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Research Article

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Clinical Pharmacology of Ketoprofen

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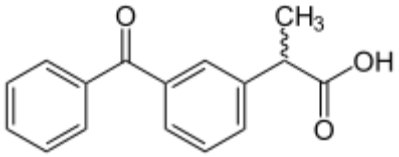
Abstract

Ketoprofen is approved for use in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, pain, ankylosing spondylitis, acute gouty arthritis, tendinitis, bursitis, headache, postoperative dental pain and swelling, and primary dysmenorrhoea. Ketoprofen is rapidly absorbed following oral administration, is bound to plasma protein to 99%, is rapidly eliminated with an elimination half-life of 0.9 to 3.3 hours, and the dose of ketoprofen is 25 to 50 mg thrice-daily or 4 times-daily. The efficacy and safely of ketoprofen, the treatment of patients with ketoprofen, and the trials conducted with ketoprofen have been reviewed. Ketoprofen is hydroxylated into 3-hydroxy-ketoprofen by CYP2C8 and by CYP2C9 and is conjugated with glucuronic acid by UGT2B7. The concentration of ketoprofen in human tissues has been reviewed, and following topical application, ketoprofen accumulates in semitendinosus muscle and in tendon more extensively than in plasma. The pharmacokinetics of ketoprofen have been reviewed and following oral administration the time to reach the peak concentration of ketoprofen is 1.94±1.25 hours. The interaction of ketoprofen with drugs has been reviewed and ketoprofen is a safe drug and limited information is available about the toxicity induced by ketoprofen. The aim of this study is to review the efficacy and safely of ketoprofen, the treatment of patients with ketoprofen, and the trials conducted with ketoprofen. In addition, the metabolism of ketoprofen, the concentration of ketoprofen in human tissues, the pharmacokinetics of ketoprofen, the interaction of ketoprofen with drugs, and the toxicity induced by ketoprofen have been reviewed.

Keywords: Drug-interaction; Efficacy-safely; Ketoprofen; Metabolism; Pharmacokinetics; Tissue-concentration; Toxicity; Treatment & trials

Introduction

Ketoprofen is a propionic acid derivative and is a nonselective cyclooxygenase inhibitor. Ketoprofen is approved for use in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, pain, ankylosing spondylitis, acute gouty arthritis, tendinitis, bursitis, headache, postoperative dental pain and swelling, and primary dysmenorrhoea. Ketoprofen is comparable in efficacy to aspirin for the control of the signs and symptoms of rheumatoid arthritis and osteoarthritis. Ketoprofen is rapidly absorbed following oral administration, is bound to plasma protein to 99%, is rapidly eliminated with an elimination half-life of 0.9 to 3.3 hours, the dose of ketoprofen is 25 to 50 mg thrice-daily or 4 times-daily, and the anti-inflammatory dose is 50 to 75 mg thrice-daily or 4 times-daily. Ketoprofen is hydroxylated into 3-hydroxy-ketoprofen by CYP2C8 and by CYP2C9, is conjugated with glucuronic acid by UGT2B7, and ketoprofen undergoes an enterohepatic recirculation. Ketoprofen causes adverse-effects in about 30% of patients and the adverse-effects are usually gastrointestinal and mild [1].



Ketoprofen molecular structure (molecular weight = 254.285 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "ketoprofen efficacy, safely", "ketoprofen treatment", "ketoprofen trials", "ketoprofen metabolism", "ketoprofen tissue

concentration", "ketoprofen pharmacokinetics", "ketoprofen drug-interaction", and "ketoprofen toxicity". In addition the book: Goodman@Gilman's. The Pharmacological basis of Therapeutics [1] has been consulted.

Results

Efficacy and safely of ketoprofen

Eight studies have been reported on the efficacy and safely of ketoprofen. A single-dose of 25 to 100 mg of ketoprofen was administered to 177 patients undergoing dental extraction and ketoprofen effectively and safely relieved the pain and was well-tolerated [2]. A total of 19,880 patients aged 72.2±6.7 years suffering for pain received ketoprofen. The overall efficacy of ketoprofen was rated as excellent or good in 70.7% of patients, the tolerability of ketoprofen was judged excellent in 60.8% of patients, good in 24.0% of patients, moderate in 8.7% of patients, and poor in 5.1% of patients. Ketoprofen caused adverse-effects in only 15.3% of patients and only 4.5% of patients interrupted the treatment because the adverse-effects. Thus ketoprofen effectively and safely relieved pain in old patients [3]. Ketoprofen was administered at the daily dose of 50 to 200 mg, ibuprofen was administered at the daily dose of 600 to 1,800 mg, and diclofenac was administered at the daily dose of 75 to 150 mg to patients suffering from pain. Ketoprofen effectively and safely relieved the pain and ketoprofen was found to be more active than ibuprofen and diclofenac in relieving the pain [4]. Patients undergoing hysterectomy received either ketoprofen at the daily dose of 50 mg or diclofenac at the daily dose of 75 mg. Ketoprofen effectively and safely relieved the postsurgical pain and was more active than diclofenac in relieving the pain and ketoprofen induced fewer adverse-effects than diclofenac [5]. Forty patients, undergoing mandibular third molar tooth extraction, received either ketoprofen at the daily dose of 100 mg (N = 20) or diclofenac at the daily dose of 75 mg (N = 20). Ketoprofen was more efficacy and safer than diclofenac in relieving the pain [6]. Sixty patients undergoing head or neck surgery received either ketoprofen at the daily dose of 100 mg (N = 30) or metamizole at the daily dose of 2.5 mg (N = 30). Ketoprofen effectively and safely relieved postsurgical pain as metamizole [7]. A total of 252 patients with moderate-to-severe pain due to hip or knee surgery received either dexketoprofen trometamol at the daily dose of 50 mg (N = 152) or ketoprofen at the daily dose of 100 mg (N = 100) and both treatments were administered thrice-daily over two days. Both treatments effectively and safely relieved postsurgical pain and were well-tolerated [8]. The efficacy and safely of ketoprofen were compared to those of diclofenac in patients with osteoarthritis of the hip and/or the knee. One-hundred-eighteen patients received 200 mg once-daily of ketoprofen and 121 patients received 75 mg twice-daily of diclofenac. Both treatments effectively and safely relieved the pain and were well-tolerated [9].

Treatment of patients with ketoprofen

Eleven studies on the treatment of patients with ketoprofen have been reported. The transdermal treatment with ketoprofen is safer than the oral treatment because transdermal treatment induces fewer adverse-effects [10]. Of 65 patients with renal colic disease, 51 patients had crystalluria (78.5%), five patients had acute colitis (7.7%), four patients had severe myositis (6.1%), and five patients had radiculitis (7.7%). All patients received ketoprofen intravenously at the daily dose of 100 mg and this treatment had powerful anti-inflammatory and analgesic effects and effectively treated acute renal colic disease [11]. Ketoprofen is an effective treatment of various forms of rheumatic, traumatic, and postsurgical pain [12]. Topical ketoprofen 2.5% gel applied twice-daily has clinical benefits in patients with a different musculoskeletal diseases and this treatment is well-tolerated [13]. Patients undergoing abdominal surgery received ketoprofen at the daily dose of 100 mg and this treatment improved the quality of analgesia without causing adverse-effects [14]. It was compared the relative analgesic efficacy of low-dose ketoprofen (6.25 mg, 12.5 mg, and 25 mg) to ibuprofen (200 mg) and to placebo in 175 patients with moderate-to-severe postoperative pain secondary to extraction of impacted third molar tooth. Ketoprofen 12.5 mg and 25 mg provided significantly greater relief of pain than ibuprofen 200 mg. The two higher doses of ketoprofen provided similar analgesia, and no additional benefit was obtained by increasing the dose of ketoprofen to 25 mg. Thus ketoprofen administered at the dose of 12.5 mg is an appropriate dose to relief pain caused by tooth extraction [15]. The efficacy and tolerability of single-doses of dexketoprofen trometamol 12.5 mg, 25 mg, and 50 mg of ketoprofen were compared in 210 patients with moderate-to-severe pain after removal of one mandibular impacted third molar tooth. Dexketoprofen trometamol administered at the dose of 25 mg is effective as the ketoprofen administered at the dose of 50 mg in the treatment of postsurgical dental pain. The onset of action was more rapidly with dexketoprofen trometamol suggesting that dexketoprofen trometamol is the most appropriate treatment of pain caused by the tooth extraction [16]. Eighty-five patients undergoing hip replacement surgery under spinal anaesthesia received either ketorolac intravenously at the dose of 90 mg followed by infusion at a rate of 90 mg every 15 hours, or diclofenac intravenously at the dose of 75 mg followed by infusion of 75 mg every 15 hours, or ketoprofen intravenously at the dose of 100 mg followed by infusion of 100 mg every 15 hours. The treatments effectively relieved postsurgical pain and were well-tolerated [17]. It was compared the efficacy of a single-dose of ketoprofen 25 mg, acetaminophen 1,000 mg, and placebo in treatment of headache. Ketoprofen demonstrated a more rapid onset of analgesia than

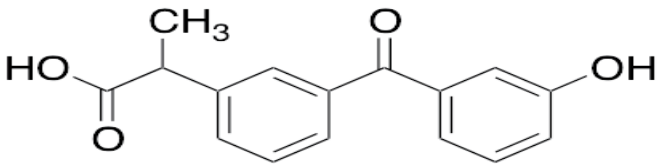
acetaminophen and placebo [18]. One-hundred-forty women undergoing Caesarean section received either diclofenac at the daily dose of 150 mg (N = 40) or ketoprofen at the daily dose of 200 mg (N = 50) or placebo (N = 50). Diclofenac and ketoprofen relieved postsurgical pain more effectively than placebo and were well-tolerated [19]. A total of 183 patients with osteoarthritis of the knee received either dexketoprofen trometamol at the dose of 25 mg thrice-daily (N = 89) or ketoprofen at the dose of 50 mg thrice-daily (N = 94). After three weeks of treatment, the relief of pain was significantly higher (P-value < 0.05) in patients treated with dexketoprofen trometamol. In addition, the clinical improvement occurred in 75% of patients treated with dexketoprofen trometamol and in 50% of patients treated with ketoprofen. The symptomatic treatment of osteoarthritis of the knee is better with dexketoprofen trometamol than with ketoprofen [20].

Trials conducted with ketoprofen

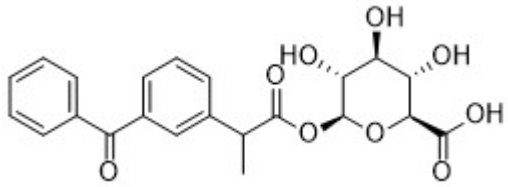
Nine trials conducted with ketoprofen have been reported. A double-blind, randomized, multicentre, prospective trial was conducted in 55 male patients, aged 35 to 74 years and weighing 57 to 119 kg, with osteoarthrosis of the hip or the knee who received 200 mg of ketoprofen in the morning and in the evening. Both the morning and the evening dose of ketoprofen reduced the degree of pain and stiffness and improved the ability of joint movement. The reduction in degree of pain was significantly higher (P-value < 0.01) for the morning dose. Ketoprofen given once-daily in the morning and in the evening effectively treated osteoarthrosis of the hip or the knee and was well-tolerated [21]. A double-blind, clinical trial was conducted in 50 patients suffering from the osteoarthritis of the hip who received ketoprofen at the daily dose of 200 mg. This treatment effectively cured the osteoarthritis of the hip and was well-tolerated [22]. A double-blind, crossover trial was conducted in 84 patients suffering from osteoarthritis of the hip and/or the knee who received either 200 mg once-daily of ketoprofen sustained-release tablets or 100 mg twice-daily of normal formulation of ketoprofen and both treatments effectively cured the patients and were well-tolerate [23]. A double-blind, parallel, multicentre trial was conducted in 102 patients with rheumatoid arthritis. Fifty patients received ibuprofen at the daily dose of 1,200 to 2,400 mg and 52 patients received ketoprofen at the daily dose of 150 to 300 mg. Ketoprofen was well-tolerated and treated the rheumatoid arthritis as ibuprofen [24]. A comparative, controlled trial was conducted in 40 patients suffering from rheumatoid arthritis, osteoarthrosis, or ankylosing spondylitis who received either ketoprofen at the dose of 100 mg twice-daily (N = 20) or ibuprofen at the dose of 400 mg thrice-daily (N = 20) and both treatments lasted three months. Ketoprofen reduced the pain, the duration of morning stiffness, and the inflammation more effectively than ibuprofen. The adverse-effects, notably nausea, epigastric discomfort, and abdominal pain, were more frequent and severe in patients who received ketoprofen [25]. A multicentre, randomized, active-controlled, open-label, parallel-group, non-inferiority, phase III, randomized trial was conducted in 236 patients with osteoarthritis of the knee who received either ketoprofen at the dose of 30 mg twice-daily (N = 118) or diclofenac at the dose of 15 mg twice-daily (N = 118) and both treatments lasted three weeks. After three weeks of treatment, ketoprofen significantly (P-value < 0.05) reduced the pain score more extensively than diclofenac. The adverse-effects were similar in patients treated with ketoprofen and in those treated with diclofenac and both treatments were well-tolerated [26]. A multicentre, randomized, double-blind, parallel-group trial was conducted in 239 patients with active osteoarthritis of the hip and/or the knee who received either ketoprofen at the dose of 200 mg once-daily (N = 118) or diclofenac at the dose of 75 mg twice-daily (N = 121). Ketoprofen and diclofenac produced rapid symptomatic relief of pain which was maintained over 4 months of treatment. Constipation and fever were more frequent with ketoprofen and liver test abnormalities were more frequent with diclofenac [27]. A split-mouth, prospective, randomized, double-blind trial was conducted in patients undergoing the removal of the third molar tooth. Eighteen patients received either ketoprofen at the daily dose of 100 mg (N = 8) or nimesulide at the daily dose of 100 mg (N = 8) and both treatments lasted three days. The peak pain score occurred at 6 hours after surgery in patients treated with nimesulide and after 12 hours in patients treated with ketoprofen. The pain relief was observed after 48 hours in patients treated with nimesulide and after 7 days in patients treated with ketoprofen. Ketoprofen and nimesulide were effective in controlling pain after the surgical removal of third molar tooth [28]. A randomized crossover, double-blind trial compared the analgesic effect of topical benzocaine gel (5%) and ketoprofen gel (1.60 mg/ml) to treat pain in 20 patients undergoing a third molar tooth extraction and ketoprofen relieved pain more effectively (P-value < 0.05) than benzocaine [29].

Metabolism of ketoprofen

Główka et al. [30] observed that ketoprofen is hydroxylated into 3-hydroxy-ketoprofen by human cytochromes P-450: CYP2C8 and CYP2C9. Patel et al. [31] stated that ketoprofen inhibits the glucuronidation of oxazepam by inhibiting UGT2B7 thus ketoprofen is glucuronidated by UGT2B7.



3-Hydroxy-ketoprofen molecular structure (molecular weight = 270.28 grams/mole)



Ketoprofen glucuronide molecular structure (molecular weight = 430.4 grams/mole)

Concentration of ketoprofen in human tissues

Sekiya et al. [32] determined the concentration of ketoprofen in the semitendinosus muscle, tendon, and in plasma following topical application of ketoprofen or following oral administration of ketoprofen to patients scheduled for anterior cruciate ligament reconstruction. Twenty-seven patients, aged 25 years (range, 15 to 51), who were scheduled to undergo anterior cruciate ligament reconstruction were enrolled. Two ketoprofen patches (20 mg each) were applied over the semitendinosus muscle and tendon 1, 6, 14, or 20 hours before surgery to 21 patients and one sustained-release capsule of 150 mg of ketoprofen was administered to 6 patients before surgery. Table 1 shows the concentration of ketoprofen in semitendinosus muscle, tendon, and in plasma following topical application of ketoprofen or following oral administration of ketoprofen.

Table 1: Concentration of ketoprofen which has been measured in semitendinosus muscle (muscle), tendon, and in plasma following topical application of ketoprofen or following oral administration of ketoprofen. Values are the mean±SEM, by Sekiya et al. [32].

Tissue	Topical application				Oral administration
	1 hour (N = 7)	6 hours (N = 6)	14 hours (N = 6)	20 hours (N = 2)	14 hours (N = 6)
Muscle (ng/gram)	56±27	257±147	80±47	63	56±12
Tendon (ng/gram)	118±57	377±170	235±162	210	211±48
Plasma (ng/ml)	3±3	132±32	196±27	138	3,365±559
*P-value	0.004	0.513	0.070	---	---
*Friedman‘s test, two-sided.					

This table shows that following topical application the concentration of ketoprofen is higher in semitendinosus muscle and in tendon than in plasma whereas following oral administration the concentration of ketoprofen is higher in plasma than in semitendinosus muscle and in tendon. In addition, there is a remarkable interindividual variability in the concentration of ketoprofen in semitendinosus muscle, tendon, and in plasma and this variability is accounted by the wide variation in the vital date of the patients included in the study. Table 2 shows the pharmacokinetic parameters of ketoprofen obtained in semitendinosus muscle, tendon, and in plasma following topical application of ketoprofen.

Table 2: *Pharmacokinetic parameters of ketoprofen which have been obtained in semitendinosus muscle (muscle), in tendon, and in plasma following topical application of ketoprofen. Values are the mean, by Sekiya et al. [32].*

Tissue	Peak concentration	Tmax (h)	$AUC_{0\text{-}20h}$
Muscle	257 (ng/gram)	6	2,588 (ng*h/gram)
Tendon	377 (ng/gram)	6	5,080 (ng*h/gram)
Plasma	196 (ng/ml)	14	2,653 (ng*h/ml)
Tmax = time to reach the peak concentration. AUC = area under the concentration-tine curve.			

This table shows that the peak concentration of ketoprofen is higher in semitendinosus muscle and in tendon than in plasma. Ketoprofen rapidly penetrates into the semitendinosus muscle and into the tendon as the time to reach the peak concentration in these tissue is 6 hours and ketoprofen penetrates into the semitendinosus muscle and tendon more rapidly than in plasma. The area under the concentration-time curve of ketoprofen is higher in tendon than in semitendinosus muscle and in plasma.

Siepsiak-Połom et al. [33] studied the pharmacokinetics of ketoprofen and tramadol in 36 patients who were divided into two groups. Group A consisted in 18 patients who received a single oral dose of 100 mg of ketoprofen and group B consisted in 18 patients who received 2 capsules of 50 mg of tramadol and all patients had pancreatitis. Table 3 provides the vital data of the patients included in the study and table 4 summarizes the pharmacokinetic parameters of ketoprofen and tramadol.

Table 3: *Vital data of the patients included in the study. Values are the mean±SD, by Siepsiak-Połom et al. [33].*

Parameter	Ketoprofen	Tramadol
Males/females	17/1	15/3
Non-alcoholic/alcoholic	10/8	9/9
Age (years)	48.6±13.3	46.8±10.3
Height (m)	1.78±0.07	1.74±0.05
Weight (kg)	73.3±20.5	74.2±14.0
Body-mass-index (kg/m^2)	22.9±6.2	24.6±4.5

Table 4: *Pharmacokinetic parameters of ketoprofen and tramadol which have been obtained in patients with pancreatitis. Values are the mean±SD and (%coeficient of variation), by Siepsiak-Połom et al. [33].*

Parameter	Ketoprofen	Tramadol
Number of patients	18	18
Peak conc. (ng/ml)	3.41±2.32 (68%)	226±80.5 (36%)
Tmax (h)	1.94±1.25 (64%)	1.78±0.73 (41%)
$AUC_{0-\infty}$ (ng*h/ml)	10.45±5.57 (53%)	1,903±875 (46%)
Distribution volume (L)	53.58±54.26 (101%)	445±182 (41%)
Total body clearance (L/h)	14.64±13.02 (89%)	65.04±32.28 (44%)
Mean residence time (h)	2.91±0.87 (30%)	4.89±0.42 (9%)
Tmax = time to reach the peak concentration. AUC = area under the concentration-time curve.		

This table shows that the peak concentration of ketoprofen is lower than that of tramadol. Ketoprofen and tramadol are rapidly absorbed following oral administration as the time to reach the peak concentration is lower than 2 hours. The area under the concentration-time curve of ketoprofen is lower than that of tramadol. The distribution volume of ketoprofen is lower than that of tramadol and the mean residence time of ketoprofen is lower than that of tramadol. In addition, there is a remarkable interindividual variability in the pharmacokinetic parameters of ketoprofen and tramadol and this variability is accounted by the wide variation of the vital data of the patients included in the study.

Interaction of ketoprofen with drugs

Only two studies have been reported on the interaction of ketoprofen with drugs. Ketoprofen co-administered with methotrexate caused a life-threatening interaction [34]. Aspirin enhanced the metabolic conversion of ketoprofen to non-conjugate metabolites thus aspirin interacts with ketoprofen [35].

Toxicity caused by ketoprofen

Ketoprofen is a safe drug and only two studies have been reported on the toxicity caused by ketoprofen. Ketoprofen, administered at the therapeutic dose, may induce dermal toxicity [36]. The perfusion of the human placenta with ketoprofen induces toxicity in human foetus [37].

Discussion

Ketoprofen is a propionic acid derivative and is a nonselective cyclooxygenase inhibitor. Ketoprofen is approved for use in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, pain, ankylosing spondylitis, acute gouty arthritis, tendinitis, bursitis, headache, postoperative dental pain and swelling, and primary dysmenorrhea. Ketoprofen is bound to plasma protein to 99% and the elimination half-life of ketoprofen is 0.9 to 3.3 hours. In adults, the dose of ketoprofen is 25 to 50 mg thrice-daily or 4 times-daily and the anti-inflammatory dose of ketoprofen is 50 to 75 mg thrice-daily or 4 times-daily [1]. The efficacy and safely of ketoprofen have been reviewed. Ketoprofen, administered at the single-dose of 25 to 100 mg, to patients undergoing dental extraction effectively and safely reliefs the pain and is well-tolerated [2], ketoprofen effectively reliefs pain in old patients, is well-tolerated, and causes only few adverse-effects which are mostly gastrointestinal [3], ketoprofen, administered at the daily dose of 50 to 200 mg, ibuprofen, administered at the daily dose of 600 to 1,800 mg, and diclofenac, administered at the daily dose of 75 to 150 mg, effectively and safely relief pain and ketoprofen is more active than ibuprofen and diclofenac in relieving pain [4], patients undergoing hysterectomy received either ketoprofen at the daily dose of 50 mg or diclofenac at the daily dose of 75 mg and ketoprofen reliefs postsurgical pain more effectively than diclofenac and induces fewer adverse-effects than diclofenac [5], patients undergoing mandibular third molar tooth extraction received either ketoprofen at the daily dose of 100 mg or diclofenac at the daily dose of 75 mg and ketoprofen is more efficacy and safer than diclofenac in relieving the pain [6], patients undergoing head or neck surgery received either ketoprofen at the daily dose of 100 mg or metamizole at the daily dose of 2.5 mg and ketoprofen effectively and safely reliefs postsurgical pain as metamizole [7], patients undergoing hip or knee surgery received either dexketoprofen trometamol at the daily dose of 50 mg or ketoprofen at the daily dose of 100 mg and both treatments were administered thrice-daily over two days and effectively and safely relief postsurgical pain and are well-tolerated [8], and patients with osteoarthritis of the hip and/or the knee received either ketoprofen once-daily at the dose of 200 mg or diclofenac at the dose of 75 mg twice-daily and both treatments effectively and safely relief pain and are well-tolerated [9].

These results indicate that ketoprofen, administered at different doses, effectively reliefs pain in patients undergoing surgery and in patients with osteoarthritis and ketoprofen is more active than ibuprofen and diclofenac in relieving pain. The treatment of patients with ketoprofen has been reviewed. The transdermal treatment with ketoprofen is safer than the oral treatment because the transdermal treatment induces fewer adverse-effects [10], patients with renal colic disease received ketoprofen intravenously at the daily dose of 100 mg and ketoprofen has powerful anti-inflammatory and analgesic effects and effectively treats patients [11], ketoprofen is an effective treatment of various forms of rheumatic, traumatic, and postsurgical pain [12], topical ketoprofen 2.5% gel has clinical benefits in patients with different musculoskeletal diseases and is well-tolerated [13], ketoprofen, administered at the daily dose of 100 mg, reliefs pain in patients undergoing abdominal surgery without causing adverse-effects [14], low-dose of ketoprofen (6.25 to 25 mg) is more effective than ibuprofen administered at the dose of 200 mg in relieving pain in patients undergoing the extraction of impacted third molar tooth [15], patients undergoing the removal of mandibular impacted third molar tooth received either a single-dose of 12.5 to 50 mg of dexketoprofen trometamol or a single-dose of 50 mg of ketoprofen. Dexketoprofen trometamol is effective as ketoprofen in relieving postsurgical pain but the onset of action is more rapid with dexketoprofen trometamol suggesting that dexketoprofen trometamol is the most appropriate treatment of postsurgical pain [16], patients undergoing hip replacement surgery received either ketorolac intravenously at the dose of 90 mg followed by an infusion at a rate of 90 mg every 15 hours, or diclofenac intravenously at the dose of 75 mg followed by an infusion of 75 mg every 15 hours, or ketoprofen intravenously at a dose of 100 mg followed by an infusion of 100 mg every 15 hours and the treatments relief the postsurgical pain and are well-tolerated [17], patients with headache received either a single-dose of 25 mg of ketoprofen or a single-dose of 1,000 mg of acetaminophen, or placebo and ketoprofen has a more rapid onset of analgesia than acetaminophen and placebo [18], women undergoing Caesarean section received either diclofenac at the daily dose of 150 mg or ketoprofen at the daily dose of 200 mg or placebo. Diclofenac and ketoprofen relief postsurgical pain more effectively than placebo and are well-tolerated [19], patients with osteoarthritis of the knee received either dexketoprofen trometamol at the dose of 25 mg thrice-daily or ketoprofen at the dose of 50 mg thrice-daily. After three weeks of treatment, the relief of the pain was significantly higher (P-value < 0.05) in patients treated with dexketoprofen trometamol. The clinical improvement occurs in 75% of patients treated with dexketoprofen trometamol and in 50% of patients treated with ketoprofen. The symptomatic treatment of knee osteoarthritis is better with dexketoprofen trometamol than with ketoprofen [20]. These results indicate that ketoprofen, administered at different doses, reliefs postsurgical pain and effectively treats different diseases. The trials conducted with ketoprofen have been reviewed. A double-blind, randomized, multicentre, prospective trial tested the efficacy of ketoprofen, administered at the dose of 200 mg in the morning and in the evening, in relieving the pain in patients with osteoarthritis of the hip or the knee. The reduction of pain is

significantly higher (P-value < 0.01) with the morning dose and this treatment effectively cures the patients [21], a double-blind, clinical trial was conducted in patients with osteoarthritis of the hip who received ketoprofen at the daily dose of 200 mg. This treatment cures the osteoarthritis of the hip and is well-tolerated [22], a double-blind, clinical trial was conducted in patients suffering from the osteoarthritis of the hip and/or the knee who received either 200 mg once-daily of ketoprofen sustained-release or 100 mg twice-daily of normal formulation of ketoprofen. Both treatments cure the patients and are well-tolerated [23], a double-blind, parallel, multicentre trial was conducted in patients with rheumatoid arthritis who received either ibuprofen at the daily dose of 1,200 to 2,400 mg or ketoprofen at the daily dose of 150 to 300 mg. Ketoprofen is well-tolerated and treats the patients as ibuprofen [24], a comparative, controlled trial was conducted in patients suffering from rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis wo received either ketoprofen at the dose of 100 mg twice-daily or ibuprofens at the dose of 400 mg thrice-daily and both treatments lasted three months. Ketoprofen reduces the pain, the duration of morning stiffness, and the inflammation more effectively than ibuprofen and the adverse-effects are more frequent and severe in patients who received ketoprofen [25], a multicentre, randomized, active-controlled, open-label, parallel-group, non-inferiority, phase III, randomized trial was conducted in patients with osteoarthritis of the knee who received either ketoprofen at the dose of 30 mg twice-daily or diclofenac at the dose of 15 mg twice-daily and both treatments lasted three weeks. Ketoprofen reduces the pain more extensively (P-value < 0.05) than diclofenac.

The adverse-effects are similar in patients who received ketoprofen or diclofenac and both treatments are well-tolerated [26], a multicentre, randomized, double-blind, parallel-group trial was conducted in patients with active osteoarthritis of the hip and/or the knee who received either ketoprofen at the dose of 200 mg once-daily or diclofenac at the dose of 75 mg twice-daily and both treatments relief the pain. Constipation and fever are more frequent in patients treated with ketoprofen and liver test abnormalities are more frequent in patients treated with diclofenac [27], a spilt-mouth, prospective, randomized, double-blind trial was conducted in patients undergoing the removal of the third molar tooth who received either ketoprofen at the daily dose of 100 mg or nimesulide at the daily dose of 100 mg. The peak pain score occurs at 6 hours after surgery in patients treated with nimesulide and after 12 hours in patients treated with ketoprofen and the pain relief occurs after 48 hours in patients who received nimesulide and after 7 days in patients who received ketoprofen. Ketoprofen and nimesulide relief pain in patients undergoing the surgical removal of the third molar tooth [28], a randomized, double-blind trial was conducted in patients undergoing a third molar tooth extraction who received either topical benzocaine gel 5% or ketoprofen gel (1.60 mg/ml) and ketoprofen reliefs the pain more extensively (P-value < 0.05) than benzocaine [29]. The metabolism of ketoprofen has been reviewed. Ketoprofen is hydroxylated into 3-hydroxy-ketoprofen by human CYP2C8 and by CYP2C9 [30] and ketoprofen inhibits the glucuronidation of oxazepam by inhibiting UGT2B7 thus ketoprofen is glucuronidated by UGT2B7 [31].

The penetration of ketoprofen into the human tissues has been described following topical application of ketoprofen or oral administration of ketoprofen [32]. Following topical application, the concentration of ketoprofen is higher in the semitendinosus muscle and in tendon than in plasma whereas, following oral administration, the concentration of ketoprofen is higher in plasma than in the semitendinosus muscle and in tendon. Siepsiak-Połom et al. [33] studied the pharmacokinetics of ketoprofen and tramadol in patients with pancreatitis. Ketoprofen was administered orally at the dose of 100 mg and two capsules of 50 mg of tramadol were administered to patients. The time to reach the peak concentration of ketoprofen and tramadol is 1.94±1.25 and 1.78±0.73 hours, respectively, suggesting that ketoprofen and tramadol are rapidly absorbed following oral administration. The peak concentration of ketoprofen and tramadol is 3.41±2.32 and 226±80.5 ng/ml, respectively, indicating that the plasma concentration of ketoprofen is lower than that of tramadol. The distribution volume of ketoprofen and tramadol is 53.58±54.16 and 445±182 L, respectively, indicating that the distribution volume of ketoprofen is lower than that of tramadol. The interaction of ketoprofen with drugs has been reviewed. Ketoprofen co-administered with methotrexate causes a life-threatening interaction [34] and aspirin enhances the metabolic conversion of ketoprofen to non-conjugate metabolites thus aspirin interacts with ketoprofen interacts [35]. Ketoprofen is a safe drug and limited information is available about the toxicity induced by ketoprofen. Ketoprofen, administered at the therapeutic dose, may induce dermal toxicity [36] and the perfusion of the human placenta with ketoprofen may induce toxicity in the human foetus [37].

In conclusion, ketoprofen is a propionic acid derivative and is a nonselective cyclooxygenase inhibitor. Ketoprofen is approved for use in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, pain, ankylosing spondylitis, acute gouty arthritis, tendinitis, bursitis, headache, postoperative dental pain and swelling, and primary dysmenorrhoea. The efficacy and safely of ketoprofen, the treatments of patients with ketoprofen, and the trials conducted with ketoprofen have been reviewed. Ketoprofen is hydroxylated into 3-hydroxy-ketoprofen by human CYP2C8 and by CYP2C9 and is conjugated with glucuronic acid by UGT2B7. The concentration of ketoprofen in human tissues has been studied following topical application of ketoprofen or following oral administration of ketoprofen. Following topical application,

ketoprofen reaches higher concentration in the semitendinosus muscle and in tendon than in plasma whereas following oral administration the concentration of ketoprofen is higher in plasma than in the semitendinosus muscle and in tendon. The pharmacokinetics of ketoprofen have been described in patients with pancreatitis and following oral administration ketoprofen rapidly appears in plasma as the time to reach the peak concentration is 1.94±1.25 hours. The interaction of ketoprofen with drugs and the toxicity induced by ketoprofen have been reviewed. The aim of this study is the review of the clinical pharmacology of ketoprofen.

Conflict of interests*:* The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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