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CLINICAL PHARMACOLOGY OF NAPROXEN

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ABSTRACT

Naproxen is a propionic acid derivative, is available in the United States, and naproxen is indicated for juvenile and rheumatic arthritis, osteoarthritis, ankylosing spondylitis, pain, primary dysmenorrhoea, tendinitis, bursitis, and acute gout. Naproxen is supplied as tablets, delayed-release tablets, extended-release tablets, gelcaps, and caplets and as oral suspension and suppositories. Naproxen is absorbed fully after oral administration and more slowly after rectal administration. Naproxen has been found efficacy and safe and the prophylaxis and treatment with naproxen and the trials conducted with naproxen have been reviewed. The metabolism of naproxen has been studied in-vitro using human liver microsomes and naproxen is oxidized into 9-O-desmethyl-naproxen by CYP2C9 and by CYP1A2 and naproxen is also conjugated with glucuronic acid by UGT2B7. The pharmacokinetics of naproxen have been studied in 8 patients with rheumatoid arthritis, aged 62±3 years, and in 6 healthy volunteers aged 24±3 years. The peak concentration of naproxen is 79±12 and 110±7 µg/ml (P-value < 0.0001) in patients and healthy volunteers, respectively, and the elimination half-life of naproxen in about 10 hours in patients and in healthy volunteers. Naproxen is bound to plasma protein for 99% and the plasma protein concentration is lower in patients than in healthy volunteers consequently all pharmacokinetic parameters of unbound naproxen are different in patient and adult volunteers. The toxicity induced by naproxen has been reviewed. The aim of this study is to review naproxen efficacy and safely, prophylaxis, treatment, trials conducted with naproxen, and naproxen metabolism, pharmacokinetics, and toxicity induced by naproxen.

KEYWORDS: Efficacy-safely, metabolism, naproxen, pharmacokinetics, prophylaxis, toxicity, treatment, and trials.

INTRODUCTION

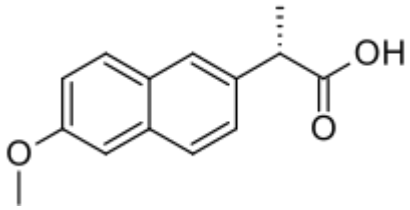
Naproxen is a propionic acid derivative, is available in the United States, and consists in two enantiomers: R-naproxen and S-naproxen. Naproxen is supplied as tablets, delayed-release tablets, extended-release tablets, gelcaps, and caplets containing 200 to 500 mg of naproxen or naproxen sodium and as oral suspensions and suppositories. Solid oral dosage forms containing 200 mg or less are available without a prescription. Naproxen is licensed for marketing alone and in fixed-dose combinations with pseudoephedrine, diphenhydramine, esomeprazole, and sumatriptan and it is packed with lansoprazole. Naproxen is indicated for juvenile and rheumatic arthritis, osteoarthritis, ankylosing spondylitis, pain, primary dysmenorrhea, tendinitis, bursitis, and acute gout.[1]

Absorption distribution, metabolism, and elimination of naproxen

Naproxen is absorbed fully after oral administration. Naproxen also is absorbed rectally but more slowly than after oral administration. Naproxen is almost completely (99%) bound to plasma protein after normal therapeutic doses. The elimination half-life of naproxen in plasma is variable and ranges from 9 to 25 hours. Age plays a role in the variability of elimination half-life of naproxen because of the age-related decline in renal function and consequently the elimination half-life of naproxen is longer in elderly and low doses should be prescribed in old patients. After the administration of tablets, liquid formulation, sodium salt, and delayed-release tablets the peak concentration occurs 2 to 4 hours, 1 to 4 hours, 1 to 2 hours, and 4 to 12 hours, respectively. Naproxen is extensively metabolised in the liver. Naproxen is oxidized into 9-O-desmethyl-naproxen by CYP2C9 and by CYP1A2 and naproxen is also conjugated with glucuronic acid by UGT2B7 and the elimination half-life of 9-O-desmethyl-naproxen is 9 to 25 hours. About 30% of naproxen undergoes 9-desmethylation, and most of this metabolite and naproxen itself are excreted in the urine as glucuronide. Naproxen crosses the placenta and appears in the milk of lactating women about 1% of the maternal plasma concentration.[1]

Adverse-effects caused by naproxen

Although the best available data were consistent with the suggestion that naproxen is a nonsteroidal anti-inflammatory drug that is not associated with an increase in myocardial infarction, based on the advisory committee recommendations, the US Food and Drug Administration issued a warning that nonsteroidal anti-inflammatory drugs can cause heart attacks and strokes and that there is inconclusive evidence regarding whether the particular risk of any nonsteroidal anti-inflammatory drug is definitively higher or lower than another nonsteroidal anti-inflammatory. About 1% to 10% of patients taking naproxen experience gastrointestinal adverse-effects that include heartburn, abdominal pain, constipation, diarrhoea, dyspepsia, and stomatitis. Adverse-effects with naproxen occur at approximately the same frequency as with indomethacin and other nonsteroidal anti-inflammatory drugs. Central nervous system adverse-effects include drowsiness (3% to 9%), headache (3% to 9%), vertigo (> 3%), and depression (< 1 %). Other common reactions include pruritus (3% to 9%), and diaphoresis (< 3%). Rare instances of jaundice, impairment of renal function, angioedema, thrombocytopenia, and agranulocytosis have been reported.[1]



Naproxen molecular structure (molecular weight = 230.263 grams/mole)

The broken bond designates the asymmetric carbon atom

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: “naproxen efficacy, safely”, “naproxen prophylaxis”, “naproxen treatment”, “naproxen trials”, “naproxen metabolism”, “naproxen pharmacokinetics”, and “naproxen toxicity”. In addition the book: Goodman@Gilman’s. The Pharmacological basis of Therapeutics[1] has been consulted.

RESULTS

Efficacy and safely of naproxen

Naproxen sodium was administered orally at the daily dose of 600 mg to patients aged < 65 years and at the daily dose of 440 mg to patients aged ≥ 65 years and patients had moderate osteoarthritis of the hip or knee. For acute management of underlying pain in patients with moderate osteoarthritis of the hip or knee, non-prescription doses of naproxen sodium were effective and well-tolerated in patients of all ages.[2] Patients, aged 60.6±12.8 years, received naproxen sodium orally at the daily dose of 600 mg and patients, aged ≥ 65 years, received naproxen sodium orally at the daily dose of 400 mg, or patients received paracetamol orally at the daily dose of 4,000 mg, or received placebo and treatments lasted 7 days and patients had osteoarthritis of hip or knee. Naproxen sodium (440/660 mg) provided greater (P-value < 0.05) improvements in pain at rest, on passive motion, on weight-bearing, stiffness after rest (morning), day and night pain than placebo, and provided greater (P-value < 0.05) relief of resting pain than paracetamol and paracetamol provided greater (P-value < 0.05) improvements in day pain than placebo. Non-prescription doses of naproxen sodium (440/660 mg) effectively relieved pain and other symptoms of osteoarthritis of hip or knee. Naproxen sodium is an alternative in the initial treatment of osteoarthritis and may be preferred to paracetamol as first-line therapy in patients with moderate or severe pain.[3] Patients with nonspecific low back pain were enrolled and received naproxen orally at the dose of 550 mg twice-daily for 7 to 14 days. The pain relief was observed in 77 patients (88.5%) during the first week of treatment and in 81 patients (93.1%) at the end of the study. Naproxen administered at the dose of 550 mg twice-daily demonstrated high efficacy and safely in patients with non-specific pain in lumbosacral spine.[4] Naproxen sodium administered orally at the daily dose of 550 mg and naproxen administered orally at the daily dose of 400 mg are effective and safe analgesics for treatment of acute postoperative pain in adults.[5]

Prophylaxis with naproxen

Naproxen was administered orally at the daily dose of 500 mg to 269 patients undergoing hip surgery and this treatment had a beneficial role in in preventing heterotopic ossification after hip surgery and hip arthroscopy.[6] Naproxen was administered orally at the daily dose of 500 mg to 270 patients undergoing hip surgery. Naproxen was associated with a reduction (P-value < 0.05) in the occurrence of heterotopic ossification at 1.5-, 3-, 6-, and 12-month follow-ups. Naproxen decreased the occurrence of heterotopic ossification without increasing complications in patients undergoing hip surgery.[7] A total of 335 patients undergoing hip surgery received naproxen orally at the dose of 500 mg twice-daily for 2 weeks. Prophylaxis with naproxen administered for 2 weeks prevents heterotopic ossification in patients undergoing hip surgery.[8] Fifty patients with migraine received either naproxen sodium orally at the daily dose of 550 mg or placebo. Naproxen sodium prevented migraine in 52.1% whereas placebo prevented migraine in only 19.0% of patients (P-value < 0.05). Naproxen sodium was better than placebo in preventing migraine.[9] Seventy-four migraine sufferers received either 550 mg naproxen sodium twice-daily or 0.5 mg pizotifen thrice-daily for 3 months. Both treatments showed a significant decline in severity of migraine (P-value = 0.001) and in frequency of attacks (P-value = 0.02) and no significant differences were detected between the two treatments. Naproxen sodium was a useful prophylactic agent for migraine.[10] It was investigated the clinical effects of naproxen

sodium in the short-term prophylaxis of menstrual migraine in 25 women who received naproxen sodium orally at the daily dose of 550 mg. Naproxen sodium was administered from 7 days before menstruation to 7 days after menstruation for 3 menstrual cycles. The duration of migraine was reduced from 25.6±4.42 hours pre-treatment to 15.50±4.43 hours in the 3rd month of treatment (P-value < 0.02) and to 13.35±4.26 hours in the 6th month of treatment (P-value < 0.001). The intensity of migraine was reduced from 2.4±0.11 pre-treatment to 1.2±0.10 in the 3rd month of treatment (P-value < 0.0001) and to 1.1±0.07 in the 6th month of treatment (P-value < 0.0001). These results indicate than naproxen sodium prevented the migraine in women during menstruation.[11]

Treatment with naproxen

Naproxen was administered orally at the daily dose of 500 to 1,000 mg to 16 patients with eosinophilic pustular folliculitis. Therapeutic effects were evaluated by 3 grades: complete remission, partial remission, and > 50% improvement. Of 16 patients, 11 patients (68.7%) showed complete remission, 3 patients (18.7%) showed partial remission and 2 patients (12.5%) showed > 50% improvement. The median time to response for good responders was 1.5 weeks. Naproxen is an effective treatment of patients with eosinophilic pustular folliculitis.[12] Naproxen was administered orally at the daily dose of 10 to 20 mg/kg to 19 children for treatment of arthritis and rheumatic fever. Fever and arthritis resolved within a median of 1 day of beginning of treatment (range, 1 to 2 days and 1 to 30 days, respectively). No gastrointestinal, dermatologic, liver, or renal adverse-effects were observed and naproxen is an effective and safe treatment of children with arthritis and rheumatic fever.[13] Naproxen was administered orally at the daily dose of 10 mg/kg divided in two doses to 21 children, aged 5 to 16 years, with juvenile rheumatoid arthritis and children were cured after 20 days of treatment.[14] Thirty-four athletes with acute musculoskeletal injuries received either piroxicam orally at the daily dose of 40 mg for two days and then received piroxicam orally at the dose of 20 mg once-daily or received naproxen orally at the dose of 500 mg twice-daily for two days and then received naproxen orally at the dose of 375 mg twice-daily. Both treatments improved all measures of physical discomfort 3 to 7 days after treatment (P-value < 0.0001). Three days after beginning treatment, the mean reduction in spontaneous pain, swelling, and tenderness was statistically superior in athletes who received piroxicam (P-value < 0.05) than in athletes who received naproxen. Piroxicam and naproxen were effective short-term treatments for acute musculoskeletal injuries in athletes.[15] Thirty patients with osteoarthritis of the hip or knee received either naproxen orally at the dose of 750 mg twice-daily or sulindac orally at the dose of 400 mg twice-daily and both drugs were administered for 4 weeks. Naproxen and sulindac improved patients' overall conditions and were well-tolerated.[16] A total of 24,081 patients with osteoarthritis or with rheumatoid arthritis received either celecoxib orally at the daily dose of 209±37 mg, or naproxen orally at the daily dose of 852±103 mg, or ibuprofen orally at the daily dose of 2,045±246 mg and all drugs were given for 20.3±16.0 months. All drugs managed the osteoarthritis and rheumatoid arthritis bud had some adverse-effects. The risk of gastrointestinal adverse-effects was significantly lower in patients who received celecoxib (P-value = 0.01) or in patients who received ibuprofen (P-value = 0.002) than in patients who received naproxen. The risk of renal adverse-effects were significantly lower in patients who received celecoxib than in patients who received ibuprofen (P-value = 0.004) but not difference was observed between patients who received celecoxib and patients who received naproxen (P-value = 0.190). Thus celecoxib, ibuprofen, and naproxen effectively treat patients with osteoarthritis and with rheumatoid arthritis, induce gastrointestinal and renal adverse-effects, and celecoxib and ibuprofen are safer than naproxen.[17] Thirty-nine women with dysmenorrhoea received either a single oral dose of 100 mg of ketoprofen or a single oral dose of 500 mg of naproxen and it was estimated the time of pain relief. Ketoprofen was significantly (P-value < 0.05) more effective than naproxen in controlling the pain at 60 min after drug administration and this difference remained significant until 120 min. Ketoprofen had therapeutic advantage over naproxen in women with menstrual pain.[18]

Trials conducted with naproxen

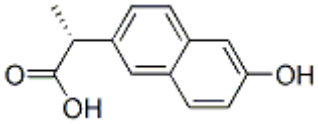
A randomized, double-blind trial was conducted in 586 patients who received either one dose of celecoxib (N = 294) or one dose of naproxen (N = 292). The primary endpoint was to assess the efficacy and tolerability of celecoxib versus those of naproxen in patients with osteoarthritis of the knee. The efficacy was achieved by 52.7% and by 49.7% (P-value > 0.05) of patients who received celecoxib and naproxen, respectively. Significantly fewer gastrointestinal adverse-effects occurred in patients who received celecoxib than in those who received naproxen (4.1% versus 15.1%, respectively, P-value < 0.05). Celecoxib was efficacious as naproxen in treating patients with osteoarthritis of the knee but celecoxib is better tolerated than naproxen.[19] A randomized, double-blind trial compared the efficacy of flavocoxid administered orally at the dose of 500 mg twice-daily (N = 120) versus that of naproxen administered orally at the dose of 500 mg twice-daily (N = 100) for treatment of moderate to severe osteoarthritis of the knee and both treatments lasted 12 weeks. Initial analysis of the entire intent-to-treat population revealed that flavocoxid was as effective as naproxen in managing signs and symptoms of osteoarthritis of the knee.[20] It was compared the analgesic efficacy of non-prescription doses of either naproxen sodium or ibuprofen or placebo in patients with osteoarthritis of the knee. In two identical multicentre, randomized, double-blind, placebo-controlled, multi-dose, parallel-design trials 444 patients, aged ≥ 25 years, received either naproxen sodium orally

at the daily dose of 600 mg or ibuprofen orally at the daily dose of 1,200 mg, or placebo and treatments lasted 7 days. Naproxen sodium and ibuprofen were more effective (P-value < 0.05) than placebo in relieving pain. Both treatments reduced the mean symptom score by 30% to 45% whereas placebo reduced the mean symptom score by 20% to 25% (P-value < 0.05). Naproxen sodium and ibuprofen relieved pain in patients with osteoarthritis of the knee better than placebo.[21] A multicentre, randomized, placebo-controlled trial was conducted in 1,061 patients with symptomatic osteoarthritis of the hip who received either celecoxib orally at the daily doses of 100 mg, 200 mg, or 400 mg or naproxen orally at the daily dose of 1,000 mg, or placebo and treatments lasted 12 weeks. All doses of celecoxib and the dose of naproxen significantly improved the symptoms of osteoarthritis of the hip better than placebo (P-value < 0.05). Celecoxib administered at the daily dose of 400 mg was similarly efficacious as naproxen administered at the daily dose of 1,000 mg in reducing the pain associated with osteoarthritis of the hip.[22] A randomized, double-blind trial was conducted in 18 patients with osteoarthritis of the knee who received nabumetone orally at the daily dose of 1,000 mg and in 19 patients with osteoarthritis of the knee who received naproxen orally at the daily dose 400 mg and both treatments effectively managed the osteoarthritis of the knee and were well-tolerated.[23] A six-month, double-blind, controlled, randomized, parallel trial compared the efficacy and safely of nabumetone administered orally at the daily dose of 1,000 mg (N = 227) versus those of naproxen administered orally at the dose of 250 mg twice-daily (N = 228) and all patients had osteoarthritis of the knee. Significant improvement of osteoarthritis occurred in both treatments and no significant differences were found between the two treatments at the end of the study. Single dose of nabumetone and double dose of naproxen are convenient, effective, and safe treatment of osteoarthritis of the knee.[24] A multicentre, twelve-week, randomized, double-blind, parallel-group, clinical trial was conducted in 190 patients who received aceclofenac orally at the dose of 100 mg twice-daily and in 184 patients who received naproxen orally at the dose of 500 mg twice-daily and all patients had osteoarthritis of the knee. Both treatments resulted in significant reduction of pain at rest, pain on movement, and pain from pressure on the joint. Aceclofenac was effective as naproxen in symptomatic treatment of osteoarthritis of the knee and both treatments were well-tolerated.[25] A prospective, randomized, open-label, equivalence trial compared the use of naproxen to that of aspirin in 33 patients with rheumatic fever. The mean time of fever resolution was 2.9$\pm$1.9 days in both treatments. Liver enzyme elevation was more frequent in patients who received aspirin (P-value = 0.002). Naproxen is effective and safer than aspirin in treatment of rheumatic fever.[26] A double-blind, crossover trial was conducted in patients who received either indoprofen orally at the daily dose of 800 mg, or naproxen orally at the daily dose of 500 mg, or placebo for treatment of pain caused by rheumatoid arthritis. Indoprofen was more effective (P-value < 0.05) than naproxen in treatment of rheumatoid arthritis and was better tolerated (P-value < 0.05) than naproxen and both indoprofen and naproxen were more effective (P-value < 0.05) than placebo in curing patients with rheumatoid arthritis.[27] A multicentre, double-blind, randomized, parallel trial compared the efficacy and safely of two dosages of naproxen sodium in 100 patients with bone pain due to metastatic cancer. Fifty-one patients received naproxen sodium orally at the dose of 550 mg thrice-daily for 3 days (high dose) and 49 patients received 550 mg of naproxen sodium orally on day 1 followed by naproxen sodium at the dose of 275 mg thrice-daily for 3 days (low dose). Pain intensity scores decreased by approximately one-third in each treatment group. Pain relief was significantly greater (P-value < 0.05) with the high dose than with low dose and both treatments were well-tolerated and caused mild gastrointestinal adverse-effects.[28] A double-blind, randomized, controlled trial was conducted in 129 patients with back pain which was present at least for 6 weeks. Patients were randomly assigned to receive either theramine (N = 43), or naproxen which was administered orally at the daily dose of 250 mg (N = 42), or both theramine and naproxen (N = 44). At day 28 of treatment, theramine plus naproxen was significantly superior to naproxen alone or to theramine alone (P-value < 0.05).[29] Two-single center, randomized, double-blind, and double-dummy trials were conducted in patients who underwent tooth extraction. Patients received naproxen sodium plus paracetamol plus codeine or placebo. The treatment with naproxen sodium plus paracetamol and plus codeine relived the pain more effectively (P-value < 0.05) than placebo.[30] A clinical trial assessed the efficacy and safely of naproxen sodium in treatment of acute migraine attacks. Patients received either naproxen sodium orally at the daily dose of 550 mg or placebo. Naproxen sodium was more effective (P-value < 0.05) than placebo in relieving pain and in providing pain-free within 2 hours in patients with moderate or severe migraine attacks. Naproxen sodium was well-tolerated and the adverse-effects were nausea, dizziness, dyspepsia, and abdominal pain.[31] A double-blind, cross-over, randomized trial compared the efficacy of naproxen versus that of placebo in treating acute migraine. The initial dose of naproxen was 750 mg, with additional doses of 250 to 500 mg which were taken if required, to a maximum of five doses of 250 mg within 24 hours in each migraine attack. Forty-one patients were enrolled in the study and they experienced at least two but not more than eight migraine attacks a month during the preceding year. Naproxen was superior to placebo (P-value < 0.05) in reducing the severity of head pain, nausea, and photophobia, in shortening the duration of head pain, nausea, vomiting, photophobia, and in diminishing the frequency of vomiting.[32] A randomized, parallel group trial was conducted in children, aged 12 to 17 years, who had 2 to 8 migraine attacks per month and children received either sumatriptan orally at the daily

dose of 85 mg plus naproxen orally at the daily dose of 500 mg or placebo. Sumatriptan plus naproxen treated migraine more effectively (P-value < 0.05) than placebo and this treatment was well-tolerated.[33] Two independent, double-blind, placebo-controlled trials were conducted to test the efficacy of naproxen sodium in treating dysmenorrhea. An initial dose of 550 mg of naproxen sodium was followed by 275 mg of naproxen sodium 4 times-daily for a maximum of 5 days. Twenty patients were included in study A: 10 patients received naproxen sodium and 10 patients received placebo. Twenty-three patients were included in study B: 12 patients received naproxen sodium and 11 patients received placebo. Each patient received the medication during 4 dysmenorrheic episodes. In both studies naproxen sodium was superior to placebo (P-value < 0.05) in treating dysmenorrhoea.[34] A double-blind, randomized, placebo-controlled trial was conducted in 80 patients who underwent endometrial biopsy. The patients were randomly allocated into two groups who received either naproxen orally at the daily dose of 500 mg (N = 40) or placebo (N = 40) 30 min before to sample endometrial biopsy. Pain score was assessed using Visual Analogue Scale during and 10 min after the procedure. The main pain score during endometrial biopsy was significantly lower (P-value < 0.001) in patients who received naproxen than in patients who received placebo. However, the mean pain score at 10 min after endometrial sampling was not different (P-value = 0.971) in the two groups of patients. Naproxen 500 mg taken 30 min before endometrial biopsy significantly reduced the pain score during the endometrial biopsy sampling.[35] A multicentre trial was conducted to test the efficacy of naproxen versus that of phenylbutazone in treatment of gout. Patients received either a single oral dose of 750 mg of naproxen which was followed by a dose of 250 mg thrice-daily (N = 20) or received phenylbutazone administered orally at the dose of 200 mg thrice-daily (N = 21) and both treatments lasted 2 days. Both drugs were equally effective in treating patients with gout and induced few mild adverse-effects.[36] Two double-blind trials compared the efficacy of naproxen ophthalmic solution versus that of placebo or diclofenac in inhibiting pre-operative miosis. The study A was a placebo-controlled study which involved 194 patients undergoing extracapsular cataract extraction. The study B was an active-controlled study (versus diclofenac) concerning 214 patients undergoing phacoemulsification. In both studies the treatment started the day before surgery. A balanced salt solution containing adrenaline was used in all patients. In both studies the pupillary diameter decreased during surgery (P-value < 0.001). Naproxen was more effective than placebo (P-value < 0.01) and was effective as diclofenac in controlling the regression of pupil diameter during cataract extraction. Naproxen ophthalmic solution penetrates the cornea and it is effective in maintaining intraoperative mydriasis.[37]

Metabolism of naproxen

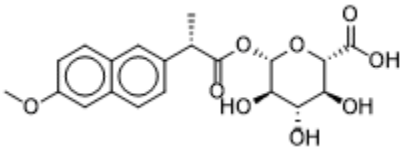
Miners et al.[38] suited the O-demethylation of R-and S-naproxen in-vitro using human liver microsomes. Sulfaphenazole, a specific inhibitor of CYP2C9, reduced the microsomal O-demethylation of R- and S-naproxen by 43% and 47%, respectively, and the CYP1A2 inhibitor furafylline decreased the microsomal O-demethylation of R- and S-naproxen by 38% and 28%, respectively. These data indicate that CYP2C9 and CYP1A2 account for the majority of R- and S-naproxen O-demethylation in human liver. The resulting metabolite which is formed by the O-demethylation of naproxen is 9-O-desmethyl-naproxen.



Molecular structure of 9-O-desmethyl-naproxen (molecular weight = 216.23 grams/mole)

The broken bond denotes the asymmetric carbon atom

Bowalgaha et al.[39] studied the glucuronidation of naproxen in-vitro using human liver microsomes. Naproxen acyl glucuronidation by human liver microsomes followed biphasic kinetics. The mean apparent Km values for the high- and low-affinity components were 29±13 and 473±108 µM, respectively. UGT2B7 glucuronidated naproxen and exhibited an apparent Km of 72 µM. UGT2B7 is responsible for human hepatic naproxen acyl glucuronidation, which is the primary elimination pathway for this drug. The metabolite which is formed by the glucuronidation of naproxen is naproxen-glucuronide.



Molecular structure of naproxen glucuronide (molecular weight = 406.38 grams/mole)

Pharmacokinetics of naproxen

Van den Ouweland et al.[40] studied the pharmacokinetics of naproxen in 8 patients with rheumatoid arthritis, aged 62±3 years, and in 6 healthy male volunteers aged 24±3 years. Both patients and healthy volunteers received naproxen orally at the dose of 500 mg twice-daily for 4 days. Table 1 summarizes the pharmacokinetic parameters of naproxen which have been obtained in 8 patients with rheumatoid arthritis and in 6 healthy male volunteers.

Table 1: Pharmacokinetic parameters of naproxen which have been obtained in 8 patients with rheumatoid arthritis, aged 62±3 years, and in 6 healthy male volunteers aged 24±3 years. Naproxen was administered orally at the dose of 500 mg twice-daily for 4 days. Values are the mean±SD, by van den Ouweland et al.[40]

	Total serum naproxen			Unbound serum naproxen		
Parameter	**Patients**	**Volunteers**	**P-value**	**Patients**	**Volunteers**	**P-value**
Peak conc. (µg/ml)	79±12	110±7	< 0.0001	0.42±0.21	0.19±0.07	< 0.02
Trough conc. (µg/ml)	38±8	57±7	< 0.0001	0.07±0.02	0.03±0.01	< 0.01
AUC (µg/ml*h)	641±101	896±85	< 0.0001	1.9±0.2	0.7±0.2	< 0.01
TBC/F (ml/min)	13.3±2.5	9.4±0.9	< 0.001	5.3±2.5	11.9±2.7	< 0.001
DV/F (L/kg)	0.18±0.03	0.11±0.01	< 0.0001	26±13	72±27	< 0.001
Elimination half-life (h)	10.4±2.0	10.0±1.8	> 0.05	3.6±0.8	4.8±0.8	< 0.02

AUC = area under the concentration-time curve. TBC = total body clearance. DV = distribution volume. F = bioavailability.

Total serum naproxen: both the peak and trough concentrations of total naproxen are lower in patients than in health volunteers. Consequently the area under the concentration-time curve of total naproxen is lower in patients than in healthy volunteers and the total body clearance and the distribution volume of total naproxen are higher in patients than in healthy volunteers. The elimination half-life of total naproxen is similar in patients and in healthy volunteers suggesting that the oral absorption of naproxen is similar in patients and in healthy volunteers.

Unbound serum naproxen: naproxen is extensively bound to plasma protein, mainly to albumin, and the concentration of plasma proteins is lower in patients than in healthy volunteers thus naproxen is bound to plasma protein in lower amounts in patients than healthy volunteers and the peak and trough concentrations of unbound naproxen are higher in patients than in healthy volunteers. Consequently the area under the concentration-time curve of unbound naproxen is higher in patients than in healthy volunteers, and the total body clearance, distribution volume, and the elimination half-life of unbound naproxen are lower in patients than in healthy volunteers.

Toxicity induced by naproxen

It was identified 11,303 patients who were hospitalized due to complicated gastric or duodenal ulcers after ingestion of overdoses of naproxen. While the risk of serious gastrointestinal complications appears to be dose-dependent, even low doses of naproxen are associated with a significant risk of serious gastrointestinal toxicity leading to hospitalization. Concomitant gastro-protective therapy should be strongly recommended in patients who are at risk regardless of naproxen use to prevent gastric and duodenal ulcers.[41] A total of 101,318 patients received naproxen sodium and 277,601 patients received ibuprofen. The incidence of upper gastrointestinal-tract bleeding occurred within 14 days after the first prescription of naproxen sodium and ibuprofen.[42] Patients who had rheumatoid arthritis received either rofecoxib orally at the dose of 50 mg twice-daily or naproxen orally at the dose of 500 mg twice-daily. The primary endpoint was the confirmation of clinical upper gastrointestinal adverse-effects. In patients with rheumatoid arthritis, treatment with rofecoxib was associated with fewer (P-value < 0.05) upper gastrointestinal adverse-effects than treatment with naproxen.[43] It was conducted a double-blind, randomized, controlled, multicentre trial which enrolled 24,081 patients with osteoarthritis or rheumatoid arthritis at moderate or high cardiovascular risk. Patients were randomized to receive either celecoxib orally at the dose of 100 to 200 mg twice-daily, or ibuprofen orally at the dose of 600 to 800 mg thrice-daily, or naproxen orally at the dose of 375 to 500 mg twice-daily. Patients using naproxen or ibuprofen experienced significantly higher risk of major toxicity (P-value < 0.05) than those using celecoxib.[44] A total of 16,286 patients received either etodolac or naproxen during a 3-year period without concurrent use of other ulcer-genic drugs. The primary outcome was to assess the clinically significant upper gastrointestinal adverse-effect-rate caused by etodolac or by naproxen. The incidence of clinically significant upper gastrointestinal adverse-effects was 78% and 24% for naproxen and etodolac, respectively (P-value = 0.006). Patients who received etodolac had lower upper gastrointestinal adverse-effects than patients who received naproxen.[45] A 16-year-old girl ingested 110 mg of prazosin, 209 grams of paracetamol, and 55 grams of naproxen and she was admitted to the paediatric intensive care unit for rapid deteriorating of hypotension (lowest blood pressure 47/19 mm Hg) refractory to aggressive fluid resuscitation and infusions of epinephrine and norepinephrine each at 0.5 µg/kg/min. Stabilization of blood pressure was eventually achieved with the use of a vasopressin infusion of 0.004 units/kg/min. After extensive detoxification the girl left the hospital.[46] A 63-year-old man with a history of hyperthyroidism and polysubstance use had an elevated concentration of total bilirubin after attempting suicide with the ingestion of 16 tablets of naproxen. The patient had vague abdominal pain and nausea and psychiatric symptoms including suicidal ideation and an elevated concentration of total bilirubin. The ingestion of an overdose of naproxen leaded to an elevated concentration of total bilirubin.[47] A 28-year-old man ingested 70 grams of naproxen along with an unknown amount of alcohol in a suicidal attempt. On examination in the emergency department 90 min later, he was drowsy but had normal vital signs apart from sinus tachycardia.

Serum naproxen level 90 min after ingestion was 1,580 µg/ml (therapeutic range is 25 to 75 µg/ml). He developed metabolic acidosis requiring renal therapy using sustained low efficiency dialysis, continuous venovenous hemofiltration, and intubation and he recovered after 48 hours. Haemodialysis and renal replacement therapy may correct the acid base disturbance and provide support in cases of renal impairment in context of naproxen overdose.[48]

DISCUSSION

Naproxen is a propionic acid derivative, is available in the United States, and consists in two enantiomers: R-naproxen and S-naproxen. Naproxen is supplied as tablets, delayed-release tablets, extended-release tablets, gelcaps, and caplets containing 200 to 500 mg of naproxen or naproxen sodium and as oral suspension and suppositories. Naproxen is absorbed fully after oral administration but more slowly after rectal administration. Age plays a role in the variability of naproxen elimination half-life because of the age-related decline in renal function and consequently the elimination half-life of naproxen is longer in old patients. Naproxen is licensed for marketing alone and in fixed-dose combinations with pseudoephedrine, diphenhydramine, esomeprazole, and sumatriptan and it is packed with lansoprazole. Naproxen is indicated for juvenile and rheumatic arthritis, osteoarthritis, ankylosing spondylitis, pain, primary dysmenorrhoea, tendinitis, bursitis, and acute gout. About 1% to 10% of patients taking naproxen experience gastrointestinal adverse-effects that include heartburn, abdominal pain, constipation, diarrhoea, and stomatitis. Adverse-effects caused by naproxen occur at approximately the same frequency as with other nonsteroidal anti-inflammatory drugs.[1] The efficacy and safely of naproxen have been reviewed. Naproxen sodium administered orally at the dose of 600 mg to patients aged < 65 years and at the daily dose of 400 mg to patients aged ≥ 65 years effectively and safely treats pain in patients with osteoarthritis of the hip or knee.[2] Patients, aged 60.6±12.8 years, received naproxen sodium orally at the daily dose of 600 mg and patients, aged ≥ 65 years, received naproxen sodium orally at the daily dose of 400 mg, or patients received paracetamol orally at the daily dose of 4,000 mg, or placebo, treatments lasted 7 days, and patients had osteoarthritis of hip or knee. Naproxen sodium provides greater (P-value < 0.05) improvement in pain at rest, on passive motion, on weight-bearing, stiffness after rest, day and night pain than placebo and naproxen causes greater (P-value < 0.05) relief of pain than paracetamol and paracetamol provides greater (P-value < 0.05) improvements in day pain than placebo. Naproxen sodium is preferred to paracetamol in treatment of moderate to severe pain.[3] Patients with nonspecific low back pain received naproxen sodium orally at the daily dose of 550 twice-daily for 7 to 14 days and pain relief was observed in 88.5% of patients during the first week of treatment and in 93.1% of patients at the end of the study. Naproxen sodium effectively and safely treats patients with non-specific pain in lumbosacral spine.[4] Naproxen sodium administered orally at the daily dose of 550 mg and naproxen administered orally at the daily dose of 400 mg effectively and safely treats postoperative pain.[5] These results indicate that naproxen sodium effectively and safely treats osteoarthritis of the hip or knee, reliefs pain better than paracetamol, naproxen effectively and safely treats patients with non-specific pain in lumbosacral spine, and treats postoperative pain. The prophylaxis with naproxen has been reviewed. Naproxen administered orally at the daily dose of 500 mg prevents heterotopic ossification in patients who underwent hip surgery and hip arthroscopy[6,7] and naproxen administered orally at the dose of 500 mg twice-daily for 2 weeks prevents heterotopic ossification in patients who underwent hip surgery.[8] Naproxen sodium administered orally at the daily dose of 550 mg prevents migraine more effectively (P-value < 0.05) than placebo.[9] Patients with migraine received either 550 mg of naproxen sodium twice-daily or 0.5 mg of pizotifen thrice-daily and treatments lasted for 3 months. Both treatments decline the severity of migraine (P-value = 0.001) and reduce the frequency of migraine attacks (P-value = 0.02)[10], and naproxen sodium administered orally at the daily dose of 550 mg prevents migraine in women during menstruation.[11] These results indicate that naproxen prevents heterotopic ossification in patients who underwent hip surgery and hip arthroscopy, naproxen sodium prevents migraine in patients and in women during menstruation, and naproxen sodium prevents migraine as pizotifen. The treatment with naproxen has been reviewed. Naproxen administered orally at the daily dose of 500 to 1,000 mg treats patients with eosinophilic pustular folliculitis.[12] Children with arthritis and rheumatic fever received naproxen orally at the daily dose of 10 to 20 mg/kg and this treatment resolves the arthritis and the rheumatic fever and is well-tolerated[13], and naproxen administered orally at the daily dose of 10 mg/kg for 20 days treats children with juvenile rheumatic arthritis.[14] Athletes with acute musculoskeletal injuries received either piroxicam orally at the daily dose of 40 mg for two days and then received piroxicam orally at the dose of 20 mg once-daily or received naproxen orally at the dose of 500 mg twice-daily for two days followed by naproxen administered at the dose of 375 mg twice-daily. Shortly after treatment the reduction in spontaneous pain, swelling, and tenderness is superior (P-value < 0.05) in athletes who received piroxicam. Piroxicam and naproxen are effective and well-tolerated short-term treatments of athletes with acute musculoskeletal injuries.[15] Patients with osteoarthritis of the hip or knee received either naproxen orally at the dose of 750 mg twice-daily or sulindac orally at the dose of 400 mg twice-daily and both treatments lasted 4 weeks. Naproxen and sulindac improve patient's overall conditions and are well-tolerated.[16] Patients with osteoarthritis or rheumatoid arthritis received either celecoxib orally at the daily dose of 209±37 mg, or naproxen orally at the daily dose of

852±103 mg, or ibuprofen orally at the daily dose of 2,045±246 mg. All drugs were administered for 20.3±16.0 months and manage the osteoarthritis and the rheumatoid arthritis. The risk of gastrointestinal adverse-effects were lower with celecoxib than with naproxen (P-value = 0.01) or with ibuprofen (P-value = 0.002) than with naproxen, the risk of renal adverse-effects were lower with celecoxib and with ibuprofen (P-value = 0.004) than with naproxen but not significant difference was found with celecoxib and naproxen (P-value = 0.190). Celecoxib and ibuprofen are safer than naproxen.[17] Women with dysmenorrhoea received either a single oral dose of 100 mg of ketoprofen or a single oral dose of 500 mg of naproxen. Ketoprofen is more effective (P-value < 0.05) than naproxen in controlling pain in women with dysmenorrhoea.[18] These results indicate that naproxen treats eosinophilic pustular folliculitis, treats children with arthritis and rheumatic fever or children with juvenile rheumatic arthritis, piroxicam is more effective than naproxen in treating athletes with acute musculoskeletal injuries, naproxen is effective as sulindac in treating patients with osteoarthritis of the hip or knee and celecoxib, naproxen, and ibuprofen treat osteoarthritis or rheumatoid arthritis, and ketoprofen is more effective than naproxen in controlling pain in women during the menstruation. The trials conducted with naproxen have been reviewed. A randomized, double-blind trial showed that celecoxib provides similar improvements in osteoarthritis of the knee as naproxen and celecoxib provides better tolerability than naproxen.[19] A randomized, double-blind trial showed that flavocoxid administered orally at the dose of 500 mg twice-daily is effective as naproxen administered orally at the dose of 500 mg twice-daily in managing signs and symptoms of osteoarthritis of the knee.[20] In two identical multicentre, randomized, double-blind placebo-controlled, multi-dose, parallel-design trials patients with osteoarthritis of the knee received either naproxen sodium administered orally at the daily dose of 600 mg or ibuprofen administered orally at the daily dose of 1,200 mg, or placebo. Naproxen sodium and ibuprofen are more effective (P-value < 0.05) than placebo in reliving the pain caused by the osteoarthritis of the knee.[21] A multicentre, randomized, placebo-controlled trial was conducted in patients with symptomatic osteoarthritis of the hip who received either celecoxib orally at the daily dose of 100, 200, or 400 mg, or naproxen orally at the daily dose of 1,000 mg, or placebo. Celecoxib administered at the dose of 400 mg is efficacious as naproxen administered at the dose of 1,000 mg and celecoxib and naproxen are more effective (P-value < 0.05) than placebo in improving the symptoms of osteoarthritis of the hip.[22] A randomized, double-blind trial compared the efficacy of nabumetone administered orally at the daily dose of 1,000 mg versus that of naproxen administered orally at the daily dose of 400 mg in treating osteoarthritis of the knee and both treatments effectively manage osteoarthritis and are well-tolerated.[23] A six-month, double-blind, controlled, randomized, parallel trial compared the efficacy and safely of nabumetone administered orally at the daily dose of 1,000 mg versus those of naproxen administered orally at the dose of 250 mg twice-daily in patients with osteoarthritis of the knee and both treatments effectively cure the patients and are safe.[24] A multicentre, twelve-week, randomized, double-blind, parallel-group, clinical trial compared the efficacy of aceclofenac administered orally at the dose of 100 mg twice-daily versus that of naproxen administered orally at the dose of 500 mg twice-daily in patients with osteoarthritis of the knee. Aceclofenac is effective as naproxen in treatment of osteoarthritis of the knee and both treatments are well-tolerated.[25] A prospective, randomized, open-label, equivalence trial compared the efficacy of naproxen versus that of aspirin in treating patients with rheumatic fever. The mean time until resolution of arthritis is 2.9±1.9 days in both treatments and the elevation of liver enzymes is higher (P-value = 0.002) in patients who received aspirin. Naproxen is effective and safer than aspirin in treatment of rheumatoid fever.[26] A double-blind, crossover trial compared the efficacy of indoprofen administered orally at the daily dose of 800 mg versus that of naproxen administered orally at the daily dose of 500 mg, or versus that of placebo in patients with rheumatoid arthritis. Indoprofen is more effective (P-value < 0.05) than naproxen in treatment of patients with rheumatoid arthritis and both indoprofen and naproxen are more active (P-value < 0.05) than placebo in curing patients with rheumatoid arthritis.[27] A multicentre, double-blind, randomized, parallel trial compared two doses of naproxen sodium in controlling bone pain due to metastatic cancer. Naproxen sodium was administered orally at the dose of 550 mg thrice-daily for 3 days (high dose) or at the dose of 550 mg followed by 275 mg thrice-daily for 3 days (low dose). Pain intensity scores decrease by about one-third in each treatment and pain relief is greater (P-value < 0.05) with the high dose and both treatments are well-tolerated and cause mild gastrointestinal adverse-effects.[28] A double-blind, randomized, controlled trial was conducted in patients with back pain. Patients received either theramine, or naproxen orally at the daily dose of 250 mg, or both theramine and naproxen. At day 28 of treatment, theramine plus naproxen controls pain more effectively (P-value < 0.05) than theramine alone or naproxen alone.[29] Two-single center, randomized, double-blind, and double-dummy trials were conducted in patients who underwent tooth extraction who received naproxen sodium plus paracetamol plus codeine or placebo. Naproxen sodium plus paracetamol plus codeine relieves pain more effectively (P-value < 0.05) than placebo.[30]. A clinical trial compared the efficacy of naproxen sodium administered orally at the daily dose of 550 mg versus that of placebo in reducing migraine. Naproxen sodium reduces migraine more effectively (P-value < 0.05) than placebo, is well-tolerated, and the adverse-effects are nausea, dizziness, dyspepsia, and abdominal pain.[31] A double-blind, cross-over, randomized trial compared the efficacy of naproxen versus that of placebo in treating acute migraine.

Naproxen was administered at the initial dose of 750 mg followed by additional doses 250 to 500 mg, which were taken if required, to a maximum of five doses of 250 mg of naproxen within a period of 24 hours in each migraine attack. Naproxen is superior to placebo (P-value < 0.05) in reducing the severity of head pain, nausea, and photophobia, in shortening the duration of head pain, nausea, vomiting, photophobia, and in diminishing the frequency of vomiting.[32] A randomized, parallel group trial compared the efficacy of sumatriptan administered orally at the daily dose of 85 mg plus naproxen administered orally at the daily dose of 500 mg versus that of placebo in treating migraine in children. Sumatriptan plus naproxen treats migraine more effectively (P-value < 0.05) than placebo and this treatment is well-tolerated.[33] Two independent, double-blind, placebo-controlled trials tested the efficacy of naproxen sodium administered at the initial dose of 550 mg followed by 275 mg of naproxen sodium 4 times-daily versus that of placebo in treating dysmenorrhoea. Each patient received the medication during 4 dysmenorrheic episode and naproxen sodium is superior (P-value < 0.05) than placebo in treating dysmenorrhoea.[34] A double-blind, randomized, placebo-controlled trial compared the efficacy of naproxen administered orally at the daily dose of 500 mg versus that of placebo in controlling pain during sampling of endometrial biopsy. Naproxen controls pain more effectively (P-value < 0.001) than placebo during endometrial biopsy but the main pain score 10 min after endometrial sampling is not different (P-value = 0.971) in patients who received naproxen and in those who received placebo.[35] A multicentre trial tested the efficacy of naproxen versus that of phenylbutazone in treating acute gout. Naproxen was administered orally at the dose of 750 mg followed by 250 mg thrice-daily and phenylbutazone was administered orally at the dose of 200 mg thrice-daily, both treatments lasted 2 days, and naproxen treats acute gout as phenylbutazone.[36] Two double-blind trials compared the efficacy of naproxen ophthalmic solution versus that of placebo or diclofenac in inhibiting pre-operative miosis. Naproxen is more effective than placebo (P-value < 0.01) and is similarly effective as diclofenac in controlling pupil diameter during cataract extraction.[37] The metabolism of naproxen has been studied in-vitro using human liver microsomes. Naproxen is oxidized into 9-O-desmethyl-naproxen by CYP2C9 and by CYP1A2. Sulfaphenazole, a specific inhibitor of CYP2C9, decreases the O-demethylation of R- and S-naproxen by 43% and 47%, respectively, and furafylline an inhibitor of CYP1A2, decreases the O-demethylation of R- and S-naproxen by 38% and 28%, respectively.[38] Naproxen is also conjugated with glucuronic acid by UGT2B6. Naproxen acyl glucuronidation follows biphasic kinetics. The mean apparent Km values for the high- and low-affinity components are 29±13 and 437±108 µM, respectively.[39] van den Ouweland et al.[40] studied the pharmacokinetics of naproxen in 8 patients with rheumatoid arthritis, aged 62±3 years, and in 6 healthy male volunteers, aged 24±3 years, and both patients and healthy volunteers received naproxen orally at the dose of 500 mg twice-daily for 4 days. These authors determined the pharmacokinetic parameters of naproxen and unbound naproxen. The peak concentration of naproxen is 79±12 and 110±7 µg/ml (P-value < 0.0001) in patients and in healthy volunteers, respectively, and the elimination half-life of naproxen is 10.4±2.0 and 10.0±1.8 hours (P-value > 0.05) in patients and in healthy volunteers, respectively. Naproxen binds to plasma protein for 99%.[1] and the plasma protein concentration is lower in patients tan in healthy volunteers consequently the peak concentration of unbound naproxen is 0.42±0.21 and 0.19±0.07 µg/ml (P-value < 0.02) in patients and in healthy volunteers, respectively, and the elimination half-life of unbound naproxen is 3.6±0.8 and 4.8±0.8 hours (P-value < 0.02) in patients and in healthy volunteers, respectively. The area under the concentration-time curve, the total body clearance, and the distribution volume of both naproxen and unbound naproxen are different in patients and in healthy volunteers. The toxicity induced by naproxen has been reviewed. Complicated gastric or duodenal ulcers are caused by the ingestion of overdose of naproxen. While the risk of serious gastrointestinal complications is dose dependent, even low doses of naproxen cause serious gastrointestinal toxicity leading to hospitalization.[41] The incidence of upper gastrointestinal blending occurs less with ibuprofen than with naproxen.[42] Patients with rheumatoid arthritis received either rofecoxib orally at the dose of 50 mg twice-daily or naproxen orally at the dose of 500 mg twice-daily and rofecoxib is associated with fewer (P-value < 0.05) upper gastrointestinal adverse-effects than naproxen.[43] Patients received either celecoxib orally at the dose of 100 to 200 mg twice-daily, or received ibuprofen orally at the dose of 600 to 800 mg thrice-daily, or received naproxen orally at the dose of 375 to 500 mg twice-daily and naproxen and ibuprofen cause higher toxicity (P-value < 0.05) than celecoxib.[44] Patients received either etodolac or naproxen for 3 years and etodolac is associated with a reduction (P-value = 0.006) of upper gastrointestinal adverse-effects.[45] A girl ingested 110 mg of prazosin, 209 grams of paracetamol, and 55 grams of naproxen. At the admission to the paediatric intensive care unit the blood pressure dropped to 47/19 mm Hg. Stabilization of blood pressure was achieved with vasopressin and after extensive detoxification she left the hospital.[46] A man ingested 16 tablets of naproxen and he had vague abdominal pain and nausea, psychiatric symptoms, and elevated concentration of total bilirubin.[47] A man ingested 70 grams of naproxen along with alcohol. The serum concentration of naproxen was 1,580 µg/ml 90 min after naproxen ingestion (therapeutic range is 25 to 75 µg/ml) and he developed metabolic acidosis requiring renal therapy using sustained low efficiency dialysis, continuous venovenous hemofiltration, and intubation and he recovered after 48 hours.[48]

In conclusion, naproxen is a propionic acid derivative, is available in the United States, and consists in two enantiomers: R-naproxen and S-naproxen. Naproxen is indicated for juvenile and rheumatic arthritis, osteoarthritis, ankylosing spondylitis, pain, primary dysmenorrhoea, tendinitis, bursitis, and acute gout. Naproxen is absorbed fully after oral administration. About 1% to 10% of patients who take naproxen experience gastrointestinal adverse-effects. Naproxen efficacy and safely, prophylaxis, and treatments and the trials conducted with naproxen have been reviewed. Naproxen is oxidized into 9-O-desmethyl-naproxen by CYP2C9 and by CYP1A2 and is also conjugated with glucuronic acid by UGT2B6. The pharmacokinetics of naproxen have been studied in patients with rheumatoid arthritis and in healthy patients. The elimination half-life of naproxen is about 10 hours in patients and in healthy volunteers. Naproxen binds to plasma protein for 99% and the concentration of plasma protein is lower in patients than in healthy volunteers consequently the elimination half-life of unbound naproxen is 3.6$\pm$0.8 and 4.8$\pm$0.8 hours (P-value < 0.02) in patients and in healthy volunteers, respectively, and all pharmacokinetic parameters of unbound naproxen are different in patients and healthy volunteers. The toxicity induced by naproxen has been reviewed. The aim of this study is to review the clinical pharmacology of naproxen.

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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