studied FXM pharmacokinetics in foals less than 24 hours old, reporting that clearance was lower than that determined for older foals and adult horses and volume of distribution was larger than in adults. Mean plasma half-life was 8.5 hours [22]. On the basis of these studies [21,22], FXM should be administered differently to foals $<$24 hours old compared with adults. Doses in foals should be increased by as much as 1.5 times to induce comparable therapeutic concentrations, but longer dose intervals would be necessary to avoid drug toxicity. The PO route of administration studied in adults [31] has not been evaluated in foals, but if ascertained by new studies, this route could be a good option, particularly when the treatment has to be administered by the owners.

3. Phenylbutazone

In 1982, Traub et al [23] studied the effects of a clinical therapeutic dosage of PBZ (10 mg/kg daily) on the gastric mucosa of 15 foals between 3 and 10 months of age for 12–42 days. The dose was divided into two treatments per day and was administered PO. Phenylbutazone treatment resulted in oral and gastric ulceration, decreased total protein, increase in blood urea nitrogen, inappetence, weight loss, and diarrhea. Some of these toxic effects, oral ulceration and diarrhea, occurred as early as treatment days 3–6. Geor et al [32] reported that ranitidine and sucralfate provided partial protection against the clinicopathologic manifestations of PBZ toxicity in neonatal foals and that sucralfate appeared superior to ranitidine. The foals receiving sucralfate did not develop diarrhea, and their gastric ulcers appeared less active with normal mucus [32].

In 1993, the study by Wilcke et al [24] suggested that there was a larger volume distribution, a longer serum half-life, and a lower total clearance of PBZ in 5- to 17-hour-old foals than in adult horses. Léveillé et al [33] reported that PBZ administration at a dosage of 5 mg/kg body weight, PO, every l2 hours for 7 days caused morphologic renal changes in two of the three 7- to 10-day-old foals included. Ultrasound evaluation showed a diffuse hyperechoic zone within the medulla near the corticomedullary junction. At necropsy, the kidney appeared grossly normal, but histologically, there were multiple foci of mineralization in the collecting tubules of the medullary region, corresponding to the hyperechoic zones.

Phenylbutazone plasma concentration was also studied in neonate foals suckling mares receiving 4.4 mg/kg every 12 hours for 7 days after parturition. Neither PBZ nor its active metabolite, oxyphenbutazone (OPBZ), was found in