American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 4 (April), 2014: pp 388-394
Available online at www.jpain.org and www.sciencedirect.com

Dexketoprofen Trometamol in the Acute Treatment of Migraine Attack: A Phase II, Randomized, Double-Blind, Crossover, Placebo-Controlled, Dose Optimization Study

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Abstract: Migraine is a disabling disease that can significantly affect a person's quality of life. This study assessed the efficacy and tolerability of the 2 doses of dexketoprofen trometamol (DKP) compared to placebo for migraine treatment. Ninety-three patients with at least 1 migraine attack per month in the preceding 6 months were enrolled and randomized to 25 mg DKP, 50 mg DKP, and placebo in a randomized, double-blind, single-center, crossover, placebo-controlled study. Primary endpoint was pain-free episodes 2 hours after drug intake. The presence of accompanying symptoms and adverse effects was also recorded. Seventy-six patients (mean age 40.5 ± 10.9 and 61% female) completed the study. At baseline, mean number of attacks/month was 3.7 ± 1.3, with a mean duration of 15.4 ± 13.5 hours. Prevalence of pain-free episodes after drug intake was significantly reduced by 50 mg DKP vs placebo (33.8 vs 14.7%, *P* = .0065) whereas the dose of DKP 25 mg was better than placebo but did not reach statistical significance (23 vs 14.7%, *P* = .1182). Both 25 mg DKP (56.8 vs 25.3%, *P* = .0002) and 50 mg DKP improved headache relief compared to placebo. Furthermore, both doses of DKP increased the absence of functional disability (25 mg DKP, 39.7 vs 24%, *P* = .045; and 50 mg DKP, 45.9 vs 24%, *P* < .0004). Both doses of DKP were effective and well tolerated for acute migraine treatment.

***Perspective:** This article demonstrates the efficacy and tolerability of DKP in the treatment of migraine without and with aura attacks. Its rapid absorption rate with higher maximum plasma concentrations and shorter time to maximum values suggest that this drug is a good option for acute migraine treatment.*

***Key words:** Migraine, anti-inflammatory, acute treatment, pain relief, quality of life.*

Received November 6, 2013; Revised December 29, 2013; Accepted December 31, 2013.

The study was financially supported by Menarini Industrie Farmaceutiche Riunite through an unconditional and unrestricted grant. The funding source did not influence or commented on planned methods, protocol, data analysis and the draft report. The authors did not receive payments to themselves for the study. F.M. has occasionally served as scientific consultant for Istituto Lusofarmaco d'Italia-Menarini group, Almirall, Pfizer, Merck. G.Z. has occasionally served as scientific consultant for Menarini International Operations Luxembourg, Almirall, Pfizer, Merck, and Allergan. F.M. has occasionally served as scientific consultant for Almirall, Pfizer, and Merck. D.P. and D.Z. are employees of Istituto Lusofarmaco d'Italia–Menarini group.

The services of Primula (Dr. Selene Mogavero and Dr. Colin Gerard Egan) were paid by Istituto Lusofarmaco d'Italia, Menarini group to revise the English version of the manuscript.

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1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.12.006

Migraine is a common disabling primary headache characterized by recurrent attacks of moderate to severe pain associated with phonophobia, photophobia, osmophobia, nausea and vomiting.[12,16,25] Diagnosis is based on clinical features that must fulfill the diagnostic criteria proposed by the International Headache Society.[14] The World Health Organization has recently described migraine as one of the most disabling chronic diseases.[31] In Western countries, overall year prevalence of migraine is 11%; prevalence in females is higher than in males.[22,26,27] Most migraine patients do not undergo medical consultation nor receive a diagnosis of migraine; therefore, these patients do not receive proper therapy, and migraine attacks are treated using over-the-counter drugs.

Drugs used for the treatment of migraine attacks include triptans, analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs]), ergot derivatives, and antiemetics.[8]

NSAIDs are indicated for treatment of mild to moderate attacks or when triptans are contraindicated or ineffective.[7,8,10,21] The rationale for their use is based on the potential involvement of prostaglandins in the pathophysiology of migraine. NSAIDs exert their action by inhibiting cyclooxygenase, thus decreasing the synthesis of prostaglandins and leukotrienes.[15]

NSAIDs are a structurally diverse group of agents with analgesic, antipyretic, and anti-inflammatory properties. Ketoprofen is a member of the arylpropionate group of NSAIDs and has a well-established analgesic and anti-inflammatory effect. Racemic ketoprofen is used as an analgesic and anti-inflammatory agent and is one of the most potent in vitro inhibitors of prostaglandin synthesis. This effect is due to the S(+)-enantiomer (dexketoprofen), whereas the R(−)-enantiomer lacks this activity.[6,11,17,28,30]

Dexketoprofen has been developed as a water-soluble tromethamine salt (dexketoprofen trometamol [DKP]) and is available in several European Union countries as standard immediate-release tablets (12.5 and 25 mg) for the symptomatic treatment of mild to moderate pain intensity, such as musculoskeletal, dysmenorrheal, and dental pain. In healthy volunteers, DKP, compared to ketoprofen, has been shown to have a more rapid absorption rate with higher maximum plasma concentrations and shorter time to maximum values, suggesting that it is a good option for acute use.[2,5]

Several studies conducted with orally administered DKP in patients affected by acute and chronic pain have confirmed its efficacy and good tolerability.[1,3,9,13,18,19,23,24,29,32]

To date, only 1 study has been performed with DKP in the treatment of acute migraine attacks.[1] However, it was a single-dose self-treatment study, performed on a small female cohort. The primary objective of this randomized crossover study was to assess the efficacy and tolerability of 2 different doses of DKP (25 and 50 mg) compared to placebo in the acute treatment of migraine attacks, with or without aura. A secondary objective was to compare the efficacy of the 2 doses of DKP in order to assess if a 50-mg dose (two 25-mg tablets) was more effective than a single 25-mg dose in the acute treatment of migraine attacks.

Methods

Participants

Patients who gave written informed consent were screened for eligibility at visit 1, blood was drawn for hematologic and biochemical tests, and a urine sample was collected for analysis. Patients who met all the inclusion/exclusion criteria (except laboratory tests, which were reported later) were enrolled in the study and randomized for administration of oral DKP or placebo in a 2:1 ratio.

All patients had to meet the following eligibility criteria to participate in the trial: age between 18 and 65 years, diagnosis of migraine within the past year, age at migraine onset younger than 50 years, frequency of migraine attacks from 2 to 6 episodes/month, total number of days with headache per month fewer than 15, negative pregnancy test (for both pre- and perimenopausal women), and use of a highly effective method of birth control (for both pre- and perimenopausal women).

Individuals were excluded from participation if they met any 1 of the following exclusion criteria: concomitant headaches, consumption of analgesic and anti-inflammatory agents or other drugs for acute treatment of migraine attacks for more than 10 consecutive days per month in the 3-month period before study entry, muscular or osteoarticular diseases that required treatment with analgesics or anti-inflammatory agents, known hypersensitivity to study medications, use of an investigational drug within the past 3 months prior to screening/enrollment, duodenal or gastric ulcer, moderate to severe renal insufficiency, pregnant and lactating women, treatment with antipsychotic or antidepressant agents (except those used for migraine prophylaxis) at the time of or within 3 months before screening/enrollment, history of alcohol and/or drug abuse, any clinical condition that may represent a risk for a safe participation of the patient according to the judgment of the investigator, or patients who were unwilling or unable to provide informed consent or to participate for the entire study period. The study was performed according to the Declaration of Helsinki following authorization from the local ethics committee. All patients provided written informed consent.

Randomization

Ninety-three patients with a diagnosis of mild to moderate migraine with or without aura fulfilling the Criteria of International Headache Society[14] were randomized to 1 of the 3 groups (group 1, group 2, and group 3) (Table 1). Subject's assignment to the treatment groups was based on the randomization list prepared before the start of the study; randomization envelopes could be opened in case of emergency.

Each patient was blindly treated for 3 consecutive migraine attacks with the 3 study drugs (DKP 25 mg, DKP 50 mg, and placebo) according to the predefined treatment sequences (Table 1). Medication was packaged into polyvinyl chloride blisters using the double-dummy technique. Each blister contained 2 tablets corresponding to the following combinations: placebo + placebo; placebo + DKP 25 mg; DKP 25 mg + DKP 25 mg. Each blister was numbered according to the sequence of its intake: blister 1 for the first,

Table 1. Predefined Treatment Sequences

	Attack 1	*Attack 2*	*Attack 3*
Group 1	DKP 25 mg	DKP 50 mg	Placebo
Group 2	Placebo	DKP 25 mg	DKP 50 mg
Group 3	DKP 50 mg	Placebo	DKP 25 mg