META-ANALYSIS OF THE THERAPEUTIC USE OF DIPYRONE IN DOGS: PHARMACOLOGICAL EFFECTS AND CLINICAL SAFETY

META-ANALÍSE DO USO TERAPÊUTICO DA DIPIRONA EM CÃES: EFEITOS FARMACOLÓGICOS E SEGURANÇA CLÍNICA

I. C. SILVA; C. A. A. MAIA; A. C. RAYMUNDO; M. N. L. PRATA; T. R. L. ROMERO; I. D. G. DUARTE; W. G. MANRIQUE; A. C. PEREZ; M. A. A. BELO

SUMMARY

Dipyrone (metamizole) is well-known for its powerful effect with central and peripheral activity. This meta-analysis involved articles published between 1973 and 2021, revealing that Brazil is the country which most published scientific articles relating the use of dipyrone in dogs, and this drug is widely recommended as an analgesic to control pain in cases of postoperative and cancer. Dipyrone is one of the favorite drugs used in small animal clinic in Brazil, and 12 commercial brands are available to use in dogs at doses among 25 to 50mg/kg for oral, intravenous and intramuscular administration. The effects of dipyrone may be potentiated when used in combination with other analgesic agents such as tramadol. In several studies, the occurrence of vomiting has been observed as an adverse effect, especially when the drug is used during surgical procedures, but metamizole has presented a low potential to cause gastric ulceration. The meta-analysis study of the use of dipyrone in dogs shows the clinical importance of this drug in Brazil, being an effective and safe medication, as long as it is used in the indicated dose of 25 mg/kg.

KEY-WORDS: Metamizole. Non-steroidal anti-inflammatory drugs (NSAIDs). Pain. Analgesic. Antipyretic

RESUMO

A dipirona (metamizol) é bem conhecida por seu poderoso efeito com atividade central e periférica. Esta meta-nálise envolveu estudos publicados entre os anos de 1973 a 2021, revelando que o Brasil é o país que mais publicou artigos científicos envolvendo o uso de dipirona em cães, sendo este fármaco amplamente recomendado como analgésico para controlar a dor em casos de câncer e dor pós-operatória. É um dos medicamentos preferidos da clínica médica de pequenos animais no Brasil. 12 marcas comerciais estão disponíveis para uso em cães em doses que variam de 25 a 50g para administração oral, intravenous e intramuscular. Os efeitos da dipirona podem ser potencializados quando usada em combinação com outros analgésicos, como o tramadol. Em vários estudos, a ocorrência de vômito tem sido observada como efeito adverso, principalmente quando o medicamento é usado durante procedimentos cirúrgicos, mas tem baixo potencial para causar úlceração gastrica. O estudo de meta-análise do uso de dipirona em cães evidencia a importância do uso clínico deste fármaco no Brasil, sendo um medicamento eficaz e seguro para cães, desde que utilizada na dose indicada de 25 mg / kg.

PALAVRAS-CHAVE: Metamizol. Antiinflamatórios não esteroidais (AINEs). Dor. Analgésico. Antipirético

1 Department of Pharmacology, Institute of Biomedical Sciences – University of São Paulo (ICB-USP). 1374 Prof. Lineu Prestes Ave., 1374. ZipCode 05508-000, São Paulo State, Brazil.
2 Veterinarian with specialization in dog clinic
3 Department of Pharmacology, Institute of Biomedical Sciences – Federal University of Minas Gerais (ICB-UFGM), Av. 6627 Antônio Carlos Ave., ZipCode 31270-100, Belo Horizonte, Minas Gerais State, Brazil.
4 Department of Veterinary Medicine, Federal University of Rondônia, UNIR. 7300 Norte Sul Ave., ZipCode: 78987-000, Rolim de Moura, Rondônia State, Brazil
5 Laboratory of Animal Pharmacology and Toxicology. Brazil University. 950 Hilário da Silva Passos Ave., ZipCode 13690-000, Descalvado, São Paulo State, Brazil.

*Corresponding author: E-mail address: charliesilva4@hotmail.com
Department of Pharmacology, Institute of Biomedical Sciences – University of São Paulo (ICB-USP). 1374 Prof. Lineu Prestes Ave., 1374. ZipCode 05508-000, São Paulo State, Brazil.

Submetido: 06/03/2021 Aceito: 29/03/2021
INTRODUCTION

Dipyrone is well-known for its powerful analgesic and antipyretic effects, in which the mechanism of action features both central and peripheral activity. Its development began in 1883, when the German chemist Ludwig Knorr discovered antipyrine, a derivative of pyrazole (NETO, 2011), also known as metamizole. The structure of pyrazolone compounds contains a pyrazole ring, conferring anti-inflammatory, analgesic and antipyretic activity. The anti-inflammatory properties of these compounds have been described as occurring due to the presence of carbons at positions 3 and 5 of the pyrazole ring (GÜRSOY et al., 2000; SOUZA et al., 2001).

Dipyrone may be used for the treatment of pain in both veterinary and human medicine. Since it was introduced in the market in 1922 it has been used in several pharmaceutical forms. It is the most used drug in Argentina, Mexico, Colombia and Brazil, as well as in parts of Europe, notably Germany, Portugal, Italy and Spain, in the Middle East, Asia, and South Africa, and other countries (Feldmann et al., 2008. Chaparro et al., 2011. Guzella et al., 2015). In addition, Lorena et al. (2014) reported that dipyrone is among the most commonly used drug in the medical treatment of small animals in Brazil. In Brazil, dipyrone is present in commercial brands from ten different companies, at concentrations from 25 to 50 g, with formulations available for oral, intravenous, and intramuscular administration, with authorization for use in dogs.

Data base

Our meta-analysis was carried out following the criteria described by Sampaio and Mancini (2007), using sources of literature data on a given topic. For these authors, this type of survey could be used in retrospective observational studies or experimental studies, aiming to perform a critical analysis of the existing literature. In this meta-analysis, we propose to study an open source called bibliometrix, to perform comprehensive analysis of scientific mapping, using a program tool R for the studies according to Balduzzi et al. (2019). Searches were carried out using a bibliographic data from PubMed, being used 64 articles published between 1973 and 2021. The following search terms were used: “dipyrone or metamizole”, with studies in “dogs” as shown in Figure 1.

Figure 1 - Frequency of words present in the 64 abstracts belonging to the articles studied.

Figure 2 presents the global map with interaction flow between research groups that have studied the use of dipyrone in dogs, as well as the main countries involved in these scientific collaboration networks, according to the 64 published studies between 1973 and 2021. This analysis revealed that Brazil was the country that presented the largest number of studies involving the use of dipyrone in dogs. Despite the low international collaboration in these studies realized in Brazil. On the other hand, the largest flows of scientific collaboration were observed between European and Asian countries (Figure 2).

Figure 3 shows the affiliations present in the 64 articles involving the use of dipyrone in dogs published between 1973 and 2021. It is worth noting in this analysis that research groups from the Universidade Estadual Paulista (UNESP) in Brazil and the University of Zurich in Switzerland were the ones that presented the greatest number of scientific collaborations in this area of knowledge.
Dipyrone is almost white, odorless crystalline powder that is rapidly solubilized as it is highly soluble in water and methanol, poorly soluble in ethanol, and practically insoluble in ethyl ether, acetone, benzene, and chloroform (FARMACOPEIA BRASILEIRA, 2010). The bioavailability for tablets is 85% and 89% for drops and 87% for intramuscular administration (Levy; Zylber-katz; Rosenkranz, 1995), and in the blood about 58% is bonded to plasma proteins, providing onset analgesia after approximately 15 minutes. Christ et al. (1973) reported a maximum plasma concentration of 40 μg/mL in dogs two hours after oral administration of 50 mg/kg. In a study by Guerrero et al. (2015) the maximum plasma concentration of dipyrone was 30 μg/kg four hours after the administration of 50 mg/kg.
According to Spinosa et al. (2011) plasma half-life of dipyrone in dogs is about five to six hours. Haritova (2001) studied the effects of drug interaction of dipyrone administered concomitantly with the antibiotic amikacin in dogs and observed that total clearance was higher when the two drugs were combined. Biotransformation of dipyrone occurs in the liver, lasting from four to seven hours. Metamizole is rapidly hydrolyzed to the active primary metabolite 4 methylaminoantipyrine and relatively active secondary metabolite 4-acetamidoantipyrine as shown in (figure 4) (Giorgi et al., 2018). When administered intravenously, hydrolysis is not as rapid, and the drug can be detected in its original form. After being hydrolyzed, dipyrone loses its functional sulfonic clustering. It is metabolized by the enzymes of the cytochrome p-450 complex (GEISSLINGER et al., 1996) and then by N-acetyltransferases (PIERSON and WIENKERS, 2008). Around 70% is excreted in the urine 24 hours after administration. Recently, Silva et al (2015) described Noradrenaline (NA) involvement in Dipyrone peripheral analgesia with activation of α1, α2C and β-adrenoceptors. According to Giorgi et al. (2018), a pharmacokinetic study with 25 mg of dipyrone / kg revealed that rectal administration seems to be the least suitable route of administration in dogs, and better pharmacokinetic results were observed in dogs after intravenous, intramuscular, and oral routes of administration.

![Figure 4 - Metabolic pathways of dipyrone, metabolites are: 4-methylamino antipyrine (MAA), 4-acetamidoantipyrine (AA), 4-acetamido antipyrine (AAA) and 4-formylamino antipyrine (FAA) (Ariza et al. 2016).](image)

**THE MECHANISM OF ACTION OF DIPYRONE**

Dipyrone displays pharmacological actions that are mainly related to the inhibition of the thermoregulatory centers, resulting in the normalization of central heat production and the reversible inhibition of the cyclooxygenase enzyme (COX), followed by a subsequent reduction of prostaglandins synthesis. Luthy et al. (1983) demonstrated that dipyrone competes with COX. Chandrasekharan et al. (2002) studied the efficacy of analgesic drugs on COX inhibition and found that dipyrone had a significantly more potent inhibitory effect on COX-3 than COX-1. Dipyrone inhibited COX-3 with an ED50 value of 52 μM, and COX-1 with an IC50 value of 350 μM, while no inhibition of COX-2 was observed by dipyrone below 1,000 μM.

There are several reports of the involvement of endogenous opioids in the effect of dipyrone in different models of nociception (Akman et al., 1996; Gloria et al., 2006 and Silva et al., 2016). The release of endogenous opioids by dipyrone also increases the effects of exogenous opioids (Gloria et al., 2006). In the last years, additional mechanisms have been proposed. Duarte et al. (1992) reported for the first time that dipyrone interferes in the balance between cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels and that the stimulation of the Nitric Oxide- cGMP (NO-cGMP) pathway may increase nociceptors sensitivity. Alves & Duarte, 2002; Hernández-Delgadillo et al. (2006) and Reis, et al. (2013) also highlighted its potent analgesic effect via the cGMP / K+ + pathway. Romero et al. (2011) reported that dipyrone activates neuronal Nitric Oxide Synthase (nNOS) and induce peripheral analgesia by NO release. Besides, dipyrone has peripheral antinociceptive effect by activation of ATP-sensitive K+ channels, but other K+ channels also appear to be involved in the process (Alves & Duarte, 2002). Queiroz et al. (2013) attributed its analgesic action to direct depression of nociceptive activity, by reducing the levels of cAMP and by blocking calcium entry into the nerve endings. In addition, a recent study of the analgesic effect of dipyrone discussed the interactions between the endogenous peroxidase, glutamate and cannabinoid systems (Dos Santos et al., 2014).

Crunfli et al. (2015) observed that specific CB1 endocannabinoid receptors contribute to the analgesic effects of dipyrone and suggested that the same mechanism of action is involved with the cyclooxygenase and hydrolyzed amide of fatty acids, both of which supply additional arachidonic as a substrate for the synthesis of endocannabinoids. The increase in the availability of endocannabinoids stimulates CB1 receptor, contributing to the analgesic effect in animals with inflammation. Escobar et al., (2012), also observed the involvement of endogenous cannabinoids, in particular CB1, in the activation of Periaqueductal Gray Matter (PAG) by the descending

---

**Figure 4 - Metabolic pathways of dipyrone, metabolites are: 4-methylamino antipyrine (MAA), 4-acetamidoantipyrine (AA), 4-acetamido antipyrine (AAA) and 4-formylamino antipyrine (FAA) (Ariza et al. 2016).**

---
antinociceptive influence of the Rostral Ventromedial Medulla (RVM). However, Silva et al. (2012) did not observe the involvement of CB1 and CB2 cannabinoid receptors in the peripheral antinociceptive mechanism of dipyrone. Elmas et al. (2013) also reported that CB1 cannabinoid receptors do not participate in the analgesic mechanism of dipyrone on acute pain without inflammation in animals.

**PHARMACOLOGICAL EFFECTS OF SDIPYRONE IN DOGS**

**Analgesc effect**

The potent analgesic effect of dipyrone in dogs is well-known and it is mainly related to the inhibition of the cyclooxygenase (COX) enzyme, and consequent decrease in prostaglandin synthesis, resulting in the reduced sensitivity of nerve endings to inflammatory mediators such as bradykinin. Several studies have found that dipyrone is effective as an analgesic in postoperative pain in dogs undergoing removal of tumors, ovarian hysterectomy, and splenic torsion (Caulkett et al., 2003; Imagawa et al., 2011; Zanuzzo et al., 2015; Guerrero et al., 2015; Bellio et al., 2015; Souza et al., 2016; Ortiz et al., 2016; Ferrigno et al., 2016; Sembenelli et al., 2016; Dalomolin et al., 2020). For Ripplinger et al. (2018), the association of metamizole and morphine or metamizole and methadone did not result in an increase in adverse effects in dogs when compared to animals treated with morphine or methadone alone. On the other hands, an intraoperative study revealed that although all patients developed hypothermia regardless of the anesthetic medication administered, and untreated dogs with metamizole reached normothermia more quickly in the postoperative period (Schidelko-Prandl et al., 2019).

There are reports that describe a potent analgesic effect of dipyrone in the control of cancer pain in dogs (Castro et al., 2013, Martins et al., 2015, D’Avila et al., 2016). In humans, dipyrone has also been widely recommended as an analgesic to control pain in oncological cases (Gaertner et al., 2016). In addition to being a potent analgesic, dipyrone helps to reduce inflammatory tumors (Brito et al., 2016). In dogs, the treatment of neoplastic pain most often occurs at advanced stages, when maintaining animal welfare becomes the main objective of the medical-oncological clinic (Gaynor 2008).

The effects of dipyrone may be potentiated in dogs in combination with different analgesics drugs such as meloxicam (figure 5) (a nonsteroidal anti-inflammatory drug, NSAID; Bellio et al., 2015, Zanuzzo et al., 2015, Souza et al., 2016), tramadol (opioid; Teixeira et al., 2013) and scopolamine (anticholinergic; Dalomolin et al., 2020). We noticed that different routes are shared between the drugs and the prostaglandin route was in all of them (figure 5 e,f,g).

Combined administration of low doses of dipyrone and opioids can produce additive or supraadditive analgesic effects (López-Muñoz et al., 2004; Zelcer et al., 2005; Gloria et al., 2006). Other aspects of this synergism is the reduction of undesirable effects of this drug, in fact it is an interesting topic for future research (Gloria et al., 2006; Schcutter et al., 2016). Guerrero et al. (2015) evaluated a new formulation containing dipyrone with a controlled release mechanism. In comparison with carprofen in postoperative analgesia in dogs, both drugs produced an adequate analgesic effect for a similar length of time.

![Figure 5](http://stitch.embl.de/cgi/)
Antipyretic effect

Few studies have evaluated dipyrone as an antipyretic agent. Pimpão et al. (2009) studied the antipyretic action of dipyrone in dogs. In this experiment, the animals were challenged with LPS (Lipopolysaccharides) to induce an immune response and consequent increase in body temperature. Body temperature was measured every 15 minutes until 180 minutes after the challenge. The authors observed that the injection of LPS induced an acute febrile state in dogs, and that oral administration of 25 mg/kg of dipyrone presented an antipyretic response, maintaining the temperature at around 38.5°C for two hours. Oborilová et al. (2002) studied the effects of dipyrone, diclofenac and propacetamol on 254 oncological patients with episodes of fever and observed that dipyrone presented the best results in reducing temperature.

Effects on gastrointestinal tract

Several studies have evaluated the gastrointestinal disorders caused by dipyrone administered either orally or intravenously. Vomiting was observed as an adverse effect in 45% of dogs receiving dipyrone-containing tablets (Guerrero et al., 2015). However, Imagawa et al. (2011) suggested that this side effect is related to the use of the anesthetic during the surgery. Bellio et al. (2015) observed emesis and hyporexia after oral administration of 25mg/kg of dipyrone in dogs. However, in a study by Teixeira et al. (2015) dipyrone was found to have low potential for causing gastrointestinal ulceration in dogs. In humans, meanwhile, it is common to observe gastrointestinal disturbances after the ingestion of dipyrone. In a study by Bentur & Cohen (2004), vomiting (n=16/39), nausea (n=3/39) and abdominal pain (n=9/39) were observed. Dipyrone displays potent pharmacological effects in the inhibition of COX1 (Chandrasekharan et al., 2002), and it may cause vomiting (Guerrero et al., 2015).

Effect on coagulation

The potential effect of dipyrone on hemostasis in dogs was recently studied by Zanuzzo et al. (2015), who evaluated platelet aggregation, time of bleeding of the buccal mucosa and thrombosis. A potent platelet aggregation effect was observed for up to three hours with only a single dose (25 mg/kg). In addition, when dipyrone was associated with other NSAIDs, such as meloxicam in dogs, it caused a more prolonged inhibition of platelet function than when acting alone. Schmitz et al. (2016) studied dipyrone and aspirin interaction in vitro in rich plasma and observed potentiation of platelet inhibition and thromboxane synthesis. These results show that the effects observed in dogs are very similar to those found in humans (Graff et al., 2007), where a decrease in thromboxane formation was observed after six hours due to a lack of selectivity and a higher affinity to COX-1 inhibition thereby inhibiting thromboxano A2 synthesis.

Clinical safety of dipyrone in dogs

The occurrence of clinical changes associated to the use of dipyrone in dogs has not been studied in detail and little is known about its incidence or prevalence. However, some data are available, such as the findings of Bellio et al. (2015), reporting that dipyrone is considered safe. Thus, appetite, mucous membrane color, and the degree of hydration of all the animals remained stable. There was no difference in heart or respiratory rate. Dilov et al. (2002) evaluated local and systemic tolerance to dipyrone in dogs. The authors compared the requirements for veterinary use in Bulgaria and reported that 3-5-fold endovenous application of ED50 for several days was safe and did not provoke reactions at the application site.

Laboratory tests did not reveal biochemical changes or hematopoietic problems, and no signs or symptoms of toxic manifestations, damage to the liver, excretory systems or metabolic disorders were observed. Some Brazilian pharmacologists have reported that the use of intravenous dipyrone may cause anaphylactic shock in dogs with hypersensitivity to the drug. However, administration by subcutaneous route should be avoided as it increases the risk of local reaction and abscess production (Spinosa et al., 2011; Barros & Di Stasi, 2012).

The hypersensitivity of dipyrone is believed to be mediated by specific IgE. In addition, dipyrone metabolites play a role in hypersensitivity and may induce basophilic activation (Ariza et al., 2016). Recently, Brazilian veterinary industry added in the drug leaflet a recommendation that dipyrone should not be applied subcutaneously in dogs, due to the occurrence of possible tissue irritations (Instructions: Algivet®Vetnil), although there is no veterinary pharmacovigilance evidence to indicate this. This control advertisement is effectively applied by the drugs administration and regulatory agencies in humans and, several batches of dipyrone-containing products are routinely tested and collected by health surveillance when they do not conform with Brazilian legislation and Farmacopeia (Farmacopeia Brasileira, 2010).

Renal effect

Alpermann & Scholtholt (1982) studied the effects of dipyrone at a dose of 100mg/kg. There was no change in renal function, urea, or creatinine serum concentrations after two days treatment in dogs. Correia et al. (2016) studied the renal function of rats receiving 0,6 - 5 g / kg for four consecutive days. The authors reported that in high doses there was an increase in urea concentration, renal congestion, and an inflammatory process in histopathological analysis.

Blood cells effect

Bellio et al. (2015) did not observe changes in total erythrocyte, hemoglobin, hematocrit, and leukocyte values. Imagawa et al. (2011) did not observe hematopoietic modulation after administration of 25 mg/kg over two days of dipyrone in dogs. A
study by Flôr et al. (2013) of 69 dogs treated with dipyrone at a dose of 25mg/kg every 12 hours, also reported the absence of blood changes. Sarchahi et al. (2017) studied tolerance to dipyrone in dogs receiving anesthesia and found no adverse effects on renal, blood and bone marrow functions. In dogs, as the therapeutic safety of dipyrone has not been studied in detail to date, the occurrence of agranulocytosis associated with dipyrone has not been described.

In humans, the use of dipyrone has been banned by the US Food and Drug Administration because of its rare depressant effect on the marrow, generating aplastic anemia and agranulocytosis, described as a sharp reduction in the levels of defense cells (granulocytes, GUZELLA et al., 2015). It was first reported in the early 1930s and some countries, such as Australia and Sweden, also banned drugs with this active ingredient (PIRES & OLIVEIRA, 2015). In contrast, several other countries sell dipyrone without restrictions (Chaparro et al., 2011; Guzella et al., 2015). To clarify the safety aspects of dipyrone in Brazil, the Health Surveillance Agency (Agência de Vigilância Sanitária, ANVISA) carried out an "International Panel for the Assessment of the Safety of Dipyrone in Humans", with specialists in the field of pharmacology and physicians. The findings of these debates were published through a report approved by an absolute majority explaining that the effectiveness of dipyrone as an antipyretic and analgesic are unquestionable, and that the risks associated with this drug reported in Brazil have so far been low (LUCCHETTI et al., 2010).

Table 1 - The therapeutic use of dipyrone in dogs.

| Indication      | Interval | Route of administration | Dose (mg/kg) | Association | Reference       |
|-----------------|----------|-------------------------|--------------|-------------|-----------------|
| Analgesic       | 12h      | VO                      | 28.5         | --          | Spinosa et al. (2011) |
| Analgesic       | 8 a 12h  | IM, SC                  | 25           | --          | Barros & Di Stasi (2012) |
| Analgesic       | 12h      | IV                      | 40           | --          | Abdellatif et al. (2014) |
| Post operative  | 12h      | VO                      | 50           | --          | Guerrero et al. (2015) |
| Post operative  | 12h      | IV                      | 25           | --          | Imagawa et al. (2011) |
| Post operative  | 24h      | IV                      | 50           | --          | SchCutter et al. (2016) |
| Post operative  | 6h       | IV                      | 30           | Tramadol    | Texeira et al. (2013) |
| Post operative  | 24h      | VO                      | 25           | Meloxicam   | Bellio et al. (2015) |
| Post operative  | 24h      | VO                      | 25           | Meloxicam   | Souza et al. (2016) |
| Post operative  | 6h       | VO                      | 25           | Tramadol +  | Ferrigno et al. (2016) |
| Post operative  | 6h       | VO                      | 25           | Meloxicam   | Ortiz et al. (2016) |
| Homeostasia     | 24h      | IV                      | 25           | Meloxicam   | Zanuzzo et al. (2015) |
| Oncological     | 24h      | IV                      | 25           | --          | D’Avila et al. (2016) |
| Oncological     | 8h       | VO                      | 25           | Tramadol    | Flôr et al. (2013) |
| Oncological     | 8h       | VO                      | 25           | Tramadol    | Castro et al. (2013) |
| Oncological     | 24h      | VO                      | 25           | --          | Martine et al. (2015) |
| Oncological     | 24h      | VO                      | 25           | --          | Mulher et al. (2010) |
| Oncological     | 24h      | VO                      | 24           | Tramadol +  | Stupak et al. (2016) |
| Antipyretic      | 24h      | VO                      | 25           | Firocoxib   | --              |
| Clinical safety | 8h       | VO                      | 30           | --          | Pimpão et al. (2009) |
| Pre anesthetic  | 12h      | IV, IM                  | 30           | --          | Sarchahi et al. (2017) |

REFERENCES

ABDELLATIF, A.; GÜNThER, C.; PEPPLER, C.; KRAMER, M. (2014). A rare case of splenic abscess with septic peritonitis in a German shepherd dog. BMC Veterinary Research, 10, 1–6.

AKMAN, H.; AKSU, F.; GULTEKIN, I.; OZBEK, H.; ORAL, U.; DORAN, F; BAYSAL, F. (1996). A possible central antinociceptive effect of dipyrone in mice. Pharmacology, 53, 71–78.

ALPERMANN, H.; SCHOLTHOLT, J. (1982) Pharmacology of dipyrone, Internal report. Pharmacology Document (00261).

ALVES, D. P. & DUARTE, I. D. (2002). Involvement of ATP-sensitive K+ channels in the peripheral antinociceptive effect induced by dipyrone. European journal of pharmacology, 444 (1), 47-52.

ARIZA, A.; GARCÍA-MARTÍN, E.; SALAS, M.; MONTAÑEZ, M. I.; MAYORGA, C.; BLANCA-LOPEZ, N.; ANDREU, I.; PERKINS, I.; BLANCA, M.; AGÚNDEZ, J. A. G.; TORRES, M. J. (2016). Pyrazolones metabolites are relevant for identifying selective anaphylaxis to metamizole. Scientific Reports, 6:23845, 1–9.

BARROS, C. M.; DI STASI, L. (2002) Farmacologia Veterinária. Editora: Manole, 1, p-596.
BALDUZZI, S.; RÜCKER, G.; SCHWARZER, G. (2019). How to perform a meta-analysis with R: a practical tutorial. Evidence-based mental health, 22(4), 153-160.

BELLIO, J. C. B.; MAGALHÃES, M. A. B.; PAREJA, C. N. G.; ROCHA, R. M. V. M.; JÚNIOR, P. V. M.; PIMPÃO, C. T. (2015). Safety and effectiveness of meloxicam associated to dipyrone in the treatment of post-surgical pain in dogs. Revista Brasileira de Ciência Veterinária, 22, 142–147.

BENTUR, Y.; COHEN, O. (2004). Dipyrone Overdose. Journal of toxicology. Clinical toxicology, 42, 261–265.

BRITO, B. E.; VAZQUEZ, E.; TAYLOR, P.; ALVARADO, Y.; VANEZAS, H.; MILLAN, A.; TORTORICI, V. (2016). Antinociceptive effect of systemically administered dipyrone (metamizol), magnesium chloride or both in a murine model of cancer. European Journal Pain, 21, 541–551.

BULA: Algivet®Vetnil available from: http://www.vetnil.com.br/produtos/algivet

CASTRO, J. L. C.; SANTALUCIA, S.; NAZARETHI, W.; CASTRO, V. S. P.; Pires, M. V. M.; LEME JR, P. T. O.; PAULA, L. R.; URURAHY, K. C. B.; CORRÊA, L. F. D.; RAISER, A. G. (2013). Axial Osteosarcoma in Dog – Case Report. Journal of Veterinary Advances, 3, 29-33.

CHANDRASEKHARAN, N. V.; DAI, H.; ROOS, K. L. T.; EVANSON, N. K.; TOMSIK, J.; ELTON, T. S.; SIMMONS, D. L. (2002). COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proceedings of the National Academy of Sciences of the United States of America, 99, 13926-13931.

CHRIST, O.; KELLNER, H. M.; ROSS, G.; RUPP, W.; SCHWARZ, A. (1973). Biopharmaceutical and pharmacokinetic studies on metamizol-14C (Novalgin 14C) given to rats, dogs and men. Arzneimittel-Forschung, 23, 1760–1767.

CORREA, B. S.; CAMPANINI, C. A.; PAIVA, L. C. M.; SILVA, R. N.; MALFARÁ, W. R.; CRISCI, A. R. (2016). Evaluation of Renal Function and Morphological Changes in rats Treated with Dipyrone in Different Dosing. Journal of Health Sciences, 18, 260 28.

CRUNFLI, F.; VILELA, F. C.; GIUSTI-PAIVA, A. (2015) Cannabinoid CB1 receptors mediate the effects of dipyrone. Clinical and experimental pharmacology & physiology, 42, 246–255.

DALMOLIN, F.; OLIVEIRA, M. T.; PINTO FILHO, S. T. L.; VAZ, M. A. B.; BERTOLETTI, B.; BOHL, V. H.; FERANTI, J. P. S.; HARTMANN, H. F.; BRUN, M. V. (2020). Metamizol and Scopolamine for Conventional or Two-Port Laparoscopic-Assisted Ovariohysterectomy in Dogs. Acta Scientiae Veterinariae, 48.

D’AVILA, G. F. L.; DA SILVEIRA, E.; BAIER, M. E.; GOUVÉA, A. S.; FAGUNDES, N.; BECK, C. A. C. (2016) Anastomosis in a Dog with Transitional Cell Carcinoma in the Vesical Trigone. Acta Scientiae Veterinariae, 44, 1–5.

DILOV, P.; ANGELOV, G.; MIHAIOV, G.; PANKOV, A.; TOTOROV, T.; ANGELOVA, T.; VRABCHEVA, V.; PARVANOV, P.; RALCHEV, I.; ZUNEV, P. (2000). Study on the local and systemic tolerance to metamizole (Analgin) in target animals. Bulgarian Journal of Veterinary Medicine, 3, 95–100.

DIPIRONA [monografia]. (2010). In: Farmacopeia brasileira. Agência Nacional de Vigilância Sanitária Fundação Oswaldo Cruz/Editora. 5ª edição. Volume 2. Brasília, 2010.

DOS SANTOS, G. G.; DIAS, E. V.; TEIXEIRA, J. M.; ATHIE, M. C. P.; BONET, I. J. M.; TAMBELI, C. H.; PARADA, C. A. (2014). The analgesic effect of dipyrone in peripheral tissue involves two different mechanisms: Neuronal KATP channel opening and CB1 receptor activation. European Journal Pharmacology, 741, 124–131.

DUARTE, I. D.; DOS SANTOS, I. R.; LORENZETTI, B. B.; FERREIRA, S. H. Analgesia by direct antagonism of nociceptor sensitization involves the arginine-nitric oxide-cGMP pathway. European Journal Pharmacology, 1992 Jul 7;217(2-3):225-7.

ELMAS, P.; ULUGOL, A. (2013). Involvement of cannabinoid CB1 receptors in the antinociceptive effect of dipyrone. Journal of Neural Transmission, 120, 1533–1538.

ESCOBAR, W.; RAMIREZ, K.; AVILA, C.; LIMONGI, R.; VANEZAS, H.; VAZQUEZ, E. (2012). Metamizol, a non-opioid analgesic, acts via endocannabinoids in the PAG-RVM axis during inflammation in rats. European Journal of Pain. 16, 676-689.

FELDMANN, D. F.; ZUEHLKE, S.; HEBERE, T. (2008) Occurrence, fate and assessment of polar metamizole (dipyrone) residues in hospital and municipal wastewater. Chemosphere, 71, 1754–1764.

FERRIGNO, C. R. A.; MARINO, P. V. T.; FERREIRA, M. P.; SANTOS, J. F.; DAL-BÓ, I. S.; PAES, F.; GALEAZZI, V. S. (2016). Use of a locking plate “notched head T plate®” for the fixation of an ilial body fracture in a dog. Semina: Ciências Agrárias, 37, 3215–3222.

FLÓR, P. B.; YAZBEK, K. V. B.; IDA, K. K.; FANTONI, D. T. (2013). Tramadol plus metamizole combined or not with anti-inflammatory drugs is clinically effective for moderate to severe chronic pain

http://www.vetnil.com.br/produtos/algivet
treatment in cancer patients. Veterinary Anaesthesia and Analgesia, 40, 316–327.

GAERTNER, J.; STAMER, U. M.; REMI, C.; VOLTZ, R.; BAUSEWEIN, C.; SABATOWSKI, R.; WIRZ, S.; MÜLLER-MUNDIT, G.; SIMON, S. T.; PRALONG, A.; NAUCK, F.; FOLLMANN, M.; RADBRUCH, L.; MEIBNER, W. (2016). Metamizole/dipyrone for the relief of cancer pain: A systematic review and evidence-based recommendations for clinical practice. Palliative Medicine, 31, 26-34.

GEISSLINGER, G.; BOCKER R.; LEVY M. (1996) Pharmacology Research. 13, 1272-1275.

GIORGI, M.; LEBKOWSKA-WIERUSZEWSKA, B.; LISOWSKI, A.; OWEN, H.; POAPOLATHEP, A.; KIM, T. W.; DE VITO, V. (2018). Pharmacokinetic profiles of the active metamizole metabolites after four different routes of administration in healthy dogs. Journal of veterinary pharmacology and therapeutics, 41(3), 428-436.

GRAFF, J.; ARABMOTLAGH, M.; CHEUNG, R.; GEISSLINGER, G.; SEBASTIAN, H. (2007). Effects of parecoxib and dipyrone on platelet aggregation in patients undergoing meniscectomy: A double-blind, randomized, parallel-group study. Clinical Therapeutics, 29, 438–447.

GUERRERO, K. S. K.; SCHWARZ, A.; WUHRMANN, R.; FELDMANN, S.; HARTNACK, S.; BETTSCHART, K.; VURAL, K.; GÜRSOY, A.; DUGAR, M. (2015). Comparison of a new metamizole formulation and carprofen for extended post-operative analgesia in dogs undergoing ovariohysterectomy. The Veterinary Journal, 204, 99–104.

GÜRSOY, A.; DEMIRAYAK, S.; ÇAPAN, G.; EROL, K.; VURAL, K. (2000). Synthesis and preliminary evaluation of new 5-pyrazolinone derivatives as analgesic agents. European Journal of Medicinal Chemistry, 35, 359-364.

GUZELLA, M. V. M.; SOUZA, M. P.; ANTUNES, L. B.; DIAS, R. X. L.; CAMPOS JUNIOR, P. C. T. (2015). Incidência de agranulocitose devido ao uso de dipirona na árnia latina. Revista de Ciências, 3, 95-103.

HARITOVA, A. (2001). Influence of metamizole and dexamethasone on amikacin pharmacokinetics in dogs. Brazilian veterinarians. Veterinary Anaesthesia and Analgesia, 41, 82–89.

HERNÁNDEZ-DORAL, V.; ALMEIDA, L. G. (2010). Pancitopenia associated with the use of perioperative analgesics in dogs and cats by Brazilian veterinarians. Veterinary Anaesthesia and Analgesia, 38, 385–393.

HESS, M.; ZYLBER-KATZ, E.; ROSENKRANZ, B. (1995). Clinical pharmacokinetics of dipyrone and its metabolites. Clinical Pharmacokinetics, 28, 216-234.

LÓPEZ-MUÑOZ, F. J.; DÍAZ-REVAL, M. I.; TERRON, J. A.; CAMPO, M. D. (2004). Analysis of the analgesic interactions between ketorolac and tramadol during arthritic nociception in rats. European journal of pharmacology, 484, 157–165.

LORENA, S.; LUNA, S. P.; LASCELLES, B. D.; CORRENTE, J. E. (2014) Current attitudes regarding the use of perioperative analgesics in dogs and cats by Brazilian veterinarians. Veterinary Anaesthesia and Analgesia, 41, 82–89.

LUCCHETTI, G.; GRANERO, A. L.; ALMEIDA, L. G. C.; BATTISTELLA, V. M. (2010). Pancitopenia associated with the use of dipirone. Relato de caso. Revista Brasileira de Clínica Médica, 8, 72-76.

LÜTHY, C.; MULTHAUP, M.; OETLIKER O.; PERISIC, M. (1983). Differential effect of acetylsalicylic acid and dipyrone on prostaglandin production in human fibroblast cultures. British Journal of Pharmacology, 79, 849–854.

MARTINS, M.; COSTA, M.; BRUNNER, C. H.; CALAZANS, S. (2015). Estudo de eficácia analgésica de metamizol, diclofenaco e propacetamol na artrite reumatoide. Revista Brasileira de Clínica Médica, 8, 72-76.

MÜLLER, D. C. M.; BASSO, P. C.; KRÜGER, R. M.; DO AMARAL, A. S.; GOMES, C.; PISSI, N. L. (2010). Hemipelvectomia in the treatment of chondrosarcoma of the acetabulum dog. Ciencia Rural, 40, 1218–1222.

NETO, R. P. S. (2011). Chronology of drug treatment of migraine attack. Headache Medicine, 2, 187-193.

OBORILOVÁ, A.; MAYER, J.; POSPÍSIL, Z.; KORÍSTEK, Z. (2002). Symptomatic intravenous antipirretic therapy: efficacy of metamizol, diclofenac, and propacetamol. Journal of Pain and Symptom Management, 24, 608-615.

OLIVEIRA, G. G. (2001). Painel Internacional de Avaliação da Segurança da Dipirona [International Panel for the Evaluation of the Safety of Dipyron]. Diário Oficial da União, sec. I, 201-202.

ORTIZ, B. C.; OLIVEIRA, C. M.; TEIXEIRA, L. G.; KOCH, M. C.; MÜLLER, V. S. (2016). Primary splenic torsion in a dog: case report. Arquivo Brasileiro de Medicina Veterinária e Zootecnia, 68, 1195–1200.

PIMPÃO, C. T.; MONTANHA, F. P.; BUDZIAK, C.; LIMA, L. A.; CAPRIGLIONE, L. G. A.; FIGUEIREDO, M.; MIKOS, P. (2009) Avaliação de carprofeno e meloxicam como antipirreticos in dogs. Revista Acadêmica: Ciência Agraria e Ambiental, 7, 331-339.
PIRES, F. D.; OLIVEIRA, V. B. (2015). Agranulocytosis related to the use of dipyrone: a review. Visão Acadêmica, 16, 187-199.

QUEIROZ, T. P.; SANTOS, P. L. DOS; ESTEVES, J. C.; STELLIN, G. M.; SHIMUZI, A. S.; BETONI JUNIOR, W.; VIEIRA, E. H. (2013). Dipyrene versus acetaminophen in the control of postoperative pain. Revista de Odontologia da UNESP, 42, 78-82.

REIS, G. M. L.; DORETTO, M. C.; DUARTE, I. D. G.; TATSUO, M. A. K. F. (2003). Do endogenous opioids and nitric oxide participate in the anticonvulsant action of dipyrone?. Brazilian journal of medical and biological research, 36(9), 1263-1268.

RICHTER, T.; PIEPER, K.; HENKE, J.; ERHARDT, W.; MATIS, U. (2007). Intraoperative analgesia in dogs with metamizole and/or fentanyl for hip replacement In: Proceedings of the AVA Autumn Meeting, Leipzig, p. 53 (2007).

RIPLINGER, A.; AIELLO, G.; CHAVES, R. O.; ANDRADES, A. O.; BECKMANN, D. V.; POLIDORO, D.; SOARES, A. V.; MAZZANTI, A. (2018). Efeitos adversos da morfina, metadona e tramadol no pós-operatório de cães submetidos à cirurgia da coluna vertebral: 180 casos (2011-2016). Pesquisa Veterinária Brasileira, 38(7), 1431-1437.

ROMERO, T. R.; RESENDE, L. C.; DUARTE, I. D. (2011). The neuronal NO synthase participation in the peripheral antinociception mechanism induced by several analgesic drugs. Nitric Oxide, 25(4), 431-435.

SARCHAHI, A. A.; VESAL, N.; KHALIGHI, F.; NAZIFI, S. (2017). Effects of preanesthetic administration of metamizole on renal function, blood parameters and bone marrow cells in healthy dogs. Comparative Clinical Pathology, 1–6.

SCHIDELKO-PRANDL, J.; MEYER-LINDBERG, A.; SCHWARZ, G.; PIEPER, K. (2019). Perioperative hypothermia in dogs receiving combined administration of acepromazin and metamizol. Tierarztliche Praxis. Ausgabe K, Kleintiere/heimtiere, 47(6), 412-418.

SCHMITZ, A.; ROßMANN, L.; KIENBAUM, P.; PAVLAKOVIĆ, G.; WERDEHAUSEN, R.; HOHLFELD, T. (2016) Dipyrene (metamizole) markedly interferes with platelet inhibition by aspirin in patients with acute and chronic pain: A casecontrol study. European Journal of Anaesthesiology, 14.

SCHÜTTER, A. F.; TÜNSMEYER, J.; KÄSTNER, S. B. (2016). Influence of metamizole on 1) minimal alveolar concentration of sevoflurane in dogs and 2) on thermal and mechanical nociception in conscious dogs. Veterinary Anaesthesia and 440 Analgesia, 43, 215–226.

SEMBENELLI, G.; WITTMAACK, M. C. N.; OLIVEIRA, L.; MORAES, P. C.; MINTO, B. W.; DIAS, L. G. G. G. (2016) Cervical Laminectomy for the Treatment of Chronic Caudal Cervical Spondylomyelopathy in a Dog. Acta Scientiae Veterinariae, 44, 1–5.

SILVA, L. C. R.; E CASTOR, M. G. M.; NAVARRO, L. C.; ROMERO, T. R. L.; DUARTE, I. D. G. (2016). κ-Opoid receptor participates of NSAIDs peripheral antinociception. Neuroscience letters, 622, 6-9.

SILVA, L. C. R.; CASTOR, M. G. M.; SOUZA, T. C.; DUARTE, I. D. G.; ROMERO, T. R. L. (2015). NSAIDs induce peripheral antinociception by interaction with the adrenergic system. Life sciences, 130, 7-11.

SILVA, L. C. R.; ROMERO, T. R. L.; GUZZO, L. S.; DUARTE, I. D. G. (2012). Participation of cannabinoid receptors in peripheral nociception induced by some NSAIDs. Brazilian Journal of Medical and Biological Research, 45(12), 1240-1243.

SOUZA, F. R.; FIGHERA, M. R.; LIMA, T. T. F.; BASTIANI, J.; BARCELLOS, I. B.; ALMEIDA, C. E.; OLIVEIRA, M. R. (2001). 3-Methyl-5-hydroxy-5-trichloromethyl-1H-1-pyrazolcarboxyamide induces antinociception. Pharmacology Biochemistry and Behavior, 68, 525.

SOUZA, V. L. S.; ESTANISLAU, C. A.; RANZANI, J. J. T.; MINTO, B. W.; KAIRALLA, L. D.; CARVALHO, C. M.; PARDINI, L. M. C.; BARONE, D. R. S.; MAMPRIM, M. J.; BRANDÃO, C. V. S. (2016). Leiomiossarcoma Vesical em Cadela – Relato de Caso. Veterinária e Zootecnia, 23, 385–390.

SPINOSA, H. S.; GÖRNIAK, S. L.; BERNARDI, M. M. Farmacologia aplicada à medicina veterinária. Rio de Janeiro, RJ 443 (Brazil). 1999. 2. Ed.5.646.

TEIXEIRA, R. C. R.; MONTEIRO, E. R.; CAMPAGNOL, D.; COELHO, K.; BRESSAN, T. F.; MONTEIRO, B. S. (2013) Effects of tramadol alone, in combination with meloxicam or dipyrone, on postoperative pain and the analgesic requirement in dogs undergoing unilateral mastectomy with or without ovariohysterectomy. Veterinary Anaesthesia and Analgesia, 40, 641–649.

ZANUZZO, F. S.; TEIXEIRA-NETO, F. J.; THOMAZINI, C. M.; TAKAHIRA, R. K.; CONNER, B.; DINIZ, M. S. (2015). Effects of dipyrone, meloxicam, or the combination on hemostasis in conscious dogs. Journal of Veterinary Emergency and Critical 452 Care, 25, 512–520.

ZELCER, S.; KOLENSKOV, Y.; KOVALYSHYN, L; PASTERNAK, D. A.; PASTERNAK, G. W. (2005). Selective potentiation of opioid analgesia by nonsteroidal anti-inflammatory drugs. Brain research, 1040, pp. 151–156.