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REVIEW ARTICLE

Efficacy, Safety, Quality Assurance of Isomers of Non-Steroidal Anti-Inflammatory Drugs: Dexketoprofen and Dexibuprofen

Elena Litvinova[1*], Mariya Zarichkova[2], Svitlana Kovalenko[1], Olga Posylkina[1], Olena Tkachenko[1], Anastasiia Lisna[1]

1. *Department of Management, Economy and Quality Assurance in Pharmacy, National University of Pharmacy of the Ministry of Health of Ukraine, Kharkiv, Ukraine.*
2. *Department of Management and Economics of Pharmacy, Institute of Pharmacy Professionals Qualification Improvement, National University of Pharmacy of the Ministry of Health of Ukraine, Kharkiv, Ukraine.*

Abstract

The aim of this work is to analyze and systematize data on efficacy, safety, and quality assurance for NSAID isomers-dexketoprofen and dexibuprofen. Studies were conducted using databases on the Internet: PubMed; Food and Drug Administration, European Medicines Agency. It has used retrospective, logical, systematic and analytical methods. The results of a multifaceted analysis of sources of data of clinical use proved the high analgesic efficacy of dexketoprofen and dexibuprofen in acute and chronic pain of various etiologies, such as toothache, dysmenorrhea, pain after surgery, muscle pain, headache, back pain, pain from bone metastases, etc. To achieve the effect obtained with the use of 1 dose of racemic NSAIDs, half the dose of their active isomers is sufficient. The high clinical effectiveness of dexketoprofen, dexibuprofen combines with their relative tolerance, in particular from the gastrointestinal tract. In large part, the safety of dexketoprofen is due to the presence of only the active S (+) - enantiomer of ketoprofen, dexibuprofen is due to the presence of only active S (+) - ibuprofen, which eliminates the side effects associated with the influence of the R (-) - enantiomers. The results of the analysis of quality assurance of generic dexketoprofen (class 1 of biopharmaceutical classification system) and dexibuprofen (class 2 of biopharmaceutical classification system) during the biowaiver procedure are systematized. It has been shown that not only high permeability and high solubility, but also the composition of the drug excipients are important for pharmaceutical equivalence in vitro. Based on the results research findings presented, it is possible to optimize the technological process and analytical methods, which allows taking into account critical factors and ensuring the quality of the medicine and its bioequivalence to the reference drug.

Keywords: *Dexketoprofen, Dexibuprofen, Efficacy, Safety, Quality assurance.*

Introduction

The first-line medicines for the treatment of acute pain syndromes of any degree of manifestation are non-steroidal anti-inflammatory drugs (NSAIDs), which have firmly taken their place in the drug therapy of various diseases manifested by pain or inflammation [1, 2]. Their widespread use was also facilitated by the absence of a number of side effects inherent in opiates: sedation, respiratory depression and addiction. Most of these medicines are considered reasonably safe. Over the past 30 years, the number of NSAIDs has increased significantly, and now this group includes a large number of drugs that differ in chemical structure, features of action and application. The most important mechanism of NSAIDs action is the ability to inhibit cyclooxygenase (COX), an enzyme that catalyzes the conversion of free polyunsaturated fatty acids into prostaglandins (PG), as well as other eicosanoids – thromboxanes (primarily thromboxane A2, TrA2) and prostacyclin (PG-I2). It has been proven that PGs have multifaceted biological activity: they are mediators of the inflammatory response; sensitize receptors to pain mediators (histamine, bradykinin) and mechanical influences, lowering the threshold of sensitivity; increase the sensitivity of the

hypothalamic centers of thermoregulation to the action of endogenous pyrogens (interleukin-1, etc.), play an important physiological role in protecting the mucous membrane of the gastrointestinal tract; affect kidney function [3]. There are at least two isoforms of COX (COX-1 and COX-2); while COX-2 is not normally present, but is formed in the inflammatory focus. The anti-inflammatory effect of NSAIDs is primarily associated with the inhibition of COX-2. At the same time, the development of side effects of treatment is associated mainly with the inhibition of the physiological isoform of COX-1. NSAIDs have a unique combination of properties-analgesic, anti-inflammatory, antipyretic and antiplatelet, which leads to their extremely widespread use in all areas of medicine. It is generally known that there are no safe drugs, but NSAIDs hold a special place as the most commonly used and leading in terms of side effects medicines [4-7].More than 30 million people in the world use NSAIDs every day [8].

To a large extent, the widespread use of NSAIDs is facilitated by an increase in the proportion of elderly and senile people in most countries of the world and, accordingly, an increase in the prevalence of diseases of the musculoskeletal system with increasing age of patients [9, 10]. The most common adverse effects of these medicines are gastrointestinal complications-inhibition of prostaglandin synthesis in the mucous membrane reduces prostaglandin-mediated production of protective mucus and bicarbonates, that leads to erosions and ulcers, which can be complicated by bleeding or perforation (the risk of side effects increases with age) [11].

The study of the mechanisms of action of NSAIDs was an incentive to create new medicines with a lower incidence of side effects. Selective COX-2 inhibitors have been developed that are highly effective and less likely to cause gastrointestinal side effects, as shown in numerous clinical studies. However, it should be noted that the analgesic potential of selective COX-2 inhibitors in comparison with non-selective NSAIDs is not always sufficient.

In addition, large-scale studies have shown that selective COX-2 inhibitors can cause cardiovascular complications [12, 13]. Moreover, the frequency of adverse reactions increases with age. Particular attention in the treatment of acute pain syndromes is given to NSAIDs with high analgesic activity, short half-life, and low incidence of side effects and rapid onset of analgesic effect [14]. A promising area of research is the use of a more effective and safer enantiomer of NSAIDs [15]. Enantiomers (optical isomers) are pairs of optical antipode substances characterized by opposite in sign and equal in magnitude rotations of polarization with the identity of all other physical and chemical properties (except for reactions with other optically active substances and physical properties in an optically active medium).

Biologically active macromolecules (enzymes, hormones, receptors) are by their nature single enantiomers, and their interactions with other molecules are stereoselective. If the NSAID is a racemic mixture, analgesic activity is associated only with the properties of one enantiomer. The aim of this work is to analyze and systematize data on efficacy, safety, and quality assurance for NSAID isomers-dexketoprofen and dexibuprofen.

Materials and Methods

Studies were conducted using databases on the Internet: PubMed; Food and Drug Administration, European Medicines Agency. It has used retrospective, logical, systematic and analytical methods.

Results and Discussion

Efficiency

Among non-selective NSAIDs, the dexketoprofen deserves special attention. Dexketoprofen is a water-soluble salt of the dextrorotatory enantiomer of ketoprofen; the medicine is from the group of propionic acid derivatives with well-studied analgesic and anti-inflammatory properties [16, 17]. Ketoprofen has been used in Europe since 1971. However, ketoprofen, like all non-selective NSAIDs, can cause serious adverse reactions, primarily from the gastrointestinal tract.

There are two enantiomers of ketoprofen-levorotatory (R-ketoprofen) and dextrorotatory (S-ketoprofen), which have a similar chemical structure and differ in physical characteristics (three-dimensional spatial configuration of the molecule and the direction of rotation of polarization) and pharmacological properties.

It has been shown that S-ketoprofen has the ability to inhibit the isoenzyme COX-1 and COX-2, while the levorotatory enantiomer R-ketoprofen lacks such activity.

Dexketoprofen has significant pharmacological benefits. Unlike ketoprofen, which is a racemic mixture of two enantiomers in a 50: 50 ratio, dexketoprofen contains 99.9% of the dextrorotatory enantiomer of S-ketoprofen; therefore its analgesic activity is two times higher than that of ketoprofen. Its active dose, respectively, is 2 times less, and its bioavailability is significantly higher-the maximum concentration is observed 15-45 minutes after oral administration, which is approximately 2 times higher than that of ketoprofen.

After taking 25 mg of dexketoprofen, the maximum plasma concentration of the drug is 3.1 mg/L, which provides a high analgesic effect of the medicine. In addition, metabolites of levorotatory R (-) - ketoprofen are responsible for the development of side effects. This avoids the development of side effects and determines the low toxicity of dexketoprofen [18-20]. Currently, in the numerous randomized controlled trials, it has been obtained evidence of good efficacy, rapid onset of therapeutic action and relative safety of short-term use of dexketoprofen for pain of a wide variety of origins.

Dexketoprofen is currently the drug of choice for the treatment of acute and chronic musculoskeletal pain. The efficacy and safety of dexketoprofen was compared with the equivalent enantiomeric dose of ketoprofen in a multicenter, randomized, double-blind, 3 week study of adult patients with pain due to osteoarthritis of the knee. Patients were randomly assigned to receive dexketoprofen 25 mg 3 times a day (n=89) or ketoprofen 50 mg 3 times a day (n=94).

The results demonstrate that dexketoprofen 25 mg 3 times a day is more effective than ketoprofen 50 mg 3 times a day for the short-term symptomatic treatment of knee osteoarthritis. Dexketoprofen is more tolerated than ketoprofen. Therefore, replacing racemic ketoprofen with dexketoprofen may be beneficial and more effective in clinical practice [21]. J. L. Marenco et al. compared the efficacy of dexketoprofen 25 mg 3 g/day and diclofenac 50 mg 3 g/day in 117 patients with osteoarthritis of the knee.

After 2 weeks of treatment, the intensity of pain on the visual analog scale decreased in 43% of patients in the dexketoprofen group and in 29% of patients in the diclofenac group. This indicates a greater effectiveness of dexketoprofen [22]. In a retrospective study K. Brzeziński and J. Wordliczek compared the effect of oral administration of dexketoprofen 50 mg/day and diclofenac 150 mg/day in 185 patients with chronic nonspecific back pain. The course of therapy lasted 6 weeks. Comparison of the two NSAIDs showed a higher efficacy of dexketoprofen at all stages of treatment in patients with chronic nonspecific back pain [23].

For a long time, dexketoprofen has been used successfully to treat dysmenorrhea. In a randomized, double-blind, parallel, placebo-controlled single- and multiple-dose study, the analgesic efficacy and safety of the dexketoprofen/tramadol 25 mg/75 mg combination was assessed versus the individual drugs (dexketoprofen 25 mg and tramadol 100 mg) at moderate to severe acute pain after abdominal hysterectomy. The results of the study provided strong evidence of the superiority of the combination of dexketoprofen/tramadol 25 mg/75 mg over the individual components in the treatment of moderate to severe acute pain, which was confirmed by the efficacy of a single dose, a sustained effect with repeated dosing and a good safety profile [24].

Use of dexketoprofen in complex analgesic therapy in patients in orthopedic surgery has great importance for assessing the role in urgent pain relief. A double-blind, randomized, placebo-controlled study evaluated the safety and analgesic efficacy of perioperative dexketoprofen in 30 patients. It was shown that the use of dexketoprofen 25 mg 4 times a day 24 hours before and within 48 hours after hip arthroplasty resulted not only in a significant reduction in postoperative pain, but also in a significant decrease in the need for morphine use [25].

The indication for the use of dexketoprofen is also the relief of pain in dental practice. The efficacy and tolerability of single doses of dexketoprofen 12.5 mg, 25 mg and 50 mg and ketoprofen 50 mg were compared in a double-

blind, randomized, placebo-controlled study in 210 patients with moderate to severe pain after removal of the third molar. The results demonstrate that dexketoprofen 25 mg is at least as effective as racemic ketoprofen 50 mg in the treatment of postoperative toothache.

A more rapid onset of action of dexketoprofen was found [26]. Dexketoprofen is an effective drug for the relief of moderate to intermediate pain in the supervision of oncological patients in outpatient practice, especially if the pain is caused by metastases in the skeletal bone or a primary malignant tumor affecting the bone tissue.

Dexketoprofen does not cause tolerance or physical dependence and is an alternative to narcotic analgesics at the first stage of pain syndrome treatment in cancer patients. In a randomized double-blind study, M. J. Rodriguez et al. studied the effectiveness of oral dexketoprofen 25 mg 4 g/day compared with ketorolac 10 mg 4 g/day in patients with pain due to bone metastases. Dexketoprofen has shown an effective analgesic effect in relieving pain in cancer patients [27].

It is known that acute and chronic administration of opioids has an inhibitory effect on antibody production, natural killer cell activity, cytokine expression and phagocytic activity. In recent years, cyclooxygenase-2 (COX-2) inhibitors have been actively investigated as new analgesics that can replace opioids or reduce their dose. In animal experiments after surgical removal of the grafted tumor, the functional activity of the immune system cells of mice is higher in the case of analgesia with dexketoprofen than in the use of omnopon.

Thus, the potential therapeutic effects of dexketoprofen have been identified: preservation of the functional activity of immune system cells in oncological surgery [28].Dexketoprofen has also been used successfully to treat migraines. In a randomized, double-blind, single-center, crossover, placebo-controlled study, the efficacy and tolerability of dexketoprofen at doses of 25 and 50 mg compared with placebo in the relief of acute migraine attacks with and without aura in 93 patients. The results of this study indicate that dexketoprofen at a dose of 25 and 50 mg is an effective drug in the treatment of acute migraine attacks, while a dose of 50 mg may be more effective. Dexketoprofen was well tolerated: the safety profiles for both doses of the drug did not differ from that of placebo.

The speed of achieving the effect, which is a distinctive characteristic of the studied NSAIDs, is an additional argument in favor of considering dexketoprofen as the drug of choice for the relief of migraine attacks regardless of the presence of an aura [29].There are data from a meta-analysis of the clinical use of dexketoprofen. The clinical efficacy of dexketoprofen was demonstrated in the systematic review and meta-analysis of 35 studies involving 6,380 patients with acute and chronic pain. In 12 of these studies, dexketoprofen was significantly more effective than placebo. In studies with active control, dexketoprofen showed at least the same efficacy as comparator drugs, but had a faster onset of action.

The safety of the study drugs for severe adverse events, such as gastrointestinal bleeding and cardiovascular events was not evaluated given the short duration of treatment [30].J. Barden et al published in the Cochrane Library a meta-analysis [31] of 14 randomized controlled trials of the efficacy of a single dose of ketoprofen at a dose of 25-50 mg (968 patients) versus placebo (520 patients) and 7 randomized controlled trials of efficacy single dose of 10-25 mg dexketoprofen (681 patients) versus placebo (289 patients).

A meta-analysis showed that dexketoprofen in the indicated doses provided effective pain relief for 4.5 hours. Ketoprofen provided effective pain relief for 5 hours, while its dose was 2 times higher, and the frequency of side effects did not differ from that of placebo. The analgesic potential of dexketoporophen is supported by an updated Cochrane meta-analysis of 24 randomized, double-blind, placebo-controlled studies in 5220 subjects.

A comparative study was conducted between oral doses of ketoprofen 50 mg and placebo, and dexketoprofen 25 mg and placebo. Studies have examined single doses of drugs after wisdom tooth extraction, as well as after other types of surgery, mainly hip replacement and gynecological operations. In dental studies, the effectiveness of both drugs was significantly higher than with other surgical procedures. Both drugs were well tolerated in single doses [32]. The effect of dexketoprofen supplementation versus

placebo on pain control in patients with migraine attacks was studied. The meta-analysis included five randomized clinical trials with 794 patients.

The authors conclude that dexketoprofen improves pain control scores at 48 hours and reduces the need for emergency medications in patients with migraine attacks [33].The Cochrane review of 3 randomized, double-blind studies with 1,853 participants showed the analgesic efficacy of a single fixed dose of oral dexketoprofen plus tramadol versus placebo for moderate to severe postoperative pain in adults. The incidence of adverse events was low [34].The enantiomers of NSAIDs also include dexibuprofen, a stereoisomer of ibuprofen, which has the ability to inhibit COX at clinically significant concentrations.

It has been shown that dexibuprofen exhibits pronounced analgesic and anti-inflammatory activity, the level of which significantly exceeds racemic ibuprofen. In addition, dexibuprofen is more bioavailable than R (-)-ibuprofen [35]. The benefits of dexibuprofen over racemic ibuprofen have been demonstrated in a number of studies.

Long-term studies have shown that dexibuprofen (600 or 1200 mg) is equally effective compared to a double dose of racemic ibuprofen (2400 mg) in 178 patients with osteoarthritis of the hip (treatment for 12 months). In the tolerability study, the overall incidence of clinical adverse events for dexibuprofen was 15.2% (gastrointestinal tract 11.7%, central nervous system 1.3%, skin 1.3%, other 0.9%) [36].

The blind multicenter study investigated the safety and tolerability of dexibuprofen 400 mg (daily dose 800 mg) versus ibuprofen 400 mg (daily dose 1600 mg) for 14 days in 489 patients with painful osteoarthritis of the hip or knee. Adverse reactions from the gastrointestinal tract were reported in 8 patients (3.3%) in the dexibuprofen group and in 19 patients (7.8%) in the ibuprofen group. For dexibuprofen, statistically significant efficacy is shown. The authors conclude that dexibuprofen is as effective as ibuprofen and has a statistically significant better safety profile [37].

There are comparative studies of dexibupprofen with other NSAIDs. In a randomized, double-blind, controlled study in 148 patients with hip osteoarthritis, the efficacy and safety of treatment with dexibuprofen 800 mg or celecoxib 200 mg per day for 15 days was assessed. The authors conclude that dexibuprofen has at least the same efficacy and comparable safety/ tolerability profile as celecoxib [38].

According to the recommendations of the World Health Organization, ibuprofen is the drug of choice for fever and pain in children. Dexibuprofen is also used in children along with ibuprofen. The multicenter, randomized, double-blind study assessed the antipyretic efficacy and tolerability of dexibuprofen versus ibuprofen in children with upper respiratory tract infection fever. The authors conclude that dexibuprofen is as effective and tolerable as ibuprofen. Doses of 5 mg/kg and 7 mg/kg dexibuprofen instead of 10 mg/kg ibuprofen will be sufficient to control fever in children [39].

The double-blind multicenter study investigated the safety and efficacy of dexibuprofen (3.5 or 7 mg/kg) compared with ibuprofen (5 or 10 mg/kg) in 264 children with fever. The authors conclude that dexibuprofen (3.5 or 7 mg/kg) is as effective and tolerable as ibuprofen for upper respiratory tract infection fever in children [40].

The effectiveness of dexibuprofen has also been shown in dysmenorrhea. In the randomized, double-blind study in 102 patients, dexibuprofen was associated with dose-dependent effective pain relief; this effect was at least equivalent to a double dose of ibuprofen. With a lower loading dose, dexibuprofen enhances the treatment options for this condition [41].

There is an analysis of post-marketing studies and Meta-analyzes of the use of dexibuprofen. At a dose ratio of 0.5: 1, dexibuprofen is reported to be at least as effective as racemic ibuprofen; 75% of the maximum daily dose of dexibuprofen was equal to the efficacy of 100% maximum daily dose of diclofenac.

The clinical efficacy of dexibuprofen in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of the hip, and osteoarthritis of the knee, lumbar-vertebral syndrome, ankle deformity and dysmenorrhea was revealed; good tolerance compared to other NSAIDs [42].

There are systematized data from the study of dexibuprofen in the Cochrane database. Dexibuprofen was found to have a high response rate: 51/96 (53%) of participants experienced at least 50% pain relief with dexibuprofen 200 mg and 35/50 (70%) with dexibuprofen 400 mg versus 75/147 (51% with racemic ibuprofen 400 mg and 12/62 (13%) with placebo [43].

Dexibuprofen in various conditions accompanied by moderate pain has shown equal efficacy compared with a double dose of racemic ibuprofen. It was also found that to achieve the effect obtained with 1 dose of racemic ibuprofen, half the dose of dexibuprofen (ratio 2: 1) is sufficient. In addition, it has the same potency as diclofenac, naproxen and celecoxib, while showing better tolerability.

Thus, dexibuprofen is effective in the treatment of pain syndrome of various etiologies and is characterized by an acceptable safety profile. Thus, dexketoprofen and dexibuprofen have many years of positive experience of use in outpatient and polyclinic practice, as well as in hospitals for therapeutic, surgical, traumatological, dental, neurological, oncological, gynecological and other profiles. It was also found that to achieve the effect obtained with the use of 1 dose of racemic NSAIDs, half the dose of their active isomers is sufficient.

Safety

The main side effects characteristic of dexketoprofen, dexibuprofen, as well as for whole group of NSAIDs, are dyspeptic symptoms, sometimes (0.1-1% of cases) there are chills, swelling of the extremities, photosensitization, rarely (0.01-0.1%) -erosive and ulcerative lesions of the gastrointestinal tract, very rarely (less than 0.01%) -allergic reactions and bronchospasm, renal dysfunction, increased blood pressure. Side effects are usually dose-dependent, and a decrease in the therapeutic dose leads to a decrease in the risk of their occurrence. Addiction syndrome has not been reported with dexketoprofen or dexibuprofen.

The safety profile of dexketoprofen was assessed in a post-marketing study of NSAIDs in a large sample of patients with mild to moderate acute pain observed by general practitioners [44, 45]. A total of 7,337 patients were included in the analysis. 5,492 patients received dexketoprofen at doses ranging from 12.5 to 75 mg, and 511 patients received ibuprofen/dexibuprofen. Dexketoprofen was associated with the lowest incidence of adverse events (3.6%), comparable to paracetamol (2.7%), ibuprofen/dexibuprofen (4.1%).

Dexketoprofen was similar to ibuprofen in gastrointestinal tolerability, while the highest prevalence of gastrointestinal complications was observed in the piroxicam and aceclofenac groups. The clinical efficacy and safety of dexketoprofen have been demonstrated in a systematic review and meta-analysis of 35 studies involving 6,380 patients with acute and chronic pain. The frequency of adverse events was generally low.

The frequency of discontinuation due to the development of adverse events was equally low for dexketoprofen and comparison drugs (ketoprofen, diclofenac, tramadol, paracetamol + opioid) [46]. There is a multicenter study that assessed the risk of developing gastrointestinal complications when using dexketoprofen in clinical practice (2813 episodes of gastrointestinal bleeding reported in 18 hospitals in Spain and Italy). 41% of bleeding was associated with the intake of various NSAIDs.

The risk of developing this complication (the odds ratio was used) while taking dexketoprofen was 4.9. This was higher than with ibuprofen (3.1), diclofenac (3.7) and nimesulide (3.2), but lower than with meloxicam (5.7), and much lower than with aspirin (8.0), ketoprofen (10.0), and especially ketorolac (24.7). Most of the cases of bleeding that occurred while taking dexketoprofen was associated with its use in a daily dose exceeding 50 mg.

Patients received dexketoprofen at a dose of less than 50 mg, the risk was significantly lower – odds ratio 2.3 (while taking ketoprofen less than 200 mg/day -4.8). The risk was significantly increased in patients with peptic ulcer disease and/or bleeding from the upper gastrointestinal tract, as well as in those taking antiplatelet drugs [47, 48]. There are results of studies over 5 years of 4836 patients who received dexibuprofen in clinical and post-marketing trials.

Only 3.7% of patients reported adverse drug reactions and 3 serious adverse drug

reactions (0.06%). At a dose ratio of 1: 0.5 (ibuprofen versus dexibuprofen), at least equivalent efficacy has been demonstrated in models of acute mild to severe somatic and visceral pain. Dexibuprofen has proven at least comparable efficacy to diclofenac, naproxen and celecoxib, and has been shown to be well tolerated [49].

The effect of a two-week treatment with dexibuprofen versus ibuprofen and diclofenac on plasma pepsinogen concentrations and the gastrointestinal mucosa in 60 patients with rheumatological disease receiving chronic NSAID therapy was evaluated. The authors conclude that dexibuprofen showed a lower incidence of damage to the mucous membrane of the gastrointestinal tract and intestines than in the case of ibuprofen and diclofenac. This effect was not mediated by modifications in plasma pepsinogen levels [50].Thus, in most of the above studies and reviews, the authors, along with the efficacy of dexketoprofen, dexibuprofen, noted the safety of their use.

Assessment of Some Parameters of Quality Assurance of Medicine Registration Dossier

The problem of quality assurance of generic drugs is extremely urgent all over the world. Most of the original medicines have a huge number of generics. According to the guideline on the investigation of bioequivalence, a generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies [51].

One of methods to prove bioequivalence of generic and reference medicine products for solid dosage forms of systemic exposure with immediate-release for oral use is simplified procedure of registration for generic medicine products, that is called “biowaiver” and is based on biopharmaceutical classification system (BCS) of active substances and category of drug regarding dissolution in media of gastrointestinal tract [52].

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability.

When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows: class I-high solubility, high permeability; class II – low solubility, high permeability; class III-high solubility, low permeability; class IV – low solubility, low permeability. It is known that medicinal products belonging to I, III class of BCS, do not require studies of bioavailability and bioequivalence in vivo.

The therapeutic equivalence of these drugs is confirmed on the basis of in vitro equivalence studies, taking into account the following characteristics: solubility and permeability of the active ingredient; profiles of dissolution of generic and reference drugs in three dissolution media with pH values of 1.2, 4.5 and 6.8; information on excipients included in the composition of the medicinal product; possible risks for patients in the event of an incorrect decision to refuse proof of bioequivalence *In Vivo*.

Class II medicines are only eligible for the biowaiver procedure in countries using the WHO criteria and then only in the case of a weak acid that is highly soluble at pH 6.8. In addition, the drug should not have a narrow therapeutic index (efficacy / safety line) and a steep dose-response curve, and should not be tablets for use in the oral cavity. According to the data of Garcia-Arieta et al., Marival Bermejo et al., dexketoprofen is classified as Class I of the BCS. This allows for the registration of the drug according to pharmaceutical equivalence data in vitro in three dissolution media with pH values of 1.2, 4.5 and 6.8 [53, 54].

There are data on the validation of methods for studying the bioqualence of dexketoprofen tablets. In a study by Garcia-Arieta et al. [53] three of the four dexketoprofen medicines from different pharmaceutical companies did not show bioequivalence for C_{max} in the first in vivo bioequivalence study. Based on in vitro studies, the authors conclude that BCS biowaivers for class I drugs should be granted only when dissolution with the paddle apparatus is complete in 30 min at 50 rpm.

The quality of the pharmaceutical excipients is also of great importance: any change in the composition of the excipients or film can significantly change the quality of the drug, its bioavailability, and lead to toxic or allergic phenomena. In a study by Bermejo Marival et al. it has been found that the presence of the excipient that has an alkalizing effect (calcium monohydrogen phosphate) in the tablet form of dexketoprofen leads to a greater degree of dissolution of the drug and failing of bioequivalence requirements [54].

Dexibuprofen is practically insoluble in water, but it is readily soluble in most organic solvents like methanol, methylene chloride, and acetone, and is soluble in aqueous solution of alkali hydroxides andcarbonates. It is slightly soluble in a buffer medium of pH 6.8 and very slightly soluble in a buffer medium of pH 4.5. Dexibuprofen is a BCS class II drug, showing high permeability and pH-dependent solubility, that is, a high solubility according to BCS requirements only above a certain pH value [55].

Hanif A.M. et al evaluated the quality and compared different generic drugs of dexibuprofen available in market of Karachi, Pakistan. The study is based on evaluation of physical chemical parameters of five different brands. Moreover, a comparative dissolution profile of selected brands of dexibuprofen was also performed by applying numerous approaches. Results of all the selected generic drugs of dexibuprofen met all the compendial requirements. Interpretation of the entire aforementioned test was evaluated using model independent, model- dependent and one - way Anova [56].

Analytical methods of quality control of a medicinal product, as well as the results of studies on their validation, are part of the registration dossier for a medicinal product. Correct analytical techniques are required at the stage of pharmaceutical development of a medicinal product.

Awad H. et al. reported a high-performance liquid chromatography-diode array detector method for quantifying dexibuprofen using ovomucoid chiral stationary phase. The authors conclude that this method is specific, accurate, reliable and exhibiting stability and can be successfully used for routine analysis of in bulk drug and dexibuprofen tablets [57].

Muralidharan S. et al. developed a high-performance liquid chromatographic and a ultraviolet methods for the quantitative determination of dexibuprofen in a pharmaceutical dosage form. The UV method was carried out with λ max at 222.0 nm. The proposed method can be applied for routine dexibuprofen analysis and monitoring the quality of the drugs [58].

Based on the results of the studies presented, it is possible to optimize the technological process and analytical methods, which allows taking into account critical factors and ensuring the quality of the medicine and its bioequivalence to the reference drug. It should also be noted that dexketoprofen, dexibuprofen do not have a narrow therapeutic index.

Conclusion

- The results of a multifaceted analysis of sources of data of clinical use proved the high analgesic efficacy of dexketoprofen and dexibuprofen in acute and chronic pain of various etiologies, such as toothache, dysmenorrhea, pain after surgery, muscle pain, headache, back pain, pain from bone metastases, etc.

- Analysis of sources of data shows that the high clinical effectiveness of dexketoprofen, dexibuprofen combines with their relative tolerance, in particular from the gastrointestinal tract. In large part, the safety of dexketoprofen is due to the presence of only the active S (+) - enantiomer of ketoprofen, dexibuprofen is due to the presence of only active S (+) - ibuprofen, which eliminates the side effects associated with the influence of the R (-) - enantiomers.

- Using sources of data of the study of dexketoprofen pharmaceutical equivalence it has been shown that not only high permeability and high solubility, but also the composition of the drug excipients are important for pharmaceutical equivalence in vitro. The presence of a filler that has an alkalizing effect (calcium monohydrophosphate) in tablet form of dexketoprofen leads to a greater degree of dissolution of the drug and violation of bioequivalence requirements.

- Sources of data of the study of the

dissolution profile of 5 generic drugs of dexibuprofen using various approaches are presented. The drugs were chemically and pharmaceutically equivalent.

- Based on the results research findings presented, it is possible to optimize the technological process and analytical methods, which allows taking into account critical factors and ensuring the quality of the medicine and its bioequivalence to the reference drug. It should also be noted that dexketoprofen, dexibuprofen do not have a narrow therapeutic index.

References

1. Felson DT (2016) Safety of Nonsteroidal Antiinflammatory Drugs. New England Journal of Medicine, 375(26): 2595-96.
2. World Health Organization Model List of Essential Medicines (2019) 21th edition (updated).
3. Ghlichloo I, Gerriets V (2020) Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). In StatPearls. Treasure Island (FL): StatPearls Publishing.
4. Ibraheem A, Humade S (2018) The Incidences of Use the Over Counter Drugs. Journal of Global Pharma Technology, 10(08):67-72.
5. Bindu S, Mazumder S, Bandyopadhyay U (2020) Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Organ Damage: A Current Perspective. Biochemical Pharmacology, 180:114147.
6. Walker C, Biasucci LM (2018) Cardiovascular Safety of Non-Steroidal Anti-Inflammatory Drugs Revisited. Postgraduate Medicine, 130(1):55-71.
7. Cooper C, Chapurlat R, Al-Daghri N, Herrero-Beaumont G, Bruyère O, et al (2019) Safety of Oral Non-Selective Non-Steroidal Anti-Inflammatory Drugs in Osteoarthritis: What Does the Literature Say? Drugs & Aging, 36(1):15-24.
8. Gunaydin C, Bilge SS (2018) Effects of Nonsteroidal Anti-Inflammatory Drugs at the Molecular Level. The Eurasian Journal of Medicine, 50(2):116-121.
9. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J (2018) A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. Aging and Disease, 9(1):143-50.
10. Atzeni F, Masala IF, Sarzi-Puttini P (2018) A Review of Chronic Musculoskeletal Pain: Central and Peripheral Effects of Diclofenac. Pain and Therapy, 7(2):163-77.
11. Bjarnason I, Scarpignato C, Holmgren E, Olszewski M, Kim D, et al (2018) Mechanisms of Damage to the Gastrointestinal Tract From Nonsteroidal Anti-Inflammatory Drugs. Gastroenterology, 154(3):500-514.
12. Khan S, Andrews KL, Chin-Dusting JPF (2019) Cyclo-Oxygenase (COX) Inhibitors and Cardiovascular Risk: Are Non-Steroidal Anti-Inflammatory Drugs Really Anti-Inflammatory? International Journal of Molecular Sciences, 20(17):4262.
13. Varga Z, Sabzwari SRA, Vargova V (2017) Cardiovascular Risk of Nonsteroidal Anti-Inflammatory Drugs: An Under-Recognized Public Health Issue. Cureus, 9(4):e1144.
14. Bellomo RG, Carmignano SM, Palermo T, Cosenza L, Saggini A, et al (2017) Nonsteroidal Anti-Inflammatory Drugs: Integrated Approach to Physical Medicine and Rehabilitation. Nonsteroidal Anti-Inflammatory Drugs, 67.
15. Hardikar MS (2008) Chiral Non-Steroidal Anti-Inflammatory Drugs - a Review. Journal of the Indian Medical Association, 106(9):615-18,622,624.
16. Hanna M, Moon JY (2019) A Review of Dexketoprofen Trometamol in Acute Pain. Current Medical Research and Opinion, 35(2):189-202.
17. Mauleón D, Artigas R, García ML, Carganico G (1996) Preclinical and Clinical Development of Dexketoprofen. Drugs, 52(5):24-45.
18. Barbanoj M J, I Gich, R Artigas, D Tost, C Moros, R M Antonijoan, M L García, D Mauleón (1998) "Pharmacokinetics of Dexketoprofen Trometamol in Healthy Volunteers after Single and Repeated Oral Doses." *Journal of Clinical Pharmacology* 38, S1: 33S-40S.
19. Barbanoj MJ, Antonijoan RM, Gich I (2001) Clinical Pharmacokinetics of Dexketoprofen. Clinical Pharmacokinetics, 40(4):245-62.

20. Walczak JS (2011) Analgesic Properties of Dexketoprofen Trometamol. Pain Management, 1(5):409-16.

21. Beltrán J, Martín-Mola E, Figueroa M, Granados J, Sanmartí R, Artigas R, et al (1998) Comparison of Dexketoprofen Trometamol and Ketoprofen in the Treatment of Osteoarthritis of the Knee. Journal of Clinical Pharmacology, 38(S1):74-80.

22. Marenco J.L., Pérez M, Navarro FJ, Martinez FG, Beltran J, Salvatierra D, et al (2000) A Multicentre, Randomised, Double-Blind Study to Compare the Efficacy and Tolerability of Dexketoprofen Trometamol versus Diclofenac in the Symptomatic Treatment of Knee Osteoarthritis. Clinical Drug Investigation, 19(4):247-56.

23. Brzeziński K, Wordliczek J (2013) Comparison of the Efficacy of Dexketoprofen and Diclofenac in Treatment of Non-Specific Low Back Pain. Annals of Agricultural and Environmental Medicine, 1:52-56.

24. Moore RA, McQuay HJ, Tomaszewski J, Raba G, Tutunaru D, Lietuviete N, et al (2016) Dexketoprofen/Tramadol 25 Mg/75 Mg: Randomised Double-Blind Trial in Moderate-to-Severe Acute Pain after Abdominal Hysterectomy. BMC Anesthesiology, 16 (9).

25. Iohom G, Walsh M, Higgins G, Shorten G (2002) Effect of Perioperative Administration of Dexketoprofen on Opioid Requirements and Inflammatory Response Following Elective Hip Arthroplasty. British Journal of Anaesthesia, 88(4):520-26.

26. McGurk M, Robinson P, Rajayogeswaran V, De Luca M, Casini A, Artigas R, et al (1998) Clinical Comparison of Dexketoprofen Trometamol, Ketoprofen, and Placebo in Postoperative Dental Pain. Journal of Clinical Pharmacology, 38:46-54.

27. Rodríguez MJ, Contreras D, Gálvez R, Castro A, Camba MA, Busquets C, et al (2003) Double-Blind Evaluation of Short-Term Analgesic Efficacy of Orally Administered Dexketoprofen Trometamol and Ketorolac in Bone Cancer Pain. Pain, 104(1-2):103-10.

28. Sydor RI, Shevchenko T, Khranovska NM, Skachkova OV, Skivka LM (2016) The Effect of Perioperative Analgesic Drugs Omnopon and Dexketoprofen on the Functional Activity of Immune Cells in Murine Model of Tumor Surgery. The Ukrainian Biochemical Journal, 88(4):40-47.

29. Mainardi F, Maggioni F, Pezzola D, Zava D, Zanchin C (2014) Dexketoprofen Trometamol in the Acute Treatment of Migraine Attack: A Phase II, Randomized, Double-Blind, Crossover, Placebo-Controlled, Dose Optimization Study. The Journal of Pain: Official Journal of the American Pain Society, 15(4):388-94.

30. Moore RA, Barden J (2008) Systematic Review of Dexketoprofen in Acute and Chronic Pain. BMC Clinical Pharmacology, 8:11.

31. Barden J, Derry S, McQuay HJ, Moore RA (2009) Single Dose Oral Ketoprofen and Dexketoprofen for Acute Postoperative Pain in Adults. The Cochrane Database of Systematic Reviews, 4: CD007355.

32. Gaskell H, Derry S, Wiffen PJ, Moore RA (2017) Single Dose Oral Ketoprofen or Dexketoprofen for Acute Postoperative Pain in Adults. The Cochrane Database of Systematic Reviews, 5:CD007355.

33. Yang B, Xu Z, Chen L, Chen X, Xie Y (2019) The Efficacy of Dexketoprofen for Migraine Attack: A Meta-Analysis of Randomized Controlled Studies. Medicine, 98(46):e17734.

34. Derry S, Cooper TE, Phillips T (2016) Single Fixed-Dose Oral Dexketoprofen plus Tramadol for Acute Postoperative Pain in Adults. Cochrane Database of Systematic Reviews, 9(9):CD012232.

35. Gabard B, Nirnberger G, Schiel H, Mascher H, Kikuta C, Mayer JM (1995) Comparison of the Bioavailability of Dexibuprofen Administered Alone or as Part of Racemic Ibuprofen. European Journal of Clinical Pharmacology, 48(6): 505-11.

36. Mayrhofer F (2001) Efficacy and Long-Term Safety of Dexibuprofen [S (+)-Ibuprofen]: A Short-Term Efficacy Study in Patients with Osteoarthritis of the Hip and a 1-Year Tolerability Study in Patients with Rheumatic Disorders. Clinical Rheumatology, 20(S1):22-29.

37. Zamani O, Böttcher E, Rieger JD, Mitterhuber J, Hawel R, Stallinger S, et al (2014) Comparison of Safety, Efficacy and Tolerability of Dexibuprofen and Ibuprofen in the Treatment of Osteoarthritis of the Hip or Knee. Wiener Klinische Wochenschrift, 126(11-12):368-75.

38. Hawel R, Klein G, Singer F, Mayrhofer F, Kähler ST (2003) Comparison of the Efficacy and Tolerability of Dexibuprofen and Celecoxib in the Treatment of Osteoarthritis of the Hip. Int. Journal of Clinical Pharmacology and Therapeutics, 41(4):153-64.

39. Yoon JS, Jeong DC, Oh JW, Lee KJ, Lee HS, Koh YY, et al (2008) The Effects and Safety of Dexibuprofen Compared with Ibuprofen in Febrile Children Caused by Upper Respiratory Tract Infection. British Journal of Clinical Pharmacology, 66(6):854-60.

40. Kim CK, Callaway Z, Choung JT, Yu JH, Shim KS, Kwon EM (2013) Dexibuprofen for Fever in Children with Upper Respiratory Tract Infection: Dexibuprofen for Fever in Children. Pediatrics International, 55(4):443-49.

41. Kollenz C, Phleps W, Kaehler ST (2009) ADIDAC Trial: Analgesia with Dexibuprofen versus Ibuprofen in Patients Suffering from Primary Dysmenorrhea: A Crossover Trial. Gynecologic and Obstetric Investigation, 67(1):25-31.

42. Phleps W (2001) Overview on Clinical Data of Dexibuprofen. Clinical Rheumatology, 20(S1):15-21.

43. Derry S, Best J, Moore RA (2013) Single Dose Oral Dexibuprofen [S (+)-Ibuprofen] for Acute Postoperative Pain in Adults. The Cochrane Database of Systematic Reviews, 10:CD007550.

44. Carne X, Rios J, Torres F (2009) Postmarketing Cohort Study to Assess the Safety Profile of Oral Dexketoprofen Trometamol for Mild to Moderate Acute Pain Treatment in Primary Care. Methods and Findings in Experimental and Clinical Pharmacology, 31(8):533-40.

45. Vellucci R (2010) The oral trometamol dexketoprofene in the treatment of mild-moderate pain. Farmaci, 9(2):1-9.

46. Moore RA, Barden J (2008) Systematic Review of Dexketoprofen in Acute and Chronic Pain. BMC Clinical Pharmacology, 8:11.

47. Laporte JR, Ibáñez L, Vidal X, Vendrell L, Leone R (2004) Upper Gastrointestinal Bleeding Associated with the Use of NSAIDs: Newer versus Older Agents. Drug Safety, 27(6):411-20.

48. Llorente Melero MJ, Tenías Burillo JM, Del Val Antoñana A, Zaragoza Marcet A (1999) Influence of Nonsteroidal Anti-Inflammatory Drugs on Clinical Course in Upper Gastrointestinal Tract Bleeding. Revista Espanola De Enfermedades Digestivas: Organo Oficial De La Sociedad Espanola De Patologia Digestiva, 91(7):497-507.

49. Kaehler ST, Phleps W, Hesse E (2003) Dexibuprofen: Pharmacology, Therapeutic Uses and Safety. InflammoPharmacology, 11(4-6):371-83.

50. Gómez BJ, Caunedo A, Redondo L, Esteban J, Sáenz-Dana M, Blasco M, et al (2006) Modification of Pepsinogen I Levels and Their Correlation with Gastrointestinal Injury after Administration of Dexibuprofen, Ibuprofen or Diclofenac: A Randomized, Open-Label, Controlled Clinical Trial. Int. Journal of Clinical Pharmacology and Therapeutics, 44(4):154-62.

51. EMA. Guideline on the investigation of bioequivalence (2010) Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

52. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System Guidance for Industry (2017) U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Available from: https://www.fda.gov/media/70963/download

53. Garcia-Arieta A, Gordon J, Gwaza L, Mangas-Sanjuan V, Álvarez C, Torrado JJ (2015) Agitation Rate and Time for Complete Dissolution in BCS Biowaivers Based on Investigation of a BCS Biowaiver for Dexketoprofen Tablets. Molecular Pharmaceutics, 12(9):3194-3201.

54. Bermejo M, Kuminek G, Al-Gousous J, Ruiz-Picazo A, Tsume Y, Garcia-Arieta A, et al. (2019) Exploring Bioequivalence of Dexketoprofen Trometamol Drug Products with the Gastrointestinal Simulator (GIS) and Precipitation Pathways Analyses. Pharmaceutics, 11(3):122.

55. Rehnasalim, Sivakumar R, Krishnapillai, Sajeeth C, Haribabu (2013) Biowaiver monograghs of dexibuprofen. International journal of pharmaceutical, chemical and biological sciences, 3(2):424-435.

56. Hanif AM, Sial AA, Ali H, Zafar F, Baig MT, Bushra R, et al (2018) Dexibuprofen: Statistical Assessment of Drug Release Kinetics and Investigative Quality Perspective. Pakistan Journal of Pharmaceutical Sciences, 31(5):2157-62.

57. Awad H, Aboul-Enein HY, Lashin S (2012) A Validated Enantioselective HPLC Assay of Dexibuprofen in Dexibuprofen Tablet Formulations: Enantioselective HPLC Assay of Dexibuprofen. Biomedical Chromatography, 26(4):502-6.

58. Muralidharan S, Meyyanathan SN (2011) Development and Validation of a HPLC and an UV Spectrophotometric Methods for Determination of Dexibuprofen in Pharmaceutical Preparations. ISRN Pharmaceutics: 948314.

