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

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

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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, intravenosa 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 ulceração gástrica. 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

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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.

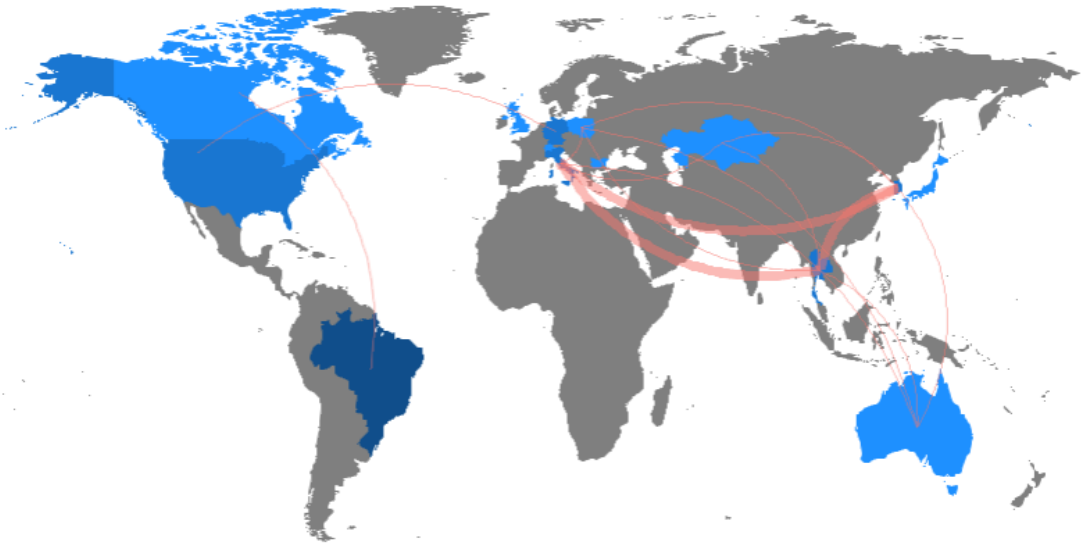

Figure 2 - Global distribution of 64 publications using dipyrone in dogs between the years 1973 to 2021. Gray represents the absence of publications, while blue represents the occurrence of studies. The more intense in the blue color was higher the number of scientific contributions. The red lines demonstrate the flow of scientific collaboration between countries.

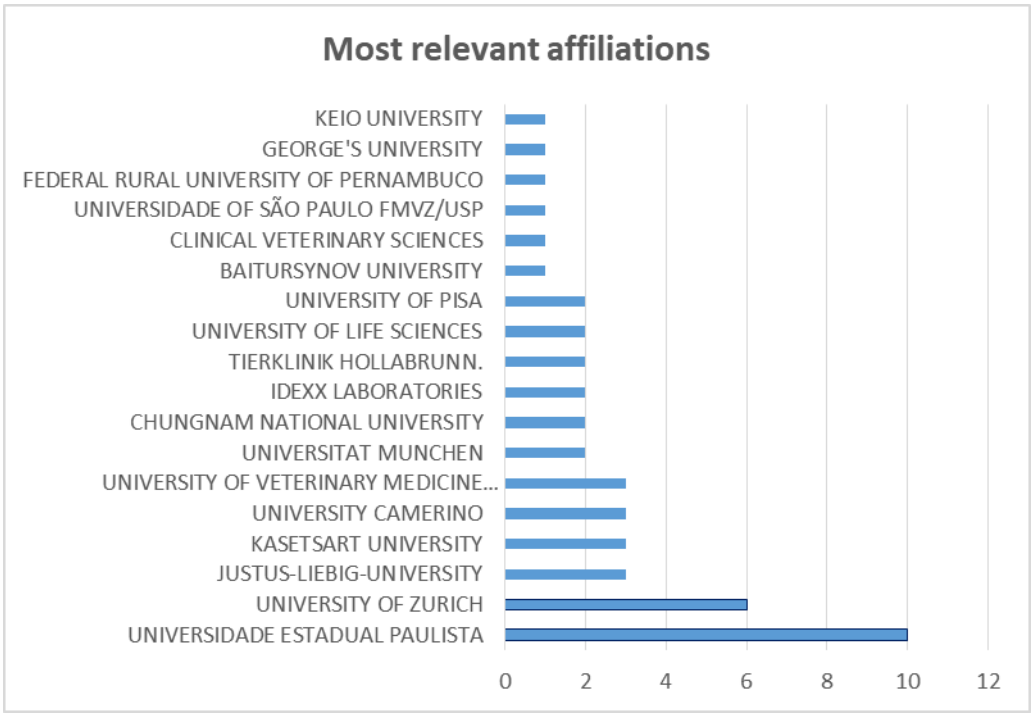

Figure 3 – Most relevant affiliations involved in studies published with dipyrone in dogs (1973 to 2021).

PHARMACOKINETICS OF DIPYRONE

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-aminoantipyrine as show 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-adrenoreceptors. 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.

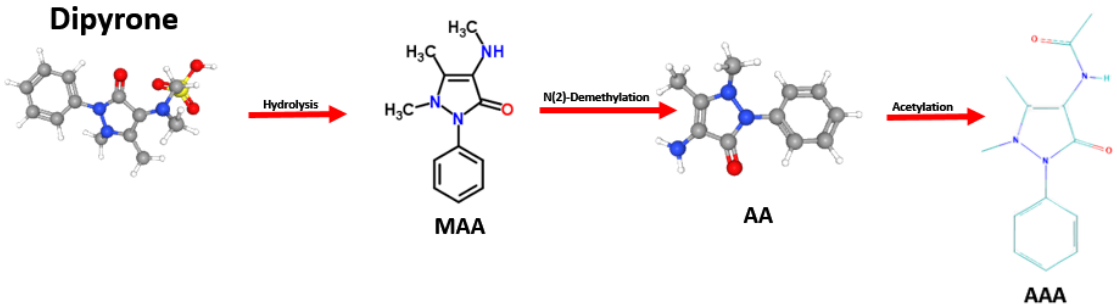

Figure 4 - Metabolic pathways of dipyrone, metabolites are: 4-methylamino antipyrine (MAA), 4-aminoantipyrine (AA), 4-acetylamino antipyrine (AAA) and 4-formylamino antipyrine (FAA) (Ariza et al. 2016).

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

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

Analgesic 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; Dalmolin 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 supra-additive analgesic effects (López-Muñoz et al., 2004; Zelcer et al., 2005; Gloria et al., 2006). Other aspect 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.

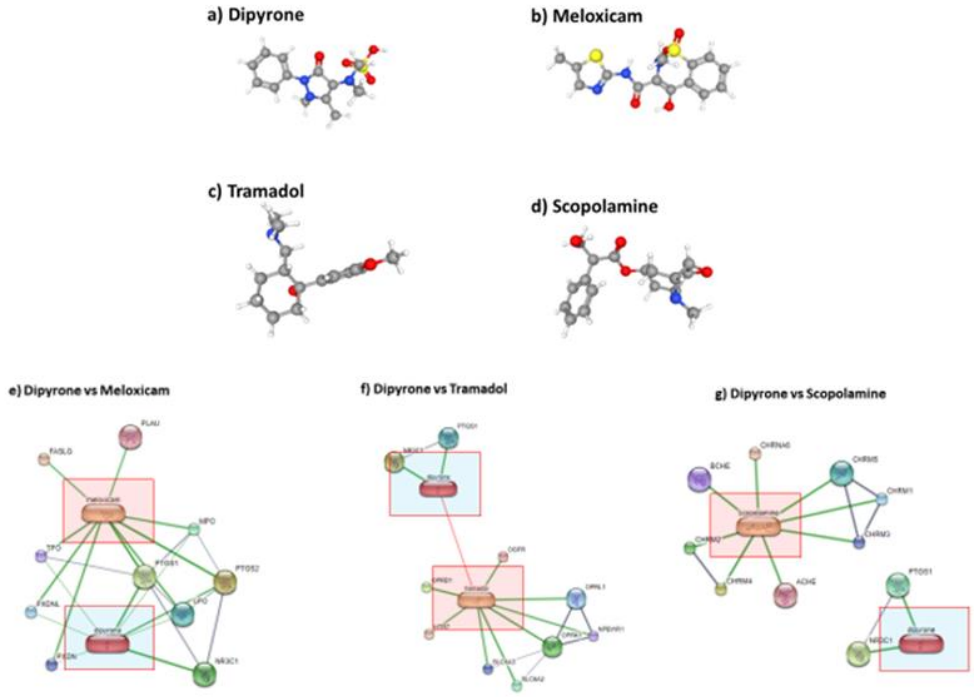

Figure 5 - 3D chemical structure, (a) dipyrone, (b) meloxicam, (c) Tramadol, (d) scopolamine and network analysis comparing the dog database using the tool Stitch http://stitch.embl.de/cgi/ (e) dipyrone vs meloxicam, (f) dipyrone vs tramadol and (g) dipyrone vs scopolamine.

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 + Meloxicam	Ferrigno et al. (2016)
Post operative	6h	VO	25	Tramadol + Meloxicam	Ortiz et al. (2016)
Post operative	6h	VO	25	Tramadol + Firocoxib	Sembenelli 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	--	Martins et al. (2015)
Oncological	24h	VO	25	--	Mulher et al. (2010)
Oncological	6h	VO	24	Tramadol + carprofeno	Stupak et al. (2016)
Antipyretic	24h	VO	25	--	Pimpão et al. (2009)
Clinical safety	8h	VO	30	--	Dilov et al. (2000)
Pre anesthetic	12h	IV, IM	30	--	Sarchahi et al. (2017)

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