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Association Between Nonsteroidal Anti-Inflammatory Drugs and Gastric Ulceration in Horses and Ponies

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely employed in equine medicine to treat acute and chronic inflammation in tendon, ligament and musculoskeletal injuries, as well as after surgery (Cunningham & Lees, 1994; Lees et al., 2004; Dirikolu et al., 2008). These drugs are used because of their analgesic, anti-inflammatory, and anti-pyretic properties; they are also used as adjuvant therapy in the treatment of endotoxemia and to suppress platelet aggregation (Johnstone, 1983; MacAllister, 1994; MacAllister & Taylor-MacAllister, 1994; Mathews, 2002).

An ideal anti-inflammatory drug is potent and has few adverse effects. In fact, several of the commonly used NSAIDs have a narrow safety margin. It is imperative, therefore, to administer a correct dose at adequate intervals. Thus, use of these drugs for controlling pain in equine is recommended for well-hydrated animals aged over six weeks with normal oncotic pressure. Kidney and liver function should be normal, there should be no signs of gastric ulcers, and the animals should not be taking corticosteroids. Furthermore, two or more NSAIDs should not be given at the same time (Mathews, 2002).

It is essential to study in depth the adverse effects, the pharmacokinetics and pharmacodynamics of NSAIDs because of their side effects. The half-life of substances differs among species as a function of biotransformation pathways, drug metabolization time, associated disease (especially renal and hepatic conditions), age (younger animals have immature hepatic enzyme systems, whereas older animals have less efficient kidneys and livers), binding of NSAIDs to food components in the gastrointestinal tract, and association of NSAIDs with other drugs.

Studies on the relation between NSAIDs and gastric ulcers in equid species are complex because several factors may cause gastric injury: the physiological status of the stomach; a pH often below 2 (Murray, 1997, 1999); prolonged fasting (where the pH may be as low as 1.55) (Murray & Schusser, 1993); intense exercising in sports animals [which increases abdominal pressure, decreases stomach volume, and results in reflux of small intestine acids into the nonglandular mucosa (squamous mucosa) of the stomach] (Vatistas et al., 1999a; Lorenzo-Figueira & Merritt, 2002; McClure et al., 2005); diseases that cause loss of appetite

or anorexia (Murray, 1999), and stress (confinement, administration of drugs, different environments, weaning), which may increase the level of circulating corticosteroids, in turn inhibiting the synthesis of prostaglandins and other chemical mediators, thereby generating favorable conditions for ulcers (MacKay et al., 1983; MacAllister et al., 1992; Andrews & Nadeau, 1999; Murray, 1999; Andrews et al., 2005; McClure et al., 2005; Pinto et al., 2009).

2. Types and mechanism of action of NSAIDs

There are several classifications of NSAIDs. These fall into five major chemical groups: carboxylic acid derivatives, enolic acid derivatives, specific cyclooxygenase 2 (COX-2) inhibitors, inhibitors of COX-2 with weak anti-inflammatory effect, and other nonsteroidal anti-inflammatory drugs. Carboxylic acid derivatives may be further subdivided into salicylic acids (e.g., aspirin and diflunisal), acetic acids (e.g., indomethacin, diclofenac, sulindac and eltenac), propionic acids (e.g., naproxen, ibuprofen, fenoprofen, flurbiprofen, ketoprofen and carprofen), aminonicotinic acids (e.g., flunixin meglumine), and fenamic acids (e.g., meclofenamic acid, sodium meclofenamate and mefenamic acid). Enolic acids may be subdivided into pyrazolones (e.g., phenylbutazone, monophenylbutazone, oxyphenbutazone, isopirin and apazone), and oxicam derivatives (e.g., piroxicam, droxicam, tenoxicam, and meloxicam). Selective COX-2 inhibitors are: celecoxib, etoricoxib, lumiracoxib, valdecoxib, parecoxib, firocoxib and nimesulide. Meloxicam and eltenac may be considered selective COX-2 inhibitors because of increased hepatic, renal and gastric tolerance in horses. Cyclooxygenase inhibitors with a weak anti-inflammatory effect include paracetamol and dipyrone. Other anti-inflammatory drugs not included in the above mentioned groups are dimethyl sulfoxide and glicosaminoglicans (Kore, 1990; Tasaka, 2006; Doucet et al., 2008; Burke et al., 2010).

After absorbing over 90% of NSAIDs bind to plasmatic proteins; the unbound fraction is biologically active (Tobin et al., 1986; Kore, 1990; Vicente, 2004). Most of these substances bind to albumin until saturation, at which point the concentration of the unbound fraction increases rapidly, which explains the relatively rapid onset of action of NSAIDs (Kore, 1990). According to Gerring et al. (1981), at least 98% of phenylbutazone is bound to plasma protein following administration at therapeutic doses.

Although NSAIDs are administered by several routes, they are generally metabolized by mixed function oxydase enzymes in the liver. A number of conjugated reactions are involved in eliminating these drugs. Excretion is primarily renal – glomerular filtration and tubular secretion – although some conjugates may be eliminated by the biliary tract. The excretion rate is often related with the pH; other weak acids may competitively inhibit secretory paths (Tobin et al., 1986; Kore, 1990; Vicente, 2004).

Effective plasmatic levels of NSAIDs administered orally are reached within an hour (Mathews, 2002). Several factors, however, may affect the absorption rate, such as the gastric pH, the presence of food, gastrointestinal motility, drug concentration, and the animal species (Kore, 1990; Mathews, 2002).

Phenylbutazone, an enolic acid pyrazolone derivative, is one of the most commonly used NSAIDs in equine medicine (Snow et al., 1979; Tobin et al., 1986; MacAllister et al., 1993; Kawcak, 2001; Dirikolu et al., 2008; Sabaté et al., 2009). This drug was synthesized by Stenzl in 1946 (Tasaka, 2006) and introduced into human medicine in 1949 for the treatment of

rheumatoid arthritis, ankylosing spondylitis, and several other musculoskeletal conditions (Shearn, 1984). Because of its efficacy and low cost, it has been used mainly in horses since the 1950s (more specifically in 1952) for treating lameness caused by articular conditions, soft tissue diseases, and gastrointestinal colic (MacAllister et al., 1993; MacAllister, 1994; Vicente, 2004; Erkert et al., 2005; Tasaka, 2006). It is excreted unmetabolized in urine and as a metabolite of glucuronic acid oxidation and conjugation; the most relevant metabolites are oxyphenbutazone (active metabolite), γ-hydroxyphenylbutazone and γ-hydroxy-oxy-phenylbutazone (inactive metabolites) (MacAllister, 1994; Vicente, 2004; Igualada & Moragues, 2005).

Bioavailability studies have shown that the plasmatic kinetics of phenylbutazone is dose-dependent (Tobin et al., 1986). Sullivan & Snow (1982) compared in horses and ponies the intramuscular (2.5 mg/kg bwt) and enteral (5 mg/kg btw) routes for administering phenylbutazone and found that the absorption rate and bioavailability were slowed with intramuscular injections. These authors suggested that the drug precipitated in the neutral muscle pH. This property precludes intramuscular use because of binding to muscle proteins, which delays absorption and causes pain (Tasaka, 2006).

The plasmatic half-life of intravenously administered phenylbutazone in horses may range from 3.5 to 7.0 hours (Tobin et al., 1986; Lees et al., 1987; Vicente, 2004); it is about six hours in ponies (Snow et al., 1981). When administered orally, the phenylbutazone presents a variable, but longer half-life (3 to 10 h) (Tobin et al., 1986).

Regarding the mechanism of action of NSAIDs, it is known that following tissue damage (by trauma, hypoxia, toxins, endotoxins, etc.) short-chain fatty acids (such as arachidonic acid) are released from the cell membrane by phospholipase A_2 (Cunningham & Less, 1994; MacAllister, 1994; Lees et al., 2004, Tasaka, 2006). This enzyme works on cell membrane phospholipids to make arachidonic acid available for the enzymatic cascade involving cyclooxygenase or lipoxygenase in the cytoplasm (MacAllister, 1994; Tasaka, 2006). Cyclooxygenase 1 (COX-1) and COX-2 are the two cyclooxygenase isoforms that have been investigated in greater depth; there is an enzymatically active variant of the COX-1 gene named COX-3 (Smyth et al., 2010).

The COX-1 catalyzes the conversion of arachidonic acid into prostaglandins, which are involved in gastrointestinal, renal, and vascular physiological processes. COX-2 isoform produces an inflammatory response based on cytokines and inflammation mediators; the lipoxygenase cascade reaction yields primarily leukotrienes (Cunningham & Less, 1994; MacAllister, 1994; Jones & Blikslager, 2001; Lees et al., 2004; Tasaka, 2006; Smyth et al., 2010). COX-1 isoform is present in most tissues, and COX-2 is upregulated in monocytes, fibroblasts, synoviocytes, as well as chondrocytes in response to inflammatory stimuli (Johnston & Fox, 1997).

The majority of anti-inflammatory drugs block COX-1 and COX-2 to a greater or lesser extent (Tasaka, 2006; Burke et al., 2010). Studies have underlined the difficulty in separating the roles of COX-1 and COX-2 (Jones & Blikslager, 2001; Fitzpatrick et al., 2004); thus, the selectivity of these compounds is still controversial. Furthermore, some drugs may appear selective for an enzyme relative to another, but not potent. In fact truly selective or specific COX-2 inhibitors licensed for veterinary use are rare. Evidence suggests that phenylbutazone, flunixin meglumine and ketoprofen are not selective (Fitzpatrick et al., 2004; Burke et al., 2010; Pozzobon, 2010). Vicente (2004) has argued that phenylbutazone

inhibit the COX-1 isoenzyme more than COX-2, where the inhibitory power of prostaglandin endoperoxide H synthase-1 (PGHS-1) is one to five times that of PGHS-2, resulting in adverse effects such as erosion or ulcers of the mucosa in the mouth and gastrointestinal tract, diffuse gastritis, hemorrhagic gastroenteritis, venous thrombosis, nephritis, and chronic renal injury, which have been widely discussed in the literature (Snow et al., 1981; MacAllister, 1983; Mathews, 2002; Fitzpatrick et al., 2004).

Price et al. (2002) argue that veterinarians working with small animals may be more concerned about the adverse effects of NSAIDs than those working with horses. The former prefer using carprofen and meloxicam, which appear to cause fewer side effects. These authors applied a questionnaire to 400 veterinary practitioners in the UK about pain management in horses. Of these 93 were used for data analysis; the data indicated that the four most frequently used analgesics in order of preference were: phenylbutazone (92%), flunixin meglumine (90%), butorphanol (89%), and dipyrone (75%). Phenylbutazone was preferred because of lower cost compared to other licensed NSAIDs. The analgesic potential was the most important criterion when choosing between NSAIDs or opioids.

Considering the analgesic potential of NSAIDs, the intravenous administration of single doses of phenylbutazone (4 mg/kg bwt), flunixin (1 mg/kg bwt) or carprofen (0.7 mg/kg bwt) to 63 horses for post-surgical pain was effective, but the mean required times for further analgesia were 8.4 h (phenylbutazone), 11.7 h (carprofen), and 12.8 h (flunixin) (Johnson et al., 1993). Erkert et al. (2005) compared the analgesic effect of phenylbutazone (4.4 mg/kg bwt at 24 h intervals) and flunixin meglumine (1.1 mg/kg bwt at 24 h intervals) in horses with the navicular syndrome and found similar responses among these drugs.

Sabaté et al. (2009) assessed the analgesic efficacy of suxibuzone and phenylbutazone for the treatment of pain caused by lameness in 155 horses aged from 2 to 25 years and body weight from 350 to 540 kg. All animals had acute or chronic nonspecific single limb lameness. The drugs were administered orally as follows: phenylbutazone (4.4 mg/kg bwt every 12 h) for 2 days, followed by phenylbutazone (2.2 mg/kg bwt every 12 h) for 6 days (n=79), and suxibuzone (6.6 mg/kg bwt every 12 h) for 2 days, followed by suxibuzone (3.3 mg/kg bwt every 12 h) for 6 days (n=76). The authors found no difference (P=0.113) between these treatments for pain relief in horses.

3. Gastric ulcers

Equine gastric ulceration is a highly prevalent multifactorial disease with vague and non-specific clinical signs. Abdominal pain, weight loss, and loss of performance may be seen. On the other hand, asymptomatic cases (Murray et al., 1987, MacAllister et al, 1992; MacAllister & Sangiab, 1993; Andrews & Nadeau, 1999; Murray et al., 2001; Murray & Pipers, 2001; Murray, 2002) diagnosed by gastroscopy have been described. Reports have shown a poor correlation between ulcer severity and clinical signs (Murray et al., 1987; MacAllister & Sangiab, 1993; Murray, 2002; Marqués, 2007; le Jeune et al., 2009); thus, animals with deeper lesions may have relatively mild signs, while others presenting with more significant abdominal discomfort may have only superficial erosions (Murray, 2002).

Murray et al. (2001) found asymptomatic gastric ulcers in 18 horses out of 209 animals that underwent gastroscopy. The practical experience of the authors of this chapter supports the above mentioned informations about clinical signs; monitoring ten ponies with untreated

gastric ulcers (diffuse or localized hemorrhagic lesions), kept in free paddocks for eight months, revealed that 90% had no signs of bruxism, sialorrhea, decrease in appetite, rough hair-coat, diarrhea, abdominal discomfort, colic or any other sign of gastrointestinal tract involvement.

Studies have shown that foals may also develop gastric ulcers without apparent clinical manifestation (Murray et al., 1987; Marqués, 2007); thus, silent gastric ulceration is a common condition in these animals (Andrews & Nadeau, 1999). Léveillé et al. (1996) also reported a lack of clinical signs in three foals aged from 7 to 10 days that were given phenylbutazone 5 mg/kg bwt orally every 12 h during 7 days. On the other hand, necropsy revealed multifocal gastric ulcers.

Sports horses, such as performance and racehorses, have a high prevalence and severity of gastric ulcers (Hammond et al. 1986; Murray et al. 1989, 1996; Vatistas et al. 1999b; Pellegrini, 2005; Jonsson & Egenvall 2006; Orsini et al., 2009). A study conducted by Pellegrini (2005) showed that almost all performance horses have some kind of ulcer and that at least 60% of them have colonic ulcers. On the other hand, le Jeune et al. (2009) described the gastric ulceration syndrome in pregnant females (66.6%) and non-pregnant females (75.8%) kept free in irrigated pastures with alfalfa and grain supplements, but with no controlled physical activity. Luthersson et al. (2009) also reported this condition in nonracehorses.

Gastric ulcers may be found throughout the stomach of horses; the most commonly affected area is nonglandular mucosa – lined by stratified squamous epithelium – along the *margo plicatus* (Hammond et al., 1986; Murray et al., 1989, 1996; Andrews & Nadeau, 1999; Sandin et al., 2000; Ferrucci et al., 2003; Bruijn et al., 2009; le Jeune et al., 2009). The pathophysiology of ulcers consists of loss of equilibrium between aggressive factors (hydrochloric acid with or without synergistic action from volatile fatty acids, lactic acid, bile acids, and pepsin), and protective factors (mucus/bicarbonate barrier; prostaglandin $E_{2;}$ adequate mucosal blood flow; cellullar restitution, and the epidermal growth factor) (Murray, 1992; Jeffrey et al., 2001; Andrews et al., 2005; Morrissey et al., 2008; Nadeau & Andrews, 2009).

Parietal cells produce a 10^6-times higher hydrogen ion concentration in gastric juices compared to plasma, a process that requires carbonic anhydrase, which catalyzes the reaction between water and carbon dioxide. Sodium bicarbonate – resulting from dissociated carbonic acid (H_2CO_3) – is transferred into the plasma from parietal cells; this process involves its exchange for chloride ions (Cl^-) by means of an HCO_3^-/Cl^- carrier protein in the basolateral membrane. The absorbed Cl^- moves to the apical membrane, exits through canaliculi, and enters the intestinal glands. Carbonic anhydrase-generated hydrogen ions are actively secreted by the membrane in apical cells into the lumen of the gland. This ion exchange process makes it possible for parietal cells to maintain a constant pH and at the same time a highly acid solution in the gastric lumen (Randall et al., 2000).

Gastrin, histamine (H_2 receptors), and acethycholine (vagus nerve) stimulate the H^+,K^+-ATPase enzyme, which in turn causes parietal cells in gastric glands to secrete chloridric acid (Andrews et al., 2005; Videla & Andrews, 2009). The stomach of adult horse secretes about 1.5 l/h of gastric juices, which contains 4–60 mMol of hydrochloric acid. The feeding regimen and the region of the stomach that is measured alter the pH of the gastric content (Luthersson et al., 2009). Andrews & Nadeau (1999) found that the pH was stratified, being neutral in the dorsal portion of the esophageal region, more acid (from 3 to 6) close to the *margo plicatus*, and even lower (from 1.5 to 4.0) close to the pylorus. The pH of the gastric

content in continuously fed equines may remain around 3.1; in fasting animals, the pH may reach 1.6 (Murray & Schusser, 1993).

Studies have shown that freely grazing horses continuously produce large amounts of bicarbonate-rich saliva as a response to chewing, which has an important gastric acid buffering effect (Murray et al., 1996; Andrews & Nadeau, 1999; Andrews et al., 2005; le Jeune et al., 2009; Martineau et al., 2009; Videla & Andrews, 2009). On the other hand, the prevalence of ulcers did not differ significantly in full-time stabled horses, part-time stabled horses, or animals kept full-time on pastures (Bell et al., 2007).

Several ulcer-classifying systems based on the number and severity of lesions have been developed (Hammond et al., 1986; Murray et al., 1987; Johnson et al., 1994; Vatistas et al., 1994; Murray & Eichorn, 1996; MacAllister et al., 1997; Anon, 1999). Murray et al. (1987) characterized ulcers by location (nonglandular surface, *margo plicatus*, glandular surface) and severity. Lesions were graded from 0 to 4 (0=normal, 1=1-2 localized lesions, 2=3-5 localized ulcers or 1 diffuse lesion, 3=1-5 localized lesions with visible hemorrhage or multiple diffuse lesions with apparent mild to moderate loss of surface epithelium, and 4=greater than 5 localized ulcers or multiple diffuse lesions with apparent extensive loss of surface epithelium and/or hemorrhage).

Risk factors associated with this disease include diet, stress (moving horses from pasture to stall confinement, hospitalization, intense exercise, feed and water deprivation, among others), and administering NSAIDs (le Jeune et al., 2009, Luthersson et al., 2009; Nadeau & Andrews, 2009; Videla & Andrews, 2009) (the topic of this chapter). Reported factors related with disease prevalence in racehorses include a high-concentrate diet, low intake of hay, meal feeding, prolonged fasting, the type and intensity of training, as well as the use of NSAIDs (Vatistas et al., 1999a; Merritt, 2003; Roy et al., 2005; Jonsson & Egenvall, 2006). Studies on the relationship between NSAIDs and equine gastric ulcer are complex because of these many factors. Use of these drugs in human patients increases 3- and 5-fold the risk of peptic ulcers respectively in *H. pylori*-positive and *H. pylori*-negative patients (Voutilainen et al., 2001).

NSAID-induced gastric ulceration in horses was described in the late 1970s; phenylbutazone has been studied in greatest detail (Snow et al., 1979, Snow et al., 1981; MacAllister, 1983; Collins & Tyler, 1984; Tobin et al., 1986; Vicente, 2004). Studies describing the side effects of flunixin meglumine, ketoprofen and phenylbutazone started to be published in the 1980s (Trillo et al., 1984; MacAllister et al., 1992; MacAllister, 1994; MacAllister & Taylor-MacAllister, 1994). Other drugs, such as suxibuzone (a prophenylbutazone drug), firocoxib, monophenylbutazone (phenylbutazone-derivate), acetylsalicylic acid, eltenac, nimesulide and meloxicam, have also been studied (Prügner et al., 1991; Goodrich et al., 1998; Monreal et al., 2004; Villa et al., 2007; Andrews et al., 2009; Sabaté et al., 2009; Videla & Andrews, 2009; Pozzobon, 2010). Nevertheless, studies of phenylbutazone (or derivatives) have not been abandoned, possibly because of ulcerogenic effect and therapeutic efficacy (Vicente, 2004; Driessen, 2007). As mentioned previously, the nonsteroidal anti-inflammatory drugs are widely employed in equine clinical practice to treat acute and chronic inflammatory conditions, especially of the locomotor apparatus (Prügner et al., 1991; Jones & Blikslager, 2001; Sabaté et al., 2009; Videla & Andrews, 2009).

Gastric injury usually occurs when NSAIDs are given at high doses or prolonged treatments (Snow et al., 1979, 1981; MacAllister, 1983; MacKay et al., 1983); nevertheless, therapeutic doses have been known to cause ulcers in horses. The most widely accepted hypothesis for

the association between NSAIDs and gastric ulcers is cyclooxygenase inhibition (See item 2 – Types and mechanism of actions of NSAIDs), in which conversion of arachidonic acid into prostaglandins is blocked (MacAllister, 1983; MacAllister et al., 1993; Murray, 1999). The physiologic vasodilating effect of prostaglandins (in particular PGE_2) on the stomach mucosa generates a bicarbonate buffering system that attenuates the corrosive action of hydrochloric acid contained in gastric secretions (Andrews & Nadeau, 1999; Murray, 1999; Morrissey et al., 2008). These substances increase gastric mucosa blood flow and mucus secretion, and reduce gastric acid production. They also facilitate basal cell migration towards the lumen for repairing the mucosa and maintaining the integrity of nonglandular and glandular mucosa; this takes place by stimulation of active surface-protecting phospholipid production. Inhibition of prostaglandin synthesis may give rise to ideal conditions for ulcers in the gastrointestinal tract (Andrews & Nadeau, 1999; Murray & Pipers, 2001; Andrews et al., 2005). According to Andrews et al. (2005), gastric mucosal ischemia may lead to hypoxia-induced cellular acidosis, and release of oxygen-free radicals, phospholipases and proteases, which may damage the cell membrane and result in necrosis.

As mentioned previously, the majority of NSAIDs are poorly selective, inhibiting COX-1 and COX-2 equally (Fitzpatrick et al., 2004; Vicente, 2004). Drugs that inhibit COX-1 are considered the main causative of stomach lesions, because this enzyme is generally – but not exclusively – responsible for the above mentioned adverse effects on the gastrointestinal tract (Jones & Blikslager, 2001; Lees et al., 2004; Videla & Andrews, 2009). Although the ulcer-causing potential may vary among NSAIDs, a study of rat stomachs with normal mucosa after acid challenge showed that inhibition of both cyclooxygenases causes gastrointestinal injury; however, inhibition of only one of these enzymes did not have this effect (Gretzer et al., 2001). Furthermore, administering NSAIDs on an empty stomach may result in local gastric irritation. Therefore, these drugs should be administered with food when given orally (Mathews, 2002; Lees et al., 2004; Monreal et al., 2004).

The site of NSAID-induced ulcers in the stomach of horses remains controversial. Some authors have stated that the glandular mucosa is more commonly affected (Carrick et al., 1989; Vatistas et al., 1999a; Monreal et al., 2004; Marqués, 2007; le Jeune et al., 2009), while others have argued that the nonglandular mucosa is affected more frequently (MacAllister et al., 1992; Andrews et al., 2005). According to Mokhber Dezfouli et al. (2009), Persian Arab horses with history of long term treatment with NSAIDs have high prevalence of the gastric ulcer in the glandular mucosa. In addition, it has been documented that phenylbutazone can cause severe ulceration of the glandular gastric mucosa following administration at high dosages for as short as a few days (Collins & Tyler, 1985; Lees, 2003). Moreover, according to Andrews et al. (2005), 80% of ulcers induced by phenylbutazone are located in the nonglandular mucosa.

MacAllister et al. concluded 1992 that flunixin meglumine (1.5 mg/kg bwt intramuscularly every 8 hours for 6 days) may result in ulcers of the nonglandular mucosa of ponies. In 1993, MacAllister et al. reported ulcers in the nonglandular and glandular mucosa of horses. The authors compared the adverse effects of phenylbutazone (4.4 mg/kg bwt), flunixin meglumine (1.1 mg/kg bwt) and ketoprofen (2.2 mg/kg bwt) given intravenously every 8 hours in horses during 12 days. The phenylbutazone presented the highest ulcerogenic potential of these three drugs. Other studies of horses

and ponies revealed that the effect of NSAIDs on the nonglandular mucosa is less evident or undetected, and if there is pain, it is generally mild (Snow et al., 1979, 1981; MacKay et al., 1983).

The glandular region has adequate blood flow, cell restitution, mucus-bicarbonate layer, prostaglandin secretion, and growth factors (Murray, 1997; Andrews et al., 2005; Marqués, 2007; Nadeau & Andrews, 2009). The nonglandular mucosa has a thinner layer, no mucus-bicarbonate layer, and often desquamation in foals aged over 35 days, and may remain in the first month of life (MacAllister et al., 1992; Murray et al., 1987; Andrews & Nadeau, 1999; Andrews et al., 2005, Murray, 1997). This region is constantly exposed to chloridric acid, pepsin and bile acids (Andrews & Nadeau, 1999; Murray, 1999). Besides the stomach, the phenylbutazone-induced ulcers may occur in the intestine – with reports in the duodenum (Snow et al., 1979; Snow et al., 1981; MacAllister et al., 1993), ceco, colon and rectum (MacAllister, 1983, Ruoff et al., 1987, Boothe, 2001).

Meschter et al. (1984) has stated that the primary target of phenylbutazone intoxication in horses is the wall of smaller veins. Other changes (ulcers on the tongue, stomach and intestine, as well as renal necrosis and venous thrombosis) should be interpreted as being secondary to vein lesions. In 1990, Meschter et al. suggested that phenylbutazone-induced gastrointestinal ulceration results from direct toxic injury to endothelial cells within the microvasculature of the mucosa. Vascular tumefaction, stagnation and cessation of blood flow, formation of fibrin, perivascular extravasation with subsequent edema, thrombosis and necrosis of the mucosa occur; finally, the mucosal epithelium breaks down. These authors argued that vasoconstriction is not the primary cause of mucosal necrosis; once formed erosions and ulcers, they could persist because of other non-prostaglandin-mediated processes, such as bacterial invasion (Nadeau & Andrews, 2009). Murray (1999) added that NSAIDs appear to cause neutrophils to adhere to the vascular endothelium of the gastric mucosa, thereby reducing mucosal perfusion and releasing chemical mediators that add further damage. Doherty et al. (2003) have suggested that phenylbutazone does not alter the baseline secretion of gastric acid in horses; rather, it decreases lipopolysaccharide-induced effects on the volume of secretions and on sodium production, and concentration in parietal cells.

4. Some experimental studies of NSAIDs

After identifying the types and mechanisms of cyclooxygenases, several studies aimed to discover NSAIDs with appropriate analgesic, antipyretic and anti-inflammatory properties and minimal ulcer-generating effects (MacAllister et al., 1993; Cunningham & Lees, 1994; MacAllister, 1994). However, these drugs should currently be used with caution in horses, as animal studies have shown varying results. There are several risk factors – especially stress – associated with gastric ulceration; these factors may potentiate the ulcerogenic effect of NSAIDs during experiments. A description is given below of selected experimental studies showing associations, or lack thereof, between nonsteroidal anti-inflammatory drugs and gastric ulceration in equid species.

Snow et al. (1981) conducted an experiment with horses and ponies in which oral phenylbutazone (8.2 mg/kg bwt) was administered every 24 h during 13 days to six horses; also, the same drug at 10 to 12 mg/kg bwt every 24 h was administered to nine ponies during 6 to 8 days. All horses remained apparently healthy, but five ponies developed

depression, hyporexia, weight loss, loose feces, and mouth ulcers; two ponies died. A biochemical analysis showed progressive decrease in total plasma proteins and albumin, a significant elevation of blood urea nitrogen, and a decrease in calcium and potassium concentrations. The authors suggested that ponies were more susceptible to the adverse effects of phenylbutazone.

The manufacturer's daily recommended dose of phenylbutazone for horses is 4.4 to 8.8 mg/kg bwt orally, and 2.2 to 4.4 mg/kg bwt intravenously (MacAllister, 1994). The risk of intoxication may increase when phenylbutazone is administered at daily doses above 8.8 mg/kg bwt for more than four days (MacKay et al., 1983). According to Hu et al. (2005), considering the toxicity of phenylbutazone, the higher dosage (8.8 mg/kg) may not be beneficial in chronically lame horses, because this dose was not associated with greater analgesic effects compared to 4.4 mg/kg dose in quarter horse-type breeding studied by Oklahoma State University (USA). In fact, the most commonly used analgesic dose for equine in the clinical setting is 2-4.4 mg/kg bwt given intravenously or orally every 12 h (Robinson & Sprayberry, 2009), for 5 to 7 days.

Although the dose of 4.4 mg phenylbutazone/kg bwt is considered safe to use in horses (Taylor et al., 1983; Tobin et al., 1986), the oral administration of this dosage every 12 h with concurrent intravenous administration of flunixin meglumine (1.1 mg/kg bwt every 12 h) for 5 days resulted in acute necrotizing colitis, with lesions most severe in the right dorsal colon in one of 29 adult horses (Keegan et al., 2008). According to the authors, considering that the drugs were lower than those that reportedly cause toxic effects, it is likely that it was the combination of NSAIDs, as well as the total increase in concentration irrespective of type, that was responsible for these abnormalities. On the other hand, neonatal foals (two days old) treated with recommended dosage of flunixin meglumine (1.1 mg/kg bwt/day) for five days, did not have clinicopathological or pathological differences compared to treatment with physiological saline, but the dose of 6.6 mg/kg/day increased total gastrointestinal ulceration, gastric ulceration and cecal petechiation (Carrick et al., 1989).

Administrating high doses of phenylbutazone (10 mg/kg btw) daily for ponies (Snow et al., 1979) and foals (Traub et al., 1983), and 8 mg/kg bwt daily for adult horses (Ruoff et al., 1987) resulted in ulcers in different parts of the gastrointestinal tract (from lips and tongue to the rectum), and marked edema and inflammation of the small intestine, colon, and rectum. In addition, MacAllister (1983) administered phenylbutazone 10 mg/kg bwt orally every 24 h to ten ponies during 14 days and found that seven animals were intoxicated, characterized by anorexia, oral ulcers, soft feces, and depression; six animals died, one of which by euthanasia. Necropsy revealed gastrointestinal ulcers, enteritis, necrotic colitis, peritonitis, and renal papillary necrosis.

Monreal et al. (2004) found ulcers on the glandular gastric mucosa in 100% of mix-breed horses (aged from 2 to 16 years, and body weight from 288 to 527 kg) treated with high doses of phenylbutazone (10.5 mg/kg bwt every 12 h, for two days, followed by 5.25 mg/kg bwt every 12 h, for 12 additional days); the same findings were present in only 40% of suxibuzone-treated animals (15 mg/kg bwt every 12 h, for two days, followed by 7.5 mg/kg bwt every 12 h, for another 12 days); the ulcers were significantly larger and deeper in the animals that were given phenylbutazone. Conversely, histopathology studies revealed similar inflammation when comparing these two drugs; there was severe neutrophilic inflammatory infiltration and signs of a healing reaction in both groups of animals. According to these authors, ulcers in the oral cavity, softened feces, anorexia, weight loss,

hypoproteinemia and hypoalbuminemia, considered classical signs of phenylbutazone toxicosis, were seen in one horse only. Further, small mouth ulcers were encountered in two animals in the suxibuzone group.

Andrews et al. (2009) evaluated the gastric ulcerogenic effect of a top-dress formulation containing suxibuzone or phenylbutazone for 18 adult horses aged from 3 to 14 years and body weights ranging from 294 to 467 kg in study conducted at the Louisiane State University (USA). There were three groups: a control group, a group given phenylbutazone (2.6 mg/kg bwt), and a group given suxibuzone (3.5 mg/kg bwt), during 15 consecutive days. Gastric ulcers in the phenylbutazone-treated group were not more severe than those in the suxibuzone-treated group, suggesting that suxibuzone has no advantage over phenylbutazone in preventing gastric ulcers at recommended label doses.

Prügner et al. (1991) reported that intravenous administration of eltenac (1 mg/kg bwt at 24 h intervals) during three days was more effective ($P<0.001$) in reducing pain caused by lameness of several causes (tendinitis, pododermatitis, navicular disease, non-infectious arthritis, etc.) in 32 horses compared to placebo controls (n=32). Goodrich et al. (1998) studied this same drug in four groups of six horses given different doses (0.5, 1.5, 2.5 mg/kg bwt or sterile saline solution every 24 h for 15 days), and found that it was not toxic for the gastrointestinal tract at a dose of 0.5 mg/kg bwt; the authors concluded that eltenac might be beneficial for horses.

Videla & Andrews (2009) reviewed firocoxib, an NSAID approved for controlling pain and inflammation due to osteoarthritis in horses. This drug (0.1 mg/kg bwt orally every 24 hours, for 30 days) did not cause ulcers in the study sample. These authors suggested that the efficacy of firocoxib in horses with abdominal pain is unknown, and that it should not be administered to animals with abdominal discomfort and gastric reflux or dysphagia, as there is currently no systemic formulation of the drug. According to Doucet et al. (2008), firocoxib appears to be a safe alternative to the long-term use of phenylbutazone in horses.

Loew et al. (1985) stated that monophenylbutazone is five to six times less toxic than phenylbutazone, but it is less effective when given at the same dose. Pinto et al. (2009) studied whether monophenylbutazone was associated or not with gastric ulcers in ponies in a two-step experiment conducted at the Universidade Federal de Viçosa (Brazil). The first step consisted of three groups of two healthy ponies each, treated with daily intravenous doses (3, 4.5 or 6 mg/kg bwt during 12 days) of the drug. One pony in each group was given omeprazole (3 mg/kg bwt orally every day). The second step, conducted six month after the first, consisted of two groups, each with two healthy ponies; the first group was given monophenylbutazone 4.5 mg/kg bwt intravenous daily for 12 days, and the second group was given 5 mL of 0.9% NaCl intravenously. All ponies underwent endoscopy before and after the trial. At the end of the first step, endoscopy revealed nonglandular gastric mucosa ulcers along the *margo plicatus* (Fig. 1) only in the two animals that were given the highest dosage (6 mg/kg bwt) of the drug. However, the occurrence of ulcers was unrelated with the dose ($P>0.05$). The authors suggested that individual variation, confinement stress, daily handling, and administration itself of the drug, may have contributed to the number and severity of ulcers, a situation that has already been reported by other authors (MacAllister et al., 1992; Murray, 1999; Andrews et al., 2005). le Jeune et al. (2009) have suggested that stress may be a major contributing factor to ulcer development.

In the second step of Pinto et al.'s (2009) study, two animals developed gastric ulcers, one of which had been given monophenylbutazone (4.5 mg/kg bwt during 12 days) (Fig. 2); the

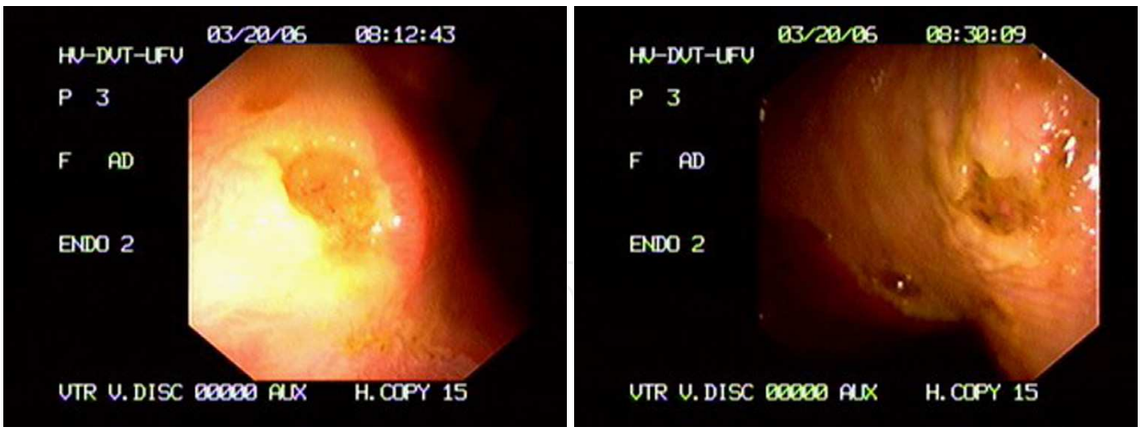

Fig. 1. Ulcers on the nonglandular gastric mucosa of a pony treated intravenously during 12 consecutive days with monophenylbutazone (6 mg/kg bwt every 24 h).

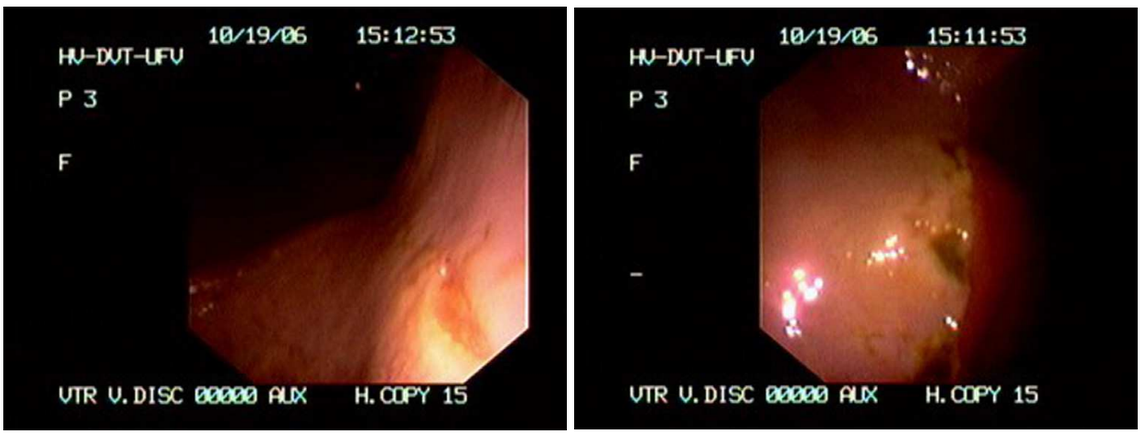

Fig. 2. Ulcers on the nonglandular gastric mucosa of a pony treated intravenously during 12 consecutive days with monophenylbutazone (4.5 mg/kg bwt every 24 h).

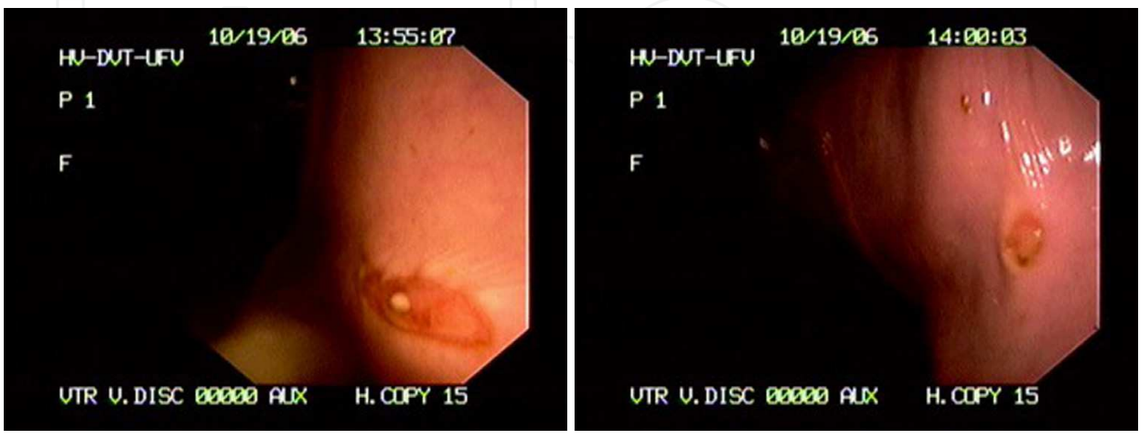

Fig. 3. Ulcers on the nonglandular gastric mucosa of a pony treated daily during 12 consecutive days with 5 mL of 0.9% NaCl intravenously.

other pony that presented gastric ulcers had been given only 5 mL of 0.9% NaCl intravenously, during 12 days (Fig. 3). Monophenylbutazone did not influence the occurrence of ulcers ($P>0.05$). The authors suggested that the discomfort associated with daily intravenous injections of saline solution may have generated enough stress to cause ulcers. MacAllister et al. (1992) also suggested an association between stress and application of medication, in a study where flunixin meglumine (1.5 mg/kg bwt every 8 h during 6 days) was given intramuscularly to ponies. MacAllister et al. (1993) encountered similar results when comparing the occurrence of ulcers following administration of flunixin meglumine and 0.9% NaCl to horses; there were no significant differences between these two groups.

Vatistas et al. (1999a) studied stress in thrirty mature Thoroughbred horses and suggested that the following situations could raise serum cortisol concentrations: road transport, exposure to a new environment, abrupt weaning in foals, physical restraint, anesthesia, nasogastric intubation, and diseases in general. Costa el al. (2007) have argued that the pathophysiology of stress-induced gastric mucosal injury remains controversial; the main suggested causal factor has been decreased blood flow in the mucosa due to splanchnic vasoconstriction associated with increased sympathetic tonus and an increased level of circulating catecholamines. Furthermore, increased endogenous corticosteroid concentrations during stress may inhibit prostaglandin synthesis. As mentioned previously, decreased prostaglandin levels result in loss of balance in mucosal protective factors; this is commonly stated as the primary cause of ulcers in foals and adult horses (Andrews & Nadeau, 1999; Andrews et al., 2005).

Villa et al. (2007) evaluated the pharmacokinetics and pharmacodynamics of nimesulide in 15 healthy horses aged from 3 to 6 years. The animals were divided into three groups. Group A was given nimesulide (1.5 mg/kg bwt) orally and intravenously; groups B and C were given nimesulide (1 mg/kg bwt) orally once. According to the authors, a 1.5 mg/kg bwt dose may yield the desired effects when administered every 12 or 24 h, depending on the severity of the animal's condition. However, as this dose exceeds the *in vitro* IC_{50} for cyclooxygenase 1 and 2 isoforms (see item 2 – Types and mechanism of action of NSAIDs), the selectivity is lost, which results in side effects due to COX-1 inhibition. Thus, the authors suggest that nimesulide should be used with caution in equid species.

Pozzobon (2010) assessed the side effects of meloxicam on the gastric mucosa and semen of six healthy ponies at the Universidade Federal de Santa Maria (Brazil). Two animals were treated with meloxicam (0.6 mg/kg bwt, orally) for 30 days, two were treated with ketoprofen (2.2 mg/kg bwt, orally) for 30 days, and two were not given anti-inflammatory drugs. The experiment was repeated three times, alternating the ponies per groups according to a Latin square design; thus, all animals were given all treatments. The study lasted 15 weeks, with a one-week interval between treatments. Gastroscopy done at the end of the study did not reveal gastric mucosal disease, even though the concentration of total prostaglandins in the seminal plasma was decreased ($P<0.05$) and the quality of semen was negatively affected; the findings suggested a physiological effect of COX-2 on the reproductive tissues of stallions.

Gastric ulcers have also been reported in donkeys from South West of England. Burden et al. (2009) examined at necropsy 426 non-working aged donkeys, and found that 41% of these animals had gastric ulcers. The mean age of the animals was 30.5 years; the study took two

years. The majority (n=96; 49%) were medium-sized ulcers (> 2 cm^2; < 10 cm^2), located mainly on the nonglandular mucosa along the *margo plicatus* (n=155; 89%). Information on NSAID use (e.g., phenylbutazone, flunixin meglumine, meloxicam, etc.) was available for 418 animals (98%); 214 donkeys (50.2%) in the study had been given NSAIDs for at least 7 days immediately prior to death, and the majority of animals had been given these drugs for months or years. The authors, however, found no relation (P=0.9) between the risk of having gastric ulcers on the glandular mucosa and use of NSAIDs in these animals.

There is an ongoing search for new analgesic and anti-inflammatory drugs because of the adverse effects of NSAIDs. Videla & Andrews (2009) have recommended xylazine (0.2-0.4 mg/kg bwt) or detomidine (20-40 µg/kg btw) as alternatives to NSAIDs, since these drugs are good analgesics and have minimal effects on the gastrointestinal tract. However, these drugs have other side effects or may increase the cost of therapy. These same authors have suggested that the choice of NSAIDs for horses should take into account the following criteria: minimal side effects on the gastrointestinal tract, the minimal pain-controlling dose, and use of an anti-ulcer drug together with the anti-inflammatory medication.

Drugs for treating ulcers in equid species have been investigated; this is a complex topic, to be addressed in another chapter of this book. However, the authors of the current chapter believe it is important to report their study with omeprazole, a drug that binds irreversibly to the H^+, K^+ -ATPase enzyme of gastric parietal cells (which secrete hydrogen ions into the stomach in exchange for K^+ ions), thereby inhibiting the production of chloridric acid. Omeprazole also selectively inhibits carbonic anhydrase, which adds to its acid suppressive properties (Daurio et al., 1999; MacAllister, 1999). Although this drug is considered the most effective inhibitor of gastric secretions (90% in 24 hour at 4 mg/kg bwt daily), it has a low bioavailability after oral intake (14-16%) (Andrews et al., 1992; Téllez et al., 2005). Murray et al. (1997) showed that the healing time of gastric ulcers was significantly shorter in horses given omeprazole (1.5 mg/kg bwt orally) daily during 28 days. MacAllister (1999) suggested that healing of ulcers using this drug appears to depend on the dose and duration of therapy; an oral dose of 4 mg/kg bwt daily during 28 days appears to have the highest success rate.

Pinto et al. (2008) administered omeprazole 4 mg/kg bwt orally for 31 consecutive days to verify its efficacy for healing gastric ulcers (score 1 to 4 in Murray et al., 1987) on the nonglandular mucosa of three ponies. Three other ponies with ulcers were controls, and were managed similarly except for therapy. At the end of the treatment, gastroscopy showed that the three controls no longer had ulcers, but two animals treated with omeprazole had marked granulomatous tissue over the ulcerated area (Figs. 4-5). Histopathology revealed tissue necrosis, fibrinous-leukocyte exudates, and exuberant granulation tissue. One of the fragments had hyperplastic squamous epithelium within the ulcer. In addition, filamentous structures similar to bacteria and spores of *Candida sp* were observed. The animals remained symptom-free throughout the treatment. Local *Candida sp* colonization may have been due to nearly complete omeprazole-induced inhibition of gastric acid secretion. Prim & Vila (2002) described a case of oropharyngeal candidiasis in a patient aged 65 years given omeprazole 20 mg daily. There are no reports of granulomas following the use of omeprazole in equid species, but findings suggesting enterochromaffin-like cell hyperplasia has been noted, and gastric carcinoid tumors has

been observed in rats (Hoogerwerf & Pasricha, 2001). The exuberant granulomatous tissues were regressing gradually until complete disappearance from 60 to 100 days after their identification (Fig 6).

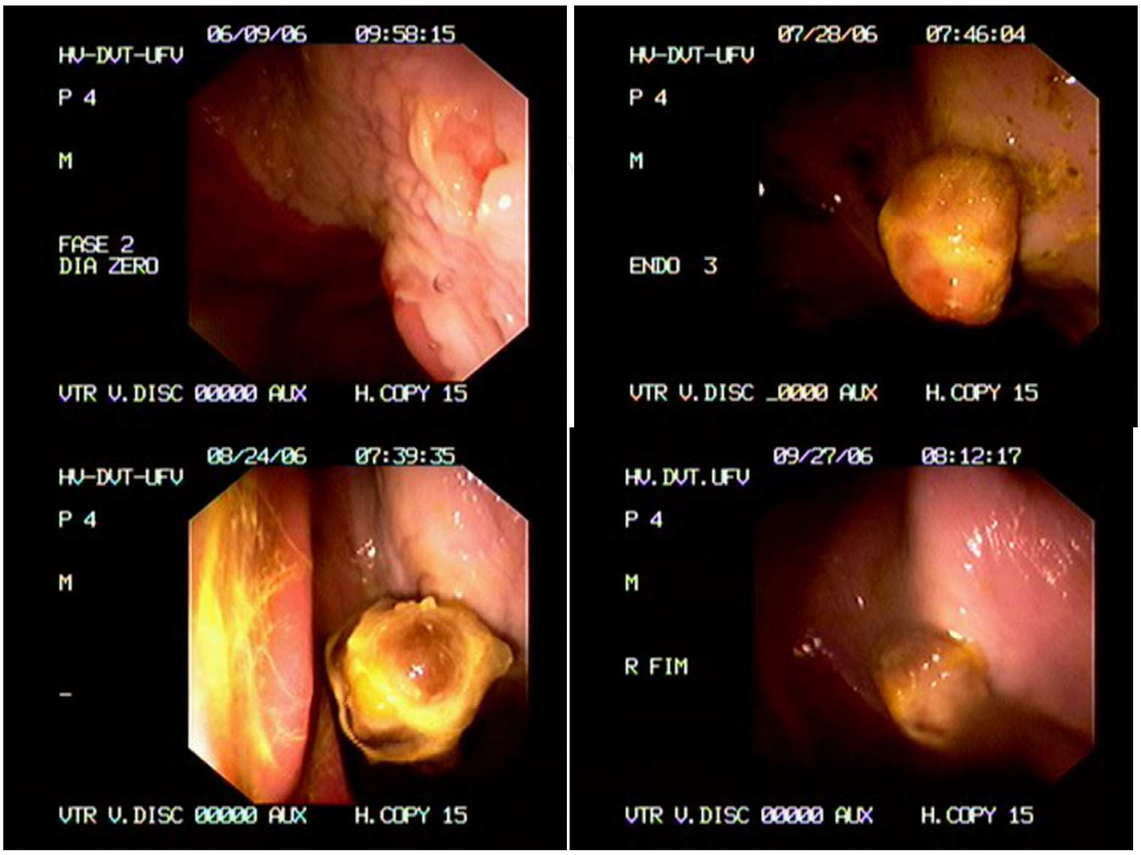

Fig. 4. Exuberant granulomatous tissue in a pony with gastric ulcers treated with omeprazole 4 mg/kg bwt orally for 31 days. The images show the monthly monitoring of the injury.

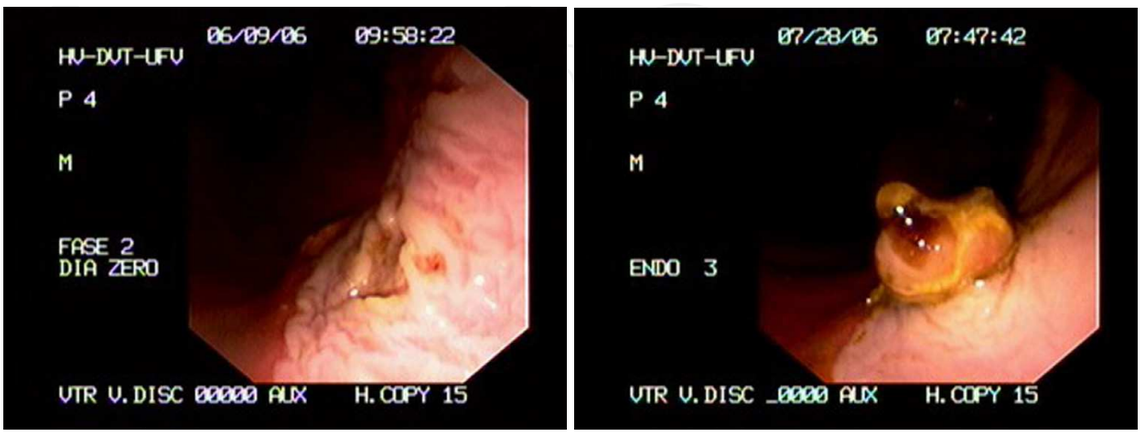

Fig. 5. Another granulomatous tissue at the ulcer on the nonglandular gastric mucosa, in pony treated with omeprazole (4 mg/kg bwt orally for 31 days).

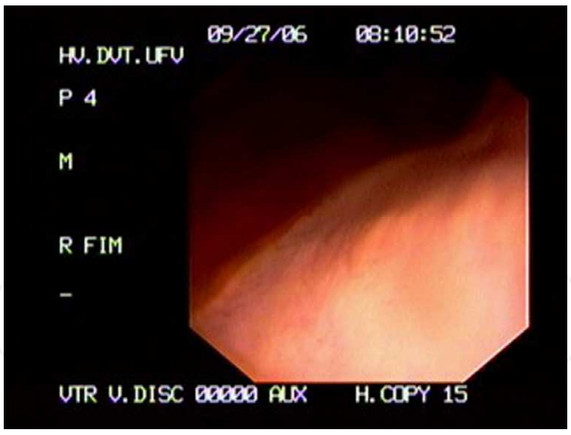

Fig. 6. Aspect of nonglandular gastric mucosa shown in Fig. 5, with complete disappearance of the granulomatous tissue about three months after its identification.

5. Conclusion

Nonsteroidal anti-inflammatory drugs are very useful for treating many clinical and surgical conditions in horses and ponies. Despite the significant amount of research, there is no single NSAID that is considered completely safe. Therefore, while the ideal drug is not discovered, careful measures (dose, application interval, and duration of treatment) should be taken when using these drugs, which are considered relevant risk factors for the gastric ulceration syndrome.

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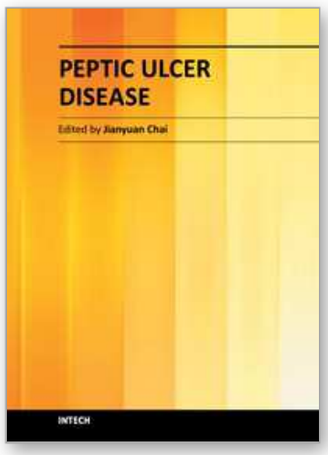

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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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