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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.*

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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

blister 2 for the second, and blister 3 for the third migraine attacks (Table 1).

In order to keep the treatment blind, the study drugs were encapsulated. Eventual rescue medication was prescribed by the investigator (F.M.) according to each patient's history and preference.

Study Design and Procedures

This was a randomized, double-blind, single-center, crossover, placebo-controlled, dose-optimization, phase II trial performed in Italy.

To avoid the treatment of a recurrent attack, a pain-free period of at least 48 hours between each attack was mandatory. All parameters have been recorded in a personal diary; a 4-point rating scale recommended by the International Headache Society criteria (0 = no headache, 1 = mild headache, 2 = moderate headache, 3 = severe headache) was used to assess the intensity of the headache attack.[14]

Patients were also requested to record the above self-assessments in their diaries at 2, 4, 6, 12, and 24 hours after taking the study medication. In addition, they were to record whether their headache improved, the time at which it improved, and headache severity at improvement, if applicable; whether there was a recurrence of migraine, time of recurrence, and headache severity at recurrence, if applicable; the use of rescue medication; and all adverse events (AEs). The patient was to record the time at which he or she considered that meaningful relief had been obtained and then complete the 24-hour Quality of Life questionnaire within 30 hours of taking the first dose of study medication. The primary end point of the study was prevalence of pain-free episodes 2 hours after medication intake.

The secondary efficacy variables assessed were headache relief (percentage of patients with a decrease in headache from severe or moderate to none or mild within 2 hours, before any rescue medication), presence of associated symptoms (percentage of patients with complete recovery from nausea, vomiting, photophobia and phonophobia after 2 hours, before any rescue medication), any functional disability (recorded prior to drug intake and up to 2 hours later, before any rescue medication), incidence of relapse (percentage of patients pain-free at 2 hours who experienced the return of headache of any severity within 24 hours), patient's preference for treatments, and use of rescue medications. Both primary efficacy measures and secondary efficacy parameters were based on the recommendations of the Guidelines for Controlled Trials of Drugs in Migraine.[29] The safety variables evaluated in this trial included frequency, seriousness, and severity of any reported AE; laboratory assessments of blood (clinical hematology, biochemistry); and vital signs (heart rate, blood pressure, and physical and neurologic examination).

Statistical Analysis

For sample size calculation, because this was a pilot study and little data are available in literature concerning the use of DKP in acute treatment of migraine attacks, we considered a study done with DKP, ketoprofen, and placebo in postoperative dental pain.[18]

The sample size was calculated considering a percentage of pain-free patients at 2 hours of 61.6 and 27.8% with DKP and placebo, respectively. Considering values of $\beta = 80\%$ and $\alpha = 5\%$, the number of patients in each treatment arm was 30. Considering the crossover design of this study, a total number of 90 patients was sufficient, including possible dropouts.

The main statistical hypothesis was to demonstrate that the percentage of patients pain free at 2 hours is statistically different between the 3 treatment groups ($P = .05$, 2-tailed test). Considering the crossover design of this study, analysis was stratified for patients and included period and carry-over effects. For both primary and secondary efficacy measures, a dichotomic data analysis (logistic regression) was performed in the overall population. All secondary efficacy parameters were expressed by using contingency tables. Comparisons between treatment groups were performed by using conditional logistic regression analysis stratified for patient that included treatments, baseline values, period, and carry-over effect. The final model was obtained by progressive elimination of nonsignificant variables on the maximum likelihood test. Results were expressed as hazard ratios with 95% confidence intervals and P value. If not indicated, the results of per-protocol analysis were similar to those reported in the intention-to-treat (ITT) analysis.

In the overall population as well as in subpopulations defined according to possible intake of rescue medications, a dichotomic data analysis (logistic regression) was performed to evaluate both primary and secondary efficacy measures, whereas analysis of variance was used for safety parameters (eg, heart rate, blood pressure, laboratory parameters). Abnormal laboratory results and AEs were analyzed by using nonparametric tests (chi-square, Kruskal-Wallis, and McNemar test). Statistical evaluations were planned, conducted, and reported using the SAS System for Windows Release 9.11 (SAS Institute Inc, Cary, NC).

Results

Patients

A total of 93 patients were enrolled; 15 discontinued prior to drug intake, 2 discontinued after 1 attack, and 1 discontinued after 2 attacks. Reasons for discontinuing were consent withdrawal (14 patients) and lost to follow-up (4 patients). Four protocol violations (2 major and 2 minor) occurred. The 2 major protocol violations were due to intake of medicines not allowed by study protocol; both patients did not have valuable attacks. Primary analyses of efficacy parameters were based on the ITT analysis set. The ITT population included all randomized patients who received at least 1 dose of study medication without any major protocol violation and comprised 76 patients. The per-protocol population included all randomized patients who completed the study (3 consecutive treated attacks) without major or minor protocol

Table 2. Baseline Characteristics

	Placebo (N = 75)	*DKP 25 mg (N = 74)*	*DKP 50 mg (N = 74)*
Demographic characteristics			
Gender			
Females	46 (61.3%)	45 (60.8%)	45 (60.8%)
Males	29 (38.7%)	29 (39.2%)	29 (39.2%)
Age (y)	40.5 ± 10.9	40.5 ± 11.0	40.5 ± 11.0
Weight (kg)	70.4 ± 13.7	67.8 ± 13.6	67.8 ± 13.6
Height (cm)	168.6 ± 9.0	168.8 ± 9.0	168.8 ± 9.0
Migraine characteristics			
Aura			
No	74 (98.7%)	73 (98.6%)	73 (98.6%)
Yes	1 (1.3%)	1 (1.4%)	1 (1.4%)
Duration (y)	17.1 ± 9.9	17.1 ± 9.9	17.1 ± 9.9
Attacks per month	3.7 ± 1.3	3.7 ± 1.3	3.7 ± 1.3
Attack duration (h)	15.4 ± 13.5	15.8 ± 14.0	15.8 ± 14.0

Abbreviation: SD, standard deviation.
NOTE. Values are reported as mean ± SD or as n (%).

violations and comprised 71 patients. Baseline demographic and clinical characteristics for patients (ITT population) are presented in Table 2. The mean age of patients at the start of the study was 40.5 ± 10.9, and 61% were female. The mean number of attacks/month was 3.7 ± 1.3, with a mean duration of 15.6 ± 13.8 hours. Clinical characteristics were similar for the different treatment groups (Table 2).

Primary Efficacy Variable

The percentage of patients with pain-free episodes at 2 hours was higher in patients treated with 50 mg DKP compared to placebo (34 vs 15%, $P < .05$; Fig 1). Although 25 mg DKP improved the proportion of patients with pain-free episodes compared to placebo, this difference did not attain statistical significance (23 vs 15%, $P = .118$). No statistical difference was observed between the percentage of patients experiencing pain-free episodes for the 2 doses of DKP.

The percentage of patients with pain-free episodes at 2 hours considering only the first attack treated were, respectively, 4% (1/25) for placebo, 39.3% (11/28) for DKP 25 ($P < .05$ vs placebo), and 39.1% (9/23) for DKP 50 ($P < .05$ vs placebo).

Secondary Efficacy Variables

The proportions of patients who experienced headache relief after 2 hours were 25%, 57%, and 65% with placebo, 25 mg DKP, and 50 mg DKP, respectively (Fig 2). The effect of both doses of DKP on the percentage of patients who had headache relief at 2 hours was significantly higher than the effect of placebo. The percentage of patients free of disability at 2 hours was higher with both doses of DKP (50 mg DKP = 46%; 25 mg DKP = 40%) compared to placebo (24%), and these differences were statistically significant (Fig 3).

The proportion of patients showing complete recovery from photophobia after 2 hours was double with 25 mg DKP (46%) or triple (72%) with 50 mg DKP compared to placebo (24%). The effect of 50 mg DKP versus placebo was statistically significant ($P < .0001$). The rate of recovery from phonophobia in patients was approximately double with DKP (52% and 44% for 25 mg and 50 mg DKP, respectively) compared to placebo (24%), attaining statistical significance for 25 mg DKP vs placebo (52% vs 24%, $P < .05$). Resolution of nausea was higher with both 25 and 50 mg DKP (62–64%) in comparison with placebo (33%), although this difference did not attain statistical significance because of the low number of patients who experienced nausea.

The proportion of patients who had recurring migraine was similar for the 3 treatments, with no statistically significant differences between DKP and placebo (placebo: 25%; 25 mg DKP: 28%; 50 mg DKP: 27%).

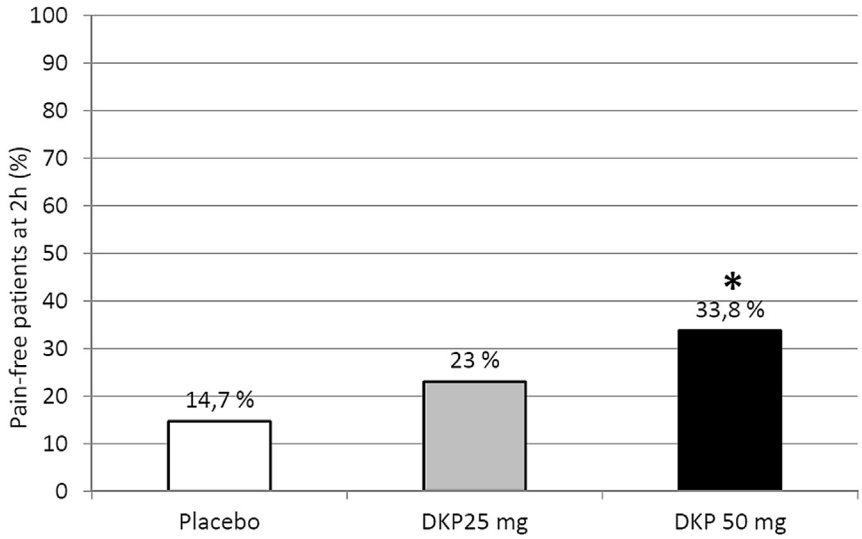

Figure 1. Prevalence of pain-free patients 2 hours after drug administration (primary end-point). DKP 25 mg versus placebo, HR [95% CI] = .483 [.194–1.204], $P = .1182$; DKP 50 mg versus placebo, HR = .290 [.119–.707], $P = .0065$; DKP 50 mg versus DKP 25 mg, HR = .600 [.277–1.301], $P = .1962$. *$P < .05$, statistically significant difference between the group treated with placebo and the group treated with DKP 50 mg. Abbreviations: HR, hazard ratio; CI, confidence interval.

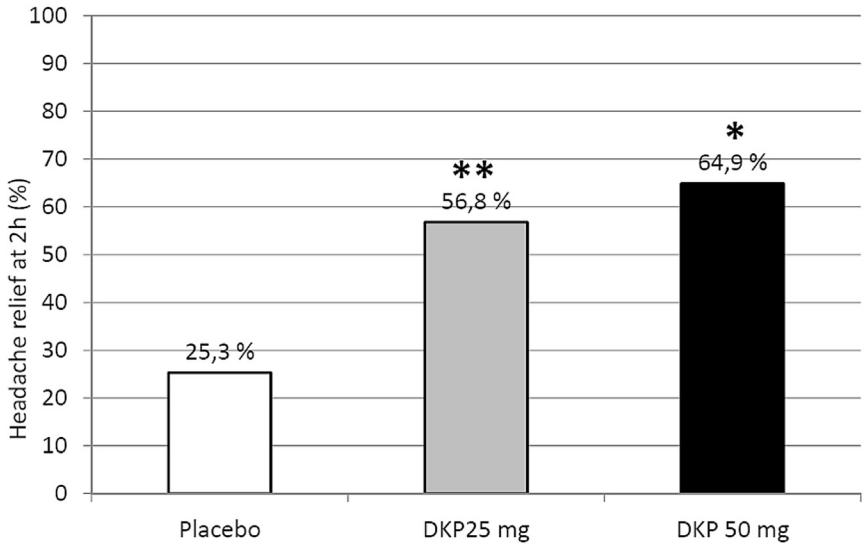

Figure 2. Prevalence of headache relief in patients 2 hours after drug administration (secondary end-point in ITT population). DKP 25 mg versus placebo, HR [95% CI] = .238 [.111–.510], $P = .0002$; DKP 50 mg versus placebo, HR = .173 [.80–.377], $P < .0001$; DKP 50 mg versus DKP 25 mg, HR = .729 [.364–1.463], $P = .3742$. $^{**}P < .05$, statistically significant difference between the group treated with placebo and the groups treated with DKP 25 mg. $^{*}P < .0001$, statistically significant difference between the group treated with placebo and the group treated with DKP 50 mg. Abbreviations: HR, hazard ratio; CI, confidence interval.

The percentages of patients who would choose the same treatment again were 72%, 62%, and 38% for 50 mg DKP, 25 mg DKP, and placebo, respectively. Differences between both doses of DKP and placebo were highly significant ($P < .05$ with DKP 25 mg and $P < .001$ with DKP 50 mg).

More than two-thirds of patients treated with placebo (68%) sought rescue medication for pain relief, compared with 37 and 32% with DKP 25 mg and DKP 50 mg, respectively ($P < .001$ for both).

Safety

A total of 78 patients were included in the safety population consisting of all enrolled patients who received at least 1 dose of any study medication (including placebo).

AEs reported by patients who participated in the study are shown in Table 3. No serious AEs were reported; 28 AEs defined as "not serious" were reported by 18 patients. Gastrointestinal system AEs were more frequent, 4 with DKP 25 mg, 7 with DKP 50 mg, and 5 with placebo. No significant differences in the incidence of AEs, abnormal laboratory values, or clinically relevant changes in mean heart rate or blood pressure were observed among the different treatment groups.

Discussion

There are different pharmacologic classes of first-line drugs used to treat migraine attacks. Parameters that

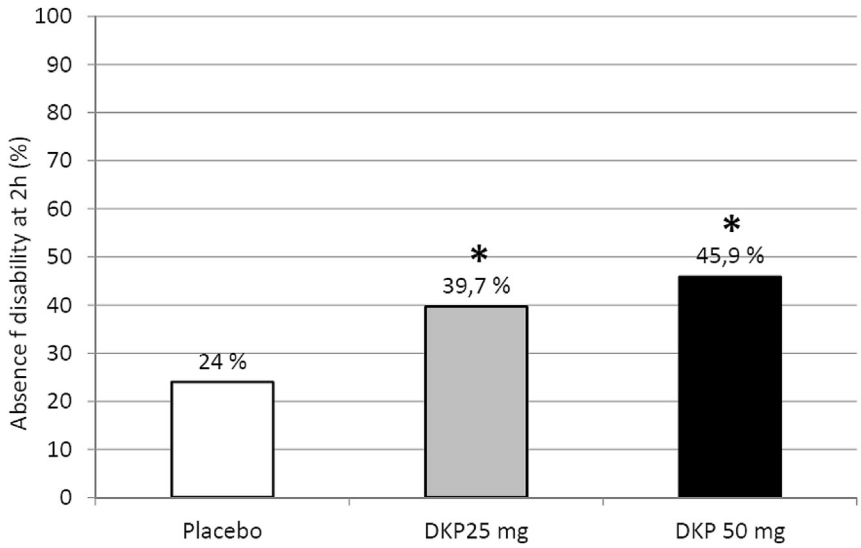

Figure 3. Absence of functional disability in patients 2 hours after drug administration (secondary end-point in ITT population). DKP 25 mg versus placebo, HR [95% CI] = .450 [.206–.982], $P = .0450$; DKP 50 mg versus placebo, HR = .322 [.148–.702], $P < .0044$; DKP 50 mg versus DKP 25 mg, HR = .716 [.356–1.439], $P = .3479$. $^{*}P < .05$, statistically significant difference between the group treated with placebo and the group treated with DKP 25 mg and DKP 50 mg. Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 3. Overall Summary of Adverse Events–Safety Population

	Placebo (N* = 77)		DKP 25 mg (N* = 76)		DKP 50 mg (N* = 76)	
	Number (%) of Attacks With at Least 1 AE	Number of AEs	Number (%) of Attacks With at Least 1 AE	Number of AEs	Number (%) of Attacks With at Least 1 AE	Number of AEs
All AEs	7 (9.1%)	8	6 (7.9%)	11	7 (9.2%)	9
Mild	7 (9.1%)	8	7 (9.1%)	11	4 (5.3%)	4
Moderate	0 (0%)	0	0 (0%)	0	2 (2.6%)	3
Not available	0 (0%)	0	0 (0%)	0	1 (1.3%)	2

*Total number of attacks.

must be met for an agent to be considered as first-line medication include quality of evidence, strength of scientific evidence, clinical evaluation and possible side effects. In addition to triptans, guidelines published by the European Federation of Neurological Societies[8] state that the following molecules have also been given first-line recommendation: acetylsalicylic acid, naproxen, ibuprofen, diclofenac, and paracetamol. The scarcity of controlled clinical trials performed according to good clinical practice on a large population constitutes one of the most frequent causes of failure to include other molecules that are widely used as first level of recommendation, regardless of their efficacy. This is the first randomized, double-blind, crossover, placebo-controlled, dose-optimization phase II study of DKP in the treatment of migraine attacks.

DKP (12.5- and 25-mg tablets) is currently marketed in European Union countries for the symptomatic treatment of pain of mild to moderate intensity, such as musculoskeletal, dysmenorrheal, and dental pain. There is limited experience with DKP 25 mg in the acute treatment of migraine attacks,[1] but data from other studies demonstrated that the 50-mg dose may be more efficacious at least in patients who underwent orthopedic surgery or who were affected by renal colic or with severe dental pain.[3,9,13,18,19,23,24,29,32]

This phase II pilot study was performed in order to assess the most appropriate dose of DKP for the acute treatment of a migraine attack. The study was designed as a pilot study with a limited number of patients enrolled, but it was performed according to the most recent recommendations of the International Headache Society for the evaluation of migraine drug treatment.[29]

As this was a pilot study and limited data were available regarding efficacy of DKP in migraine treatment, sample size was calculated on efficacy data obtained in a different setting, postoperative dental pain, for both DKP and placebo, considering rates of being pain free at 2 hours that ended up to be twice of that expected.[18] However, we did a post hoc power calculation that resulted in a very similar sample size needed to reach statistical significance.

In fact, assuming a comparison of 2 independent binomial proportions (pain free at 2 hours 15% for placebo and 35% for DKP) using a Pearson's chi-square test with $\alpha = 5\%$ and $\beta = 80\%$, the total number of patients required is 73, very close to the number of patients of this study.

It is important to point out that there were a lot of data with pain-free rates for placebo at 2 hours in migraine that could have provided better placebo estimation for this study.[4,11,20]

Overall, the ITT analysis of primary endpoint (percentage of patients pain free at 2 hours) indicated that DKP 50 mg is better than placebo (34 vs 15%, $P < .05$) in the acute treatment of mild to moderate migraine attacks (NTT = 6). However, 25 mg DKP had an intermediate efficacy, not differing in statistical significance compared with placebo or 50 mg DKP.

Secondary efficacy parameters analysis, as headache relief at 2 hours and functional disability, confirmed the efficacy of both 25 and 50 mg DKP, compared to placebo.

All DKP dosages were safe and well tolerated in this study and there was no significant difference between the safety profile of DKP 50 mg, DKP 25 mg, and placebo.

Findings from the present study indicate that the 25-mg dose of DKP was effective and well tolerated in the treatment of symptomatic migraine attacks. The rapidity by which the molecule acts is a feature that makes this drug a good option in crises of migraine, regardless of the speed at which the peak of maximum intensity of pain is reached. In addition, concomitant use with long-acting triptans may be suggested in patients who present crises with rapid achievement of peak pain intensity and distant recurrences. Further controlled studies are needed to confirm these encouraging results from this pilot study.

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