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Review

Pharmacological characteristics of metamizole

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Abstract

Metamizole (dipyrone) is a popular analgetic, non-opioid drug, commonly used in human and veterinary medicine. In some cases, this agent is still incorrectly classified as a non-steroidal anti-inflammatory drug (NSAID). Metamizole is a pro-drug, which spontaneously breaks down after oral administration to structurally related pyrazolone compounds. Apart from its analgesic effect, the medication is an antipyretic and spasmolytic agent. The mechanism responsible for the analgesic effect is a complex one, and most probably rests on the inhibition of a central cyclooxygenase-3 and activation of the opioidergic system and cannabinoid system. Metamizole can block both PG-dependent and PG-independent pathways of fever induced by LPS, which suggests that this drug has a profile of antipyretic action distinctly different from that of NSAIDs. The mechanism responsible for the spasmolytic effect of metamizole is associated with the inhibited release of intracellular Ca^{2+} as a result of the reduced synthesis of inositol phosphate. Metamizole is predominantly applied in the therapy of pain of different etiology, of spastic conditions, especially affecting the digestive tract, and of fever refractory to other treatments. Co-administration of morphine and metamizole produces superadditive, antinociceptive effects. Metamizole is a relatively safe pharmaceutical preparation although it is not completely free from undesirable effects. Among these side-effects, the most serious one that raises most controversy is the myelotoxic effect. It seems that in the past the risk of metamizole-induced agranulocytosis was exaggerated. Despite the evidence showing no risk of teratogenic and embryotoxic effects, the drug must not be administered to pregnant women, although it is allowed to be given to pregnant and lactating animals. This paper seeks to describe the characteristics of metamizole in the light of current knowledge.

Key words: metamizole, analgesics, non-opioids, NSAIDs, antinociception

Introduction

Metamizole (dipyrone) is a pyrazolone derivative (Brogden 1986), introduced to pharmacotherapy in 1922 (Hinz et al. 2007). This is one of the strongest non-opioid analgesic drugs, used in both human and veterinary medicine (Baumgartner et al. 2009). At

present, metamizole is classified as a non-opioid analgesic (Vazquez et al. 2005, Chaparro et al. 2012, Escobar et al. 2012), although for years it was claimed to belong to non-steroidal anti-inflammatory drugs (NSAIDs) (Batu and Erol 2007, López-Muñoz et al. 2008, Smith et al. 2008, Domínguez-Ramírez et al. 2010). In the light of what we know today, the latter

classification appears erroneous because, in contrast to NSAIDs, the mechanism through which metamizole acts relies on the inhibition of a central cyclooxygenase-3 (COX-3) (Chandrasekharan et al. 2002, Muñoz et al. 2010).

Chemically, metamizole is sodium *N*-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-*N*-methylaminomethanesulphonate (Rogosch et al. 2012). In Poland, metamizole (as metamizole sodium) is available in the form of solutions for injections registered for human use [Amizolmet (Sanitas, Lithuania), Pyralgin (Polpharma, Poland)] and for such animal species as cattle, sheep, goats, horses, pigs and dogs [monopreparations: Biovetalgin (Biowet Drwalew, Poland), Injectio Pyralgini (Biowet Puławy, Poland), Pyralgivet (Vet-Agro, Poland), Vetalgin (Intervet International, Poland); a complex preparation containing metamizole sodium and hyoscine butylbromide: Buscopan Compositum Vet (Boehringer Ingelheim Vetmedica, Germany)]. Metamizole is one of just six non-opioid analgesics (apart from metamizole, these are carprofen, flunixin meglumine, ketoprofen and tolafenamic acid) present in preparations registered for use on cattle in Poland.

In some countries, metamizole has been withdrawn from the market (e.g. Sweden, the USA, Japan, the UK, Australia and Iran), but in many more countries (some European states, Asia, South America) it is still broadly used, both in human medicine (as an OTC drug) and in veterinary practice (Edwards et al. 2001, Wessel et al. 2006, Baumgartner et al. 2009, Imagawa et al. 2011). In Canada, metamizole is registered for use only on small animals and horses, whereas in the USA it has been prohibited from use on food producing animals (Fajt 2001, Smith et al. 2008).

Pharmacokinetics

The available literature lacks any data on the pharmacokinetic properties of metamizole in animals, although we have information about the fate of metamizole administered to people. When discussing the pharmacokinetic properties of metamizole, we actually mean the characteristics of its metabolites because metamizole is a pro-drug, which in a hydrous environment undergoes spontaneous breakdown to numerous metabolic products (Vlahov et al. 1990, Levy et al. 1995). The parent drug is detectable in blood serum for just 15 minutes after intravenous administration, but when given orally it is detectable neither in plasma nor in urine (Vlahov et al. 1990). In the digestive tract, metamizole is hydrolyzed to 4-methylaminoantipyrine (MAA) and absorbed in this form. It has been demonstrated that after oral administration of meta-

mizole in a dose of 750 mg, the bioavailability of MAA was 85%, maximum concentration (C_{max}) of this metabolite was reached in 1.2-2.0 h, and its volume of distribution (V_d) was around 1.15 l/kg. The absolute bioavailability after intramuscular and rectal administration was 87% and 54%, respectively (Levy et al. 1995). MAA is further metabolized with a mean elimination half-life ($t_{1/2_{kel}}$) of 2.6 to 3.25 h to 4-formylaminoantipyrine (FAA), which is an end-metabolite, and to 4-aminoantipyrine (AA) (Levy et al. 1995). AA is acetylated to 4-acetylaminoantipyrine (AAA) (Vlahov et al. 1990, Levy et al. 1995, Rogosch et al. 2012). MAA and AA are active metabolites, whereas AAA and FAA are compounds which do not show pharmacological activity (Weithmann and Alpermann 1985, Vlahov et al. 1990). Moreover, MAA and AA undergo further transformations to active arachidonoyl amides, whose presence was detected in the brain and spinal cord of mice (Rogosch et al. 2012). Arachidonoyl amides are formed with the participation of fatty acid amide hydrolase (FAAH), an enzyme which appears in high concentrations in the brain, hence the suggestion that these compounds are created in the CNS. However, one must not reject the possibility that these compounds originate peripherally because the liver is another organ which shows high expression of FAAH. Furthermore, it is known that metamizole derivatives (i.e. MAA, AA, FAA, AAA) can easily permeate through the blood-brain barrier and their concentration in the cerebrospinal fluid, though lower than in plasma, is sufficiently high to induce a therapeutic effect (Cohen et al. 1998).

The mechanism of the drug's activity and pharmacological effects

Although metamizole has been successfully used for over 90 years, the mechanism of its effect has not been thoroughly elucidated. For a long time, metamizole was considered to be a non-selective COX-1 and COX-2 inhibitor (Hinz et al. 2007, Pierre et al. 2007, Rogosch et al. 2012). The mechanism involved in its analgesic effect is complex (Fig. 1). Most probably, this effect is achieved through both the action of COX-3 and the impact on the opioidergic system and cannabinoid system.

The re-interpretation of the mechanisms involved in the action of this medication was encouraged by the discovery of cyclooxygenase isoforms. According to the available references, metamizole acts as a pain reliever by blocking COX-3 (Chandrasekharan et al. 2002, Schug and Manopas 2007, Muñoz et al. 2010). This mechanism, is for example, implied by the results obtained by Chandrasekharan et al. (2002), who

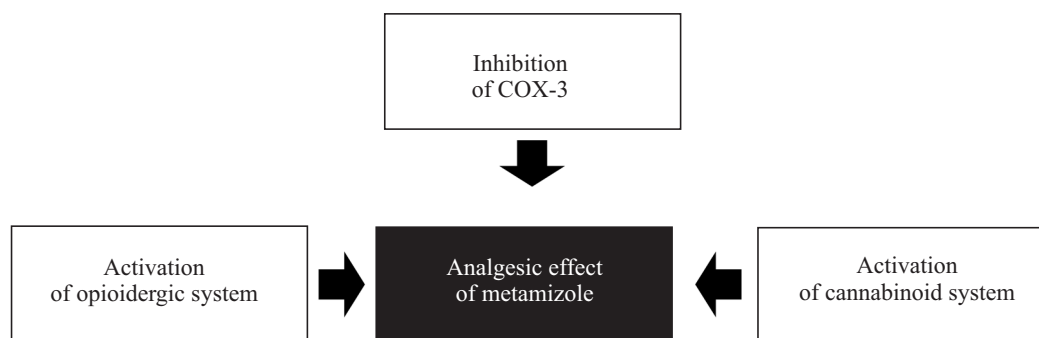


Fig. 1. Possible mechanisms responsible for the analgesic effect of metamizole.

concluded that metamizole, like acetaminophen, phenacetin or antipyrine, has an inhibitory effect on the activity of COX-3 in a dog's brain. COX-3 is a splice variant of COX-1, which occurs mainly in the CNS (Chandrasekharan et al. 2002). Retardation of COX-3 leads to a reduction in the synthesis of prostaglandin E₂ (PGE₂) (Chandrasekharan et al. 2002). As a result of the blocking of the PGE₂ synthesis in the CNS, the sensitivity of nociceptors (i.e. peripheral pain receptors) to pain mediators decreases, which also means that the excitability of these receptors is lower, and thus an analgesic effect is achieved (Chandrasekharan et al. 2002, Muñoz et al. 2010).

Irrespective of the inhibition of PGE₂ synthesis, other mechanisms participate in the production of the analgesic effect of metamizole. The cannabinoid system, which is the system which plays an important role in the regulation of pain sensation, is most probably involved. Rogosch et al. (2012) determined that arachidonoyl amides of the active metabolites of metamizole, i.e. MAA and AA, are agonistic towards type 1 (CB₁) cannabinoid receptors, which are also the receptors included in the descending antinociceptive system. It is a well-known fact that activation of CB₁ receptors reduces GABAergic transmission in periaqueductal grey matter (PAG), which disinhibits activating neurons (mainly glutaminergic ones) and initiates antinociception, as a consequence of the activation of the descending pathway (Rutkowska and Jamontt 2005). The contribution of the cannabinoid system to the analgesic mechanism of metamizole has also been implied by Escobar et al. (2012), who proved that the antinociceptive effect of this agent was reduced by a microinjection of an antagonist at the CB₁ cannabinoid receptor, either into the PAG or into the rostral ventromedial medulla (RVM).

The third mechanism most likely to be involved in the induction of metamizole's analgesic effect is the activation of the endogenous opioidergic system. This mechanism is implied by Tortorici and Vanegas (2000), who have shown that PAG microinjection

of metamizole induces antinociception in awake rats and, when carried out repetitively, induces tolerance to metamizole and cross-tolerance to morphine (PAG is the main site of opioidergic analgesia). Moreover, these investigators indicate that since the effects of PAG-microinjected metamizole are diminished by a microinjection of naloxone (i.e. an antagonist of opioidergic receptors) in the same site, these effects must be related to local endogenous opioids. Their conclusion is corroborated by other researchers, e.g. Vazquez et al. (2005), who found that the application of naloxone into the rat's PAG abolished the antinociceptive effect of systematically administered metamizole, a development suggesting that the effect is mediated by the opioidergic system (Vazquez et al. 2005).

Although for many years metamizole was classified as a NSAID, today it is thought that the drug produces only a very weak anti-inflammatory effect (Campos et al. 1999, Botting 2000, Chandrasekharan et al. 2002, Rogosch et al. 2012), which is most probably the consequence of its being a weak COX-1 and COX-2 inhibitor (Botting 2000). Unquestionably, the drug inhibits COX-3 more strongly (Chandrasekharan et al. 2002). Although it has been shown that metamizole inhibits both COX-1 and COX-2 (Campos et al. 1999, Hinz et al. 2007, Pierre et al. 2007), it is uncertain whether the effect is clinically significant because we lack a substantial body of evidence proving that this medication can cause a significant anti-inflammatory effect.

It is possible that the weak peripheral anti-inflammatory effect of the drug together with the strong inhibition of the centrally located COX-3 are connected to the high activity of FAAH in the CNS (Rogosch et al. 2012). This conclusion implies a particularly intensive conversion of metamizole to active metabolites in the CNS.

The mechanisms involved in the antipyretic action of NSAIDs have generally been attributed to their ability to block PGE₂ synthesis by inhibiting COX-1

and/or COX-2 in the CNS (Botting 2006). Similarly to NSAIDs, metamizole shows an evident antipyretic action, but the data concerning this mechanism are contradictory. Whereas some studies have reported that the antipyretic effect of dipyrone depends on inhibition of PGE₂ synthesis (Shimada et al. 1994, Kanashiro et al. 2009), others suggest that it does not (De Souza et al. 2002, Pessini et al. 2006, Malvar et al. 2011). Recently, it has been demonstrated that metamizole can block both PG-dependent and PG-independent pathways of fever induced by LPS, which suggests that this drug has a profile of antipyretic action distinctly different from that of other COX inhibitors, which could be advantageous in treating fever (Malvar et al. 2011). Interestingly, this study demonstrated that even though metamizole reduces PGE₂ concentration in the plasma and cerebrospinal fluid, it does not inhibit the hypothalamic PGE₂ synthesis, unlike indomethacin, which is a drug that belongs to NSAIDs (Malvar et al. 2011). These data suggest that the antipyretic effect of metamizole is unrelated to the inhibition of hypothalamic PGE₂ synthesis (Malvar et al. 2011).

Metamizole shows a spasmolytic effect (Gulmez et al. 2006, Hinz et al. 2007). Gulmez et al. (2006) proved the spasmolytic influence of metamizole on a guinea pig's isolated tracheal smooth muscle. Their results indicate that metamizole produced the said effect through the inhibition of the release of intracellular Ca²⁺ as a result of the reduced synthesis of inositol phosphate (IP). In their later study, these researchers demonstrated that the drug had a spirometrically and eventually clinically evident smooth muscle relaxing effect, especially on small airways, supporting *in vitro* results about the occurrence of a spasmolytic effect of dipyrone on precontracted smooth muscle. The question whether dipyrone potentiates the effect of standard bronchodilatory agents may be another research subject, as it has not yet been evaluated (Gulmez et al. 2007).

It is most probable that metamizole can affect the estrous cycle. It has been proven that this drug, unlike acetylsalicylic acid or indomethacin, stimulated the secretion of progesterone by cultured bovine luteal cells, which suggests that this effect was independent of the influence on COX-1 and COX-2 (Jaroszewski et al. 2009).

Clinical applications in people

Non-opioid analgesics are a group of medications most popular worldwide, usually administered in treatment of acute and chronic pain states. Over recent years, they have gained popularity as a medica-

tion to relieve postoperative pain; used alone to stop mild to moderate pains, but even more importantly as a component of multimodal analgesia (Schug and Manopas 2007). Very good effects have been attained in treatment of acute pain using metamizole in combination with NSAIDs, including ketoprofen (Oberhofer et al. 2005) or with opioid analgesics (López-Muñoz et al. 2008, Baumgartner et al. 2009). The efficacy of metamizole in post-operative pain therapy has been confirmed in studies conducted on humans (Edwards et al. 2001, Chaparro et al. 2012) and on animals (Imagawa et al. 2011). Bigal et al. (2002) determined that metamizole administered intravenously was effective for the acute treatment of episodic tension-type headache. Taylor et al. (1998) demonstrated the efficacy of metamizole as an analgesic in combating visceral pains. Moreover, metamizole finds some applications in the therapy of pains associated with neoplasms (Edwards et al. 2001, Hinz et al. 2007).

Owing to its strong analgesic and relaxing action, metamizole is frequently administered in the treatment of spastic states, including colics affecting the gastrointestinal, biliary or urinary tracts (Arellano et al. 1990, Edwards et al. 2001, Hinz et al. 2007). The analgesic and spasmolytic properties of metamizole make it a drug of choice in the therapy of colic pains (Arellano et al. 1990). However, despite having antipyretic properties, metamizole is not a drug of choice in the therapy of fever but is applicable in cases of fever refractory to other treatments (Hinz et al. 2007).

Clinical applications in animals

Despite the widespread administration of metamizole in veterinary practice, the relevant literature lacks reports which would assess the clinical efficacy of the drug in the therapy of animal diseases. The most important recommendations declared by manufacturers of veterinary medical preparations containing metamizole are: symptomatic treatment of pain, including colic pain, control of fever in the course of different diseases (*mastitis*, MMA syndrome in sows, swine flu), meteorism and intestinal constipation in horses, acute and chronic rheumatic diseases, as well as inflammation of the nerves, joints, muscles and tendon sheaths (Biovetalgin, summary of product characteristics). Interestingly, metamizole is not recommended for use on cats (Maddison et al. 2008).

Side effects

Compared to other non-opioid analgesics, metamizole seems to be a relatively safe drug (Bigal et al.

2002, Imagawa et al. 2011). The most common adverse effects are: gastrointestinal disorders, such as nausea, vomiting, abdominal pain and diarrhea (Edwards et al. 2001). These notwithstanding, metamizole appears to be a safer drug in terms of its influence on the digestive tract than, for example, NSAIDs. In an experiment performed on rats, which were administered metamizole twice a day for 14 days, no pathological changes within the small intestine were observed (Shnchez et al. 2002). Berenguer et al. (2002) did not demonstrate any effect of multiple administration of metamizole on experimentally induced gastric ulcer in rats. Moreover, Batu and Erol (2007) proved experimentally that the drug might have a protective effect against some types of gastric ulcers. They demonstrated that metamizole decreased the ulcer index of rats with histamine- and diethyldithiocarbamate-induced gastric ulcer, but it did not change the ulcer index of rats with stress-induced gastric ulcer. Their results suggest that the common factor engaged in the protective effect of the drug could be its ability to increase synthesis and/or release of gastric mucus. In addition, some of the protective effect of metamizole may be paradoxically due to its ability to increase the gastric PGE₂ content (Batu and Erol 2007). Thus, regarding the influence on the digestive tract, metamizole seems to be much safer than NSAIDs.

Other side effects described are headaches and dizziness, renal dysfunctions and hypersensitivity skin reactions, such as rash, urticaria or erythema (Żukowski and Kotfis 2009), which are most probably induced by an E immunoglobulin-dependent mechanism (Gómez et al. 2009).

Metamizole shows some hepatotoxic potential, but – as indicated by Drobnik (2010) – the risk of hepatic disorders during metamizole treatment is relatively low. This claim is based on the information included in the database on side effects of medications, in which 105 patients were recorded in 1997-2009, who had experienced certain disturbances in liver action following an administration of metamizole; in contrast, the number of patients reporting such disorders after taking paracetamol was about 4 500 (Drobnik 2010).

The most controversial side effect produced by metamizole seems to be agranulocytosis. For years, there has been a debate on the safety of administration of metamizole in the context of its potential myelotoxic effect. There is some evidence suggesting that after prolonged administration metamizole might cause some damage to the blood system, being responsible for leukopenia, agranulocytosis and even aplastic anemia (Hedenmalm and Spigset 2002, García-Martínez et al. 2003, Basak et al. 2010). This is the reason why the drug has been withdrawn from the

market in several countries (Wessel et al. 2006, Schug and Manopas 2007, Baumgartner et al. 2009, Basak et al. 2010). Reports by Hedenmalm and Spigset (2002) suggested that the risk of developing metamizole-induced agranulocytosis is substantial. Based on eight community cases in which patients were exposed to the drug and 10 892 prescriptions drawn in 1995-1999 in Sweden, they estimated the incidence rate at one case for 1 439 prescriptions (Hedenmalm and Spigset 2002, Ibáñez et al. 2005). More recent analyses (Maj and Lis 2002, Ibáñez et al. 2005, Basak et al. 2010) suggested that the risk of metamizole-induced agranulocytosis has been exaggerated (Żukowski and Kotfis 2009). A study conducted by Basak et al. (2010) in Poland, from April 2006 to March 2007, implies that the risk rate of the occurrence of metamizole-induced agranulocytosis was 0.7 case per 1 million adult Poles. It has been reported that while the total number of person-days of exposure to oral metamizole sodium in Poland between 1997 and 2001 was 141 941 459, a crude estimate of the incidence of agranulocytosis associated with metamizole sodium was 0.2 cases per million person-days of use (Maj and Lis 2002). In turn, Ibáñez et al. (2005) claimed that the frequency of metamizole-induced agranulocytosis was 0.56 cases per million inhabitants per year.

The results of *in vitro* studies (García-Martínez et al. 2003) did not prove that metamizole was characterized by higher myelotoxicity than diclofenac or acetylsalicylic acid, that is the drugs which are not associated with a significant risk of agranulocytosis. In the above research, no effect of metamizole administered in a therapeutic concentration on the granulocytic differentiation process and on the apoptosis of terminally differentiated granulocytes was demonstrated. It was only at concentrations much above the ones obtained *in vivo* that metamizole-induced apoptosis affected about 30% of promyelocytes, while granulocytic differentiated cells were more resistant to this apoptotic action. When the effects of metamizole were compared with those of acetylsalicylic acid and diclofenac on cell viability, at equivalent concentrations used in analgesic and antipyretic therapy, their apoptotic effects were found to be similar (García-Martínez et al. 2003).

The above investigations prove that agranulocytosis attributable to metamizole is rare, although it will be necessary to conduct a large-scale, prospective research project in countries where metamizole is prescribed routinely in order to arrive at a univocal solution to this problem.

The mechanism of metamizole-induced agranulocytosis has not been completely clarified, but it is generally accepted that this disorder is of immunological origin (García-Martínez et al. 2003). One of

the hypotheses states that the underlying mechanism may involve cytotoxic lymphocytes which generate killer cells against drug-coupled bone marrow granulocytic cells (Nikolova et al. 2012). There are also reports suggesting that the side effect discussed could be a result of a direct toxic effect of the drug towards granulocytes (Utrecht et al. 1995). There is also evidence indicating that the mechanism of pyrazolone-induced agranulocytosis involves the oxidation of these compounds into a reactive intermediate, which then reacts with neutrophils (Utrecht et al. 1995). The direct toxic mechanism of the mentioned adverse effect is not supported by the previously cited study of García-Martínez et al (2003), because it did not reveal any toxic influence of the drug on granulocytes. These authors, having excluded the toxic effect of metamizole, indirectly support the hypothesis that the mechanism of agranulocytosis induced by this drug should be of immunological origin (García-Martínez et al. 2003). From the point of view of the immunological mechanism involved in metamizole-induced agranulocytosis, the severity of this side effect should be unrelated to the dose taken. However, it is possible that higher doses or longer exposure are more likely to induce sensitization (Ibáñez et al. 2005).

It should be added that the accessible literature lacks any data on the incidence of agranulocytosis or other haematotoxic effects attributed to administration of metamizole in animals.

Interactions with other analgesics

Combinations of analgesic drugs with different mechanisms of action may produce effective analgesia and limit side effects by reducing doses of one or both compounds (López-Muñoz et al. 2008). This is also true for metamizole, as it has been proven that co-administration of metamizole with morphine (López-Muñoz et al. 2008, Domínguez-Ramírez et al. 2010), paracetamol (Muñoz et al. 2010) or ketoprofen (Oberhofer et al. 2005) is able to produce potentiation of antinociceptive effects. Domínguez-Ramírez et al. (2010) demonstrated that co-administration of morphine and metamizole under acute treatment produced a significantly higher antinociceptive effect than that obtained with morphine alone. Interestingly, simultaneous administration of both drugs caused a nearly triple increase in the C_{max} of morphine, which was most likely caused by the enzymatic inhibition of the glucuronosyl-transferase system involved in the metabolism of morphine. Domínguez-Ramírez et al. (2010) claim that the discussed effect was caused by mutual competition of

both drugs for the same enzymatic mechanism of their metabolism. Thus, most probably the potentiation of morphine antinociception by metamizole originates not only from the interaction at the pharmacodynamic level, but also from the modification of the pharmacokinetics of morphine. An experiment conducted by López-Muñoz et al. (2008) implies that the synergism between metamizole and morphine is of a super-additive nature; these researchers demonstrated that co-administration of the two drugs ensured a potentiated and better antinociceptive effect than each drug given individually or their expected theoretical aggregated effects. This finding verifies the existence of some superadditive synergism between metamizole and morphine.

Contraindications

Compared to opioid analgesics or NSAIDs, there are few contraindications for use of metamizole in humans and animals (Baumgartner et al. 2009, Imagawa et al. 2011). Due to a possible haematotoxic effect, the drug is contraindicated in patients with a history or presence of blood dyscrasia. The question whether metamizole is safe for pregnant women is unclear. The research completed by Bar-Oz et al. (2005) and da Silva Dal Pizzol et al. (2009) suggests that administration of metamizole for pregnant women did not cause fetal malformation, congenital abnormalities, intrauterine death, preterm birth or low birth weight, which may indicate that metamizole is safe to pregnant women. Nevertheless, the pregnancy category of metamizole is C (first and second trimester) and D (third trimester) (Nikolowa et al. 2012), which means that the drug can be prescribed to pregnant women only exceptionally and under a doctor's supervision. It is worth mentioning that the manufacturer of the drug containing metamizole sodium and registered in Poland (Pyralgín) states that pregnancy and lactation periods are contraindications to administration of this preparation. The situation is different in the case of animals because the producer of the metamizole sodium preparation (Biovetalgín) registered for use on many animal species allows its administration to pregnant and lactating animals. It is thought that metamizole does not demonstrate the contraindications or limitations usually observed with NSAIDs (Edwards et al. 2001, Baumgartner et al. 2009, Imagawa et al. 2011), which is most probably associated with the fact that – unlike most NSAIDs – the drug is a very weak inhibitor of COX-1. For instance, it is acceptable to administer metamizole to patients with gastric ulcerations, which are a contraindication to the use of NSAIDs (Pyralgín, summary of

product characteristic, Sánchez et al. 2002, Imagawa et al. 2011).

This paper seeks to present the current state of knowledge on metamizole. As the gathered information implies, although metamizole has been used in medicine for a very long time, the mechanism of its action is scantily recognized, despite significant progress made in this respect over recent years. The high analgesic efficacy of metamizole as well as its antipyretic and spasmolytic effects make it a very important pharmaceutical agent in the therapy of various diseases and disorders in humans and in animals. The greatest concern related to the administration of metamizole is the risk of causing agranulocytosis, but the most recent research indicates that metamizole is a relatively safe drug with respect to the risk of inducing this complication. Nevertheless, in the case of long-lasting therapy with metamizole the patient should be monitored in the context of this risk and other haematological disorders.

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