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Efficacy and tolerability of a new powdered formulation of diclofenac potassium for oral solution for the acute treatment of migraine: Results from the International Migraine Pain Assessment Clinical Trial (IMPACT)

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Abstract

Objective: This study assessed the efficacy of diclofenac potassium for oral solution, a novel water-soluble buffered powder formulation, versus placebo for the acute treatment of migraine. Diclofenac potassium for oral solution has a time to maximum plasma concentration (T_{max}) of 15 minutes, suggesting the potential for a rapid onset of therapeutic effects.

Methods: This was a randomized, double-blind, parallel-group, placebo-controlled study conducted in 23 US centers. Adult sufferers with an established migraine diagnosis according to the International Classification of Headache Disorders, second edition (ICHD-II), treated one moderate or severe attack with 50 mg diclofenac potassium for oral solution (dissolved in approximately 2 ounces of water; $N = 343$) or matching placebo ($N = 347$). Four co-primary endpoints included the percentage of subjects who at two hours post-treatment reported no headache pain, no nausea, no photophobia and/or no phonophobia.

Results: Significantly more subjects treated with diclofenac potassium for oral solution ($N = 343$) achieved a two-hour pain-free response (25% vs. 10%, $p < .001$), no nausea (65% vs. 53%; $p = .002$), no photophobia (41% vs. 27%; $p < .001$) and no phonophobia (44% vs. 27%; $p < .001$) compared to placebo. Pain intensity differences between treatments were significantly lower in the diclofenac potassium oral solution group, starting at 30 minutes post-treatment ($p = .013$) with significant differences at all time points thereafter ($p < .001$). Twenty-four-hour sustained pain-free response favored diclofenac potassium oral solution treatment versus placebo (19% vs. 7%, $p < .0001$). The most common adverse event considered to be treatment related was nausea (diclofenac potassium for oral solution [4.6%]; placebo [4.3%]).

Conclusions: This study shows that this formulation of diclofenac potassium for oral solution is effective in reducing pain intensity within 30 minutes, which may be related to the 15-minute T_{max} associated with this formulation. The rapid-onset benefits were sustained through 24 hours post-treatment.

Keywords
migraine, diclofenac potassium, acute treatment, buffered formulation

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Introduction

Migraine is a common headache disorder that is characterized by severe pain, nausea, sensory sensitivity and disability (1). Acute treatments taken at the time of the attack are a mainstay of migraine management (2). Surveys reveal that migraine patients want rapid

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onset of pain relief, often within 30 minutes, when using an oral therapy (3,4). First-line acute treatments of migraine include a variety of oral analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) (2).

In an effort to deliver more rapid onset of pain relief, a variety of formulation alternatives to oral triptan tablets have been developed, including injections, nasal sprays and rapidly dissolving oral wafers (2). NSAIDs are widely used for the acute treatment of migraine, and a number of different compounds have proven efficacy as oral tablets or injections (5). While parenteral (intramuscular, intravenous) NSAIDs deliver migraine relief within 30 minutes, oral NSAIDs generally do not (2,5). However, despite their efficacy, use of injectable and nasal spray formulations for migraine has been limited, perhaps because of a strong patient preference for oral therapy (3,4). A non-steroidal oral anti-inflammatory agent that delivers rapid relief within 30 minutes is clearly needed.

Diclofenac is a non-steroidal anti-inflammatory analgesic agent available as either sodium or potassium salts. The diclofenac anion, the active ingredient, is believed to exert its effect as a cyclo-oxygenase enzyme inhibitor, thereby causing a decrease in prostaglandin production (6). Though head-to-head studies are not available, the potassium salt is more rapidly absorbed and appears to be more effective as a migraine treatment as compared to the sodium salt formulation (6).

Previous studies show that oral diclofenac potassium tablets are effective for the acute and chronic treatment of several different pain conditions (7–11). In migraine, oral tablet formulations of diclofenac potassium 50 mg and 100 mg have been proven effective for acute treatment of migraine two hours following dosing (6,12). However, patients seek rapid pain relief, and therefore two-hour pain relief is less than ideal. To improve the absorption rate, diclofenac potassium has been developed as a new 50-mg diclofenac potassium for oral solution (CAMBIA^{TM}). In fasting healthy volunteers, diclofenac was detected in plasma within five minutes following administration of diclofenac potassium for oral suspension (13).

A rapid onset of efficacy of diclofenac potassium for oral suspension has previously been reported for pain conditions other than migraine. In a study by Olson and colleagues, 50 mg powdered diclofenac potassium was significantly more effective than aspirin in reducing episiotomy pain as early as 30 minutes following dosing (9). The favorable pharmacokinetic profile and the results of a prior study assessing this formulation in migraine suggest that diclofenac potassium for oral solution may be an effective treatment of migraine. Indeed, a prior report showed efficacy in relief of migraine pain, but this small study was not adequately powered to assess the efficacy of diclofenac potassium on associated symptoms such as nausea, photophobia and phonophobia (14). Accordingly, herein we compare the efficacy and tolerability of a single oral dose of 50 mg diclofenac potassium for oral solution, a buffered, flavored, powder formulation, versus placebo in the acute treatment of migraine with or without aura in adults.

Methods

Study design

This study was a multicenter (23 US centers), double-blind, double-dummy, randomized, placebo-controlled, single-attack trial comparing diclofenac potassium for oral solution (a buffered flavored formulation of diclofenac potassium 50 mg dissolved in approximately 2 ounces of water) and placebo for the acute treatment of moderate or severe migraine. All clinical work conducted was in compliance with Good Clinical Practice Guidelines and in accordance with the regulations of the Declaration of Helsinki and approved by local ethics committees at individual study centers (Institutional Review Boards). Study subjects provided informed consent prior to enrollment.

Subjects

Subjects recruited for the trial (the study was conducted from 18 May 2006 to 21 December 2006) had an established one-year history of migraine with or without aura according to the diagnostic criteria of the International Classification of Headache Disorders, second edition (ICHD-II) (15). Male and female subjects between the ages of 18 and 65 participated in the trial and had an average of one to six migraine attacks per month for the previous 12 months. To qualify, the subject must have had a history, on average, of at least one migraine attack per month, but an average of no more than six migraine attacks monthly during the previous year. Subjects had to have 10 or fewer headache days per month. Prophylactic treatment for migraine was permitted provided the patient had been on a consistent dosing regimen for longer than three months. Exclusion criteria included: pregnancy; risk of pregnancy (not on birth control); lactating; hypersensitivity or allergy to NSAIDs, prostaglandin-synthase inhibitors, aspirin, diclofenac or excipients of study medication products; headache symptoms likely due to, or aggravated by, traumatic injury to the head or neck region, such as whiplash, within the last six months; secondary headache or abnormal findings with neurological exam; or any clinically significant medical history. These criteria were aimed to exclude individuals so disabled that they would be unable to complete the

tasks required for study participation (e.g. recording diary card information; use of rescue medications). Subjects with a history of vomiting 20% of the time during migraine attacks or were usually so incapacitated as to require bed rest during the attack were also excluded. These criteria were designed to exclude individuals who were potentially unable to perform or complete the study protocol or were likely to vomit after taking this liquid medication. (These criteria do not raise challenges to the statistical conclusion validity of the study but do limit its generalizability as noted in the discussion).

Treatment

This was a single-attack study where participants treated one moderate or severe migraine episode with study medication. Study medication was self-administered in an outpatient setting. Study medication was not used within 48 hours of treating a previous migraine or within 24 hours of taking analgesic medications for another reason.

All information was recorded using a standard headache diary. Participants visited the clinic twice during the study: at study enrollment (visit 1) and within 2 weeks after treating their migraine attack (visit 2). At visit 1, subjects completed a migraine qualifying form, which confirmed the ICHD-II criteria for migraine. Subjects participated in an eight-week treatment period in which they were to treat a single migraine attack (with or without aura) of moderate or severe intensity (with physician consent, this treatment phase could be extended to 12 weeks).

Participants were assigned subject numbers in ascending numerical order within each site according to a predetermined random code. The randomization was based on a ratio of 1 : 1 in blocks of undisclosed (to the investigational site) size. After randomization, each subject received study medication (which was coded for blinding), a stopwatch and a headache diary.

Study participants took a single dose of 50 mg diclofenac potassium for oral solution or placebo by opening the study medication pouch and adding the contents to approximately 2 ounces of water, stirring gently and drinking the entire contents when the solution cleared. If any residual remained in the glass, the subjects were instructed to add additional water and drink the remaining solution. Completion of diary card information began at 15 minutes post-dose and extended up to 24 hours following dosing with study medication.

Subjects were asked to wait two hours after taking study medication before taking rescue migraine medication. Subjects who used rescue medication prior to the two-hour evaluation were considered non-responders and were in violation of the protocol. Prior to taking the first dose of rescue medication, the subjects recorded evaluations of headache pain intensity, nausea, photophobia, phonophobia, vomiting and ability to function.

Outcome measures

Efficacy assessment was based on four co-primary variables, which included the percentage of subjects who, at two hours, were (a) pain-free, (b) without nausea, (c) without photophobia or (d) without phonophobia. Pain and associated symptoms were assessed on a 4-point scale ranging from 0 (no pain) to 3 (severe pain). Pain-free response was defined as a reduction from moderate or severe pain to no pain following treatment.

Secondary endpoints included reduction in pain intensity difference (PID) at each evaluation time (PID = pre-dose value – post-dose value), sustained pain-free response, headache response (reduction of moderate or severe pain to mild or no pain at two hours), presence or absence of vomiting, frequency of headache recurrence and improvement in the ability to function. Secondary endpoints were measured at baseline, 15, 30, 45, 60 and 90 minutes as well as at 2, 2.5, 3, 4, 8, 16 and 24 hours following treatment.

Tolerability and safety

Subjects recorded all adverse events in their headache diaries occurring subsequent to dosing and through the 24-hour post-dosing period. Any adverse event occurring after 24 hours and reported by the subject at visit 2 were recorded on the adverse event case report form. All adverse events occurring during the study were classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Statistics

Of the four co-primary endpoints, freedom from nausea, is often the most difficult to achieve because it is less common than other features. Our goal was to have 80% power to detect a significant difference in freedom from nausea at two hours. Based on prior data, it was estimated that the nausea-free rate at two hours would be 45.6% for diclofenac potassium for oral solution-treated subjects and 34.4% of the placebo-treated subjects (16). With a sample size of 325 subjects per treatment arm (in a modified intent-to-treat analysis [MITT]) 81% power was estimated to detect a statistically significant difference in nausea (alpha = 0.05). With pain-free rates at two hours of 24.7% for the diclofenac potassium for oral solution and 11.7% for placebo, a sample of 325 subjects

per arm provided a 98% power to detect a statistically significant difference (alpha = 0.05). The sample size computation program, nQuery Advisor version 5.0 (Statistical Solutions, Saugus, MA, USA), was used to compute these powers based on a two-sided test of the equality of proportions using the two-group continuity corrected $\chi 2$ test of equal proportions (odds ratio [OR] = 1; equal numbers). Therefore, the target sample size was estimated to be 325 MITT subjects in the active treatment and 325 for the placebo treatment.

The safety population consisted of all randomized subjects who used study medication and provided a safety evaluation. The intent-to-treat (ITT) population consisted of all subjects randomized. The MMT population included all subjects who were randomized, took study medication and provide efficacy data. The per-protocol (PP) population included all subjects in the MITT population who did not use rescue medication prior to the two hours post-dose evaluation and had no other major protocol deviations. The primary efficacy parameters were analyzed for the ITT population and the PP population. If subjects took rescue medication within 24 hours from the time of dosing with the study medication, pain intensity, nausea, photophobia, phonophobia, vomiting and ability to function scores were recorded at the time the rescue medication was taken.

All statistical processing was performed using SAS software (SAS Institute, Cary, NC, USA). Statistical significance was based on two-tailed tests of the null hypothesis resulting in p values of .05 or less. Baseline values of demographic and clinical parameters were analyzed to assess the degree to which randomization achieved comparability between the treatment groups. Analysis of the primary endpoint efficacy evaluations used the Cochran-Mantel-Haenszel test and the analysis of variance, stratified by center.

Results

Demographics

Eight hundred and seven subjects were enrolled and randomized to treatment, of which 690 comprised the ITT population (Figure 1) and 656 were included as the PP population. Reasons for study discontinuation or exclusion after randomization are listed in Table 1.

The majority of each treatment group were female (85.4% diclofenac potassium for oral solution; 84.1% placebo) and the mean ages were 40.5 and 39.9, respectively (Table 1). More subjects in the diclofenac potassium for oral solution group had phonophobia (91.0%) compared to those in the placebo group (95.1%; $p = .027$). More subjects in the diclofenac potassium for oral solution group were able to perform routine activities (3.5%) compared to those in the placebo group (2.3%; $p = .034$). Otherwise, there were no significant differences between treatment groups in demographic or baseline headache characteristics.

Primary endpoints

Efficacy results are based on the ITT population analysis as there were no significant differences noted between the ITT and PP groups. All four co-primary endpoints were significantly different from the placebo treatment group in favor of diclofenac potassium for oral solution. Two-hour pain-free response was significantly higher in the diclofenac potassium for oral solution treatment group versus the placebo group

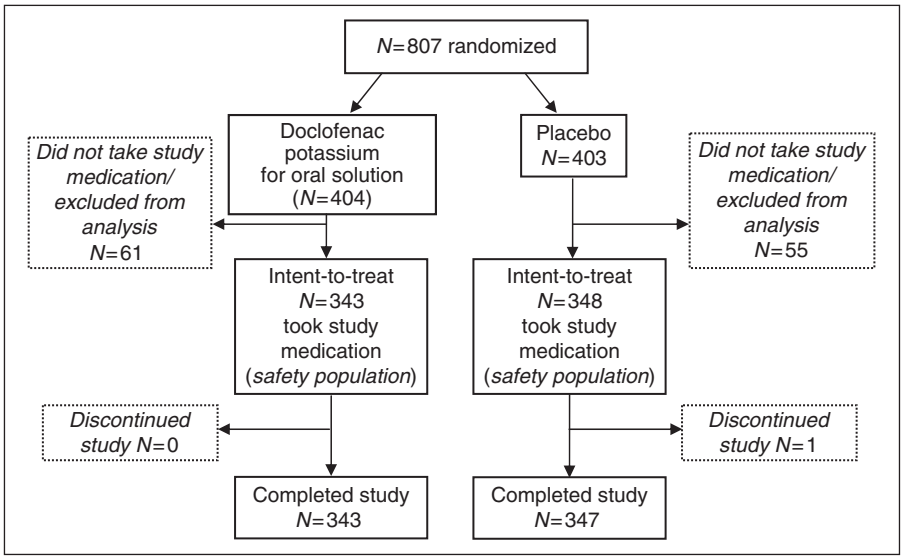

Figure 1. Study participant enrollment and study completion.

Table 1. Discontinuation and demographics

Study discontinuation after randomization	Diclofenac potassium for oral solution	Placebo
Number of subjects randomized	404	403
Did not take study medication	61	55
Reasons for not taking study medication		
Did not take medicine within time limit	22	21
Study withdrawal	4	3
Lost to follow-up	15	13
Adverse event or intercurrent illness	2	0
Other	18	18
Number who took study medication	343	347
Demographic characteristics of study subjects (safety population)		
Mean age (years)	40.5	39.9
Range	18.0–65.0	19.0–65.0
Female	293 (85.4%)	292 (84.1%)
Race		
American Indian/Alaska native	0 (0%)	1 (0.3%)
Asian	3 (0.9%)	3 (0.9%)
Black/African American	52 (15.2%)	59 (17.0%)
Caucasian	276 (80.5%)	276 (79.5%)
Other	12 (3.5%)	8 (2.3%)
Pain severity		
Moderate	250 (72.9%)	242 (69.7%)
Severe pain	93 (27.1%)	105 (30.3%)
Diagnosis		
Migraine without aura	303 (88.3%)	297 (85.6%)
Migraine with aura	40 (11.7%)	50 (14.4%)
Presence of nausea	224 (65.3%)	224 (64.6%)
Presence of photophobia	333 (97.1%)	330 (95.1%)
Presence of phonophobia*	312 (91%)	330 (95.1%)
Presence of vomiting	7 (2.0%)	11 (3.2%)
Disability		
Able to perform routine activities*	12 (3.5%)	8 (2.3%)
Mild disability	66 (19.2%)	50 (14.4%)
Moderate disability	145 (42.3%)	153 (44.1%)
Severe disability	92 (26.8%)	98 (28.2%)
Unable to perform daily activities	28 (8.2%)	38 (11.0%)

*$p < .05$ from Cochran-Mantel-Haenszel test, stratified by analysis center.

(25.1% [$N = 86/343$]; confidence interval [CI]: 20.6%, 30.1%; vs. 10.1% [$N = 35/347$]; CI: 7.1%, 13.8%) with a therapeutic gain of 15% ($p < .001$; Figure 2). Treatment with diclofenac potassium for oral solution was associated with freedom from nausea at two hours in comparison with placebo (64.7% [$N = 222/343$]; CI: 59.4%, 69.8%] vs. 52.7% [$N = 183/347$; CI: 47.3%, 58.1%]; therapeutic gain of 12%; $p < .002$; Figure 3). Photophobia-free rates were also higher on active treatment (40.5% [$N = 139/343$; CI: 35.3%, 45.9%] vs. placebo 27.4%; [$N = 95/347$; CI: 22.8%, 32.4%]; therapeutic gain of 14%; $p < .001$; Figure 3). Similarly, phonophobia-free rates were also higher with diclofenac potassium for oral solution 44.3%

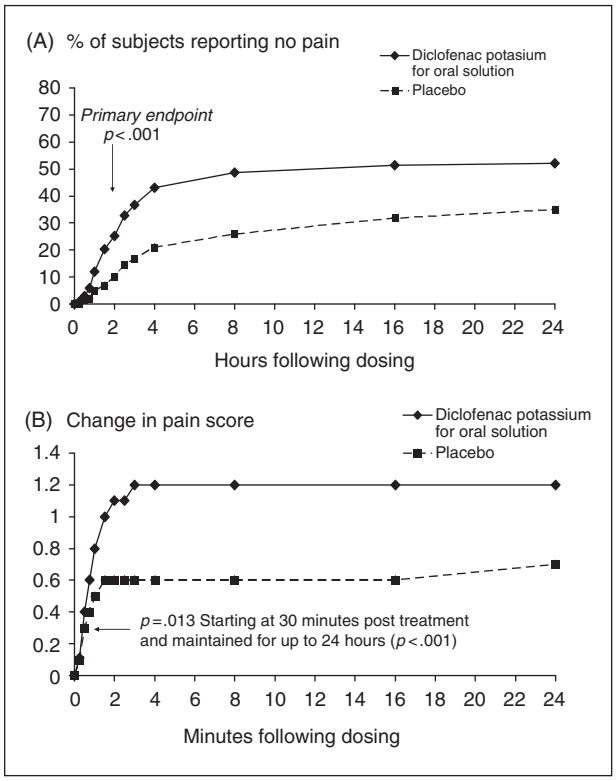

Figure 2. (A) Pain-free response by treatment group over 24 hours: Subjects in the diclofenac potassium treatment group demonstrated a statistically significant improvement over placebo in achieving a pain-free response two hours following treatment. (B) Pain intensity difference (PID) by treatment group over 24 hours. Subjects in the diclofenac potassium powder treatment group demonstrated a significant improvement over placebo in reducing pain intensity scores as early as 30 minutes following treatment.

($N = 152/343$; CI 39.0%, 49.8%) vs. placebo 27.4% ($N = 95/347$; CI: 22.8%, 32.4%); therapeutic gain of 17% ($p < .001$; Figure 3).

Secondary endpoints

Mean reduction in pain intensity from baseline. PIDs were calculated as the change in pain intensity scores between baseline and various time points following treatment. Starting as early as 30 minutes following treatment, the reduction in pain intensity score was significantly greater compared to placebo (least-square [LS] mean diclofenac potassium for oral solution = 0.4 [$N = 343$] vs. placebo = 0.3 [$N = 347$]; Figure 2B). This reduction in pain intensity score was significantly different from placebo for up to 24 hours (the duration of the treatment period recorded).

Sustained pain free. For sustained pain-free rates (defined as the percentage of subjects who reported a pain-free response at two hours with no use of rescue medication or recurrence of pain for up to 24 hours post-treatment) 19.0% ($N = 65/343$; CI 14.9%, 23.5%), of the subjects had a sustained pain-free response through 24 hours for the diclofenac potassium for oral solution treatment group compared with 7.2% ($N = 25/347$; CI 4.7, 10.5) for the placebo treatment group (therapeutic gain of 12%; $p < .001$).

Headache response rates. Headache response rate was calculated based on the subjects recording of pain

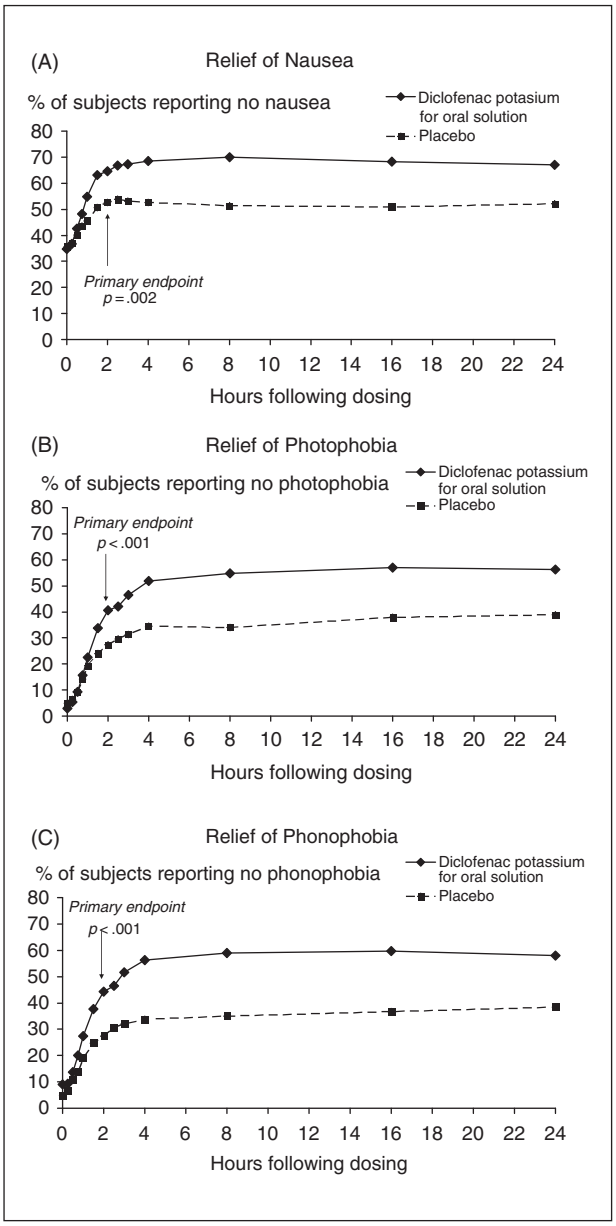

Figure 3. Proportion of subjects with migraine symptoms other than pain by treatment group over 24 hours. (A) Proportion with nausea. (B) Proportion with photophobia. (C) Proportion with phonophobia. Two hours following treatment significantly more subjects in the 50 mg diclofenac potassium for oral solution treatment group achieved relief from nausea, photophobia or phonophobia compared to the placebo treatment group.

intensity scores two hours after treatment. More subjects in the diclofenac potassium for oral solution treatment group achieved a two-hour headache response compared to the placebo treatment group (64.7% [CI 59.4%, 69.8%)] vs. 41.6% [CI 35.4; 46%]; [therapeutic gain of 22%]). Headache response was not defined as a secondary endpoint in the study protocol; however, given its prevalence throughout the literature as a common endpoint in migraine studies, it was calculated herein as a post-hoc analysis. Headache response rates favored diclofenac potassium for oral solution over placebo for up to 24 hours with (54.5% of subjects in the diclofenac potassium for oral solution group vs. 36.9% of placebo group).

Vomiting. At baseline, the incidence of vomiting was only 2.0% in the diclofenac potassium for oral solution treatment group compared to 3.2% in the placebo group. This was reduced to 2% in each treatment group, which was too small a decrease to detect a difference between treatment groups.

Recurrence. For the subjects who were pain free at two hours post-dose, 24% ($N = 21/86$) in the diclofenac potassium for oral solution treatment group had a recurrence, defined as mild, moderate or severe pain and/or taking rescue medication within 24 hours, compared with 29% ($N = 10/35$) in the placebo treatment group. For both treatment groups, the median time to recurrence was >24 hours.

Restoration of function. The percent of subjects who reported being able to return to routine activities favored the diclofenac potassium for oral solution treatment versus placebo. At two hours following treatment, 33.2% ($N = 114/343$) of the diclofenac potassium for oral solution treatment group and 16.1% ($N = 56/347$) of placebo were able to perform all routine activities. This reduction in disability persisted at 24-hours post-treatment with 54.5% ($N = 187/343$) of diclofenac potassium for oral solution versus 36.9% ($N = 128/347$) of placebo treated patients reporting no migraine related disability (therapeutic gain of 17%).

Adverse events. Following treatment, 87 adverse events were reported by 66 subjects in the diclofenac potassium for oral solution treatment group and 71 events reported by 52 subjects in the placebo treatment group. No significant differences between treatments were found for frequency of adverse events. No events were reported as serious and there were no deaths.

The most common overall adverse events reported following treatment (>1% incidence) in the diclofenac potassium for oral solution treatment group included gastrointestinal disorders (12%), general disorders and administration site conditions (1.5%), nervous system disorders (4.1%) and psychiatric disorders (2.6%). The specific events occurring >1% included nausea (7%), dyspepsia (1.5%), vomiting (1.5%) and dizziness (1.5%). In the organ class of psychiatric disorders, there was a significantly higher frequency of events in the diclofenac potassium for oral solution vs. placebo ($p = .011$); however, none of these were considered treatment related. These events included agitation (.6% vs. 0%), anxiety (.3% vs. 0%), confusional state (.3% vs. 0%), déjà vu (.3% vs. 0%), disorientation (0% vs. .3%), insomnia (.9% vs. 0%), nervousness (.3% vs. 0%) and restlessness (.9% vs. 0%).

Table 2. Adverse events considered possibly or probably treatment related and occurring in ≥1% of study participants

Adverse event	Diclofenac potassium for oral solution	Placebo
Nausea	16 (4.6%)	12 (3.5%)
Dizziness	5 (1.5%)	3 (.9%)
Dyspepsia	4 (1.2%)	5 (1.4%)
Vomiting	4 (1.2%)	1 (.3%)

Events considered treatment related included the class of gastrointestinal disorders (9.4%), nervous system disorders (2.6%), and psychiatric disorders (1.5%). These included nausea (4.6%), dizziness (1.5%), dyspepsia (1.2%) and vomiting (1.2%). Adverse events considered treatment related and occurring in ≥1% of study participants are listed in Table 2.

In the diclofenac potassium for oral solution treatment group, the severity of adverse events included 56% mild, 34% moderate and 5% severe. In the placebo group, 63% were mild, 30% moderate and 7% severe. Out of the 158 reported adverse events, only nine were considered severe; three severe events were in the diclofenac potassium for oral solution treatment group and included nausea ($N = 2$), hyperesthesia ($N = 1$) and insomnia ($N = 1$).

Discussion

The results from this study demonstrate that a new buffered formulation of 50 mg diclofenac potassium for oral solution is more effective than placebo for the acute treatment of migraine with moderate or severe pain. This was shown by statistically significant improvements over placebo for all four co-primary endpoints: two-hour pain-free response, freedom from nausea, freedom from photophobia and freedom from phonophobia. Significant improvement in PID scores favoring diclofenac potassium for oral solution occurred 30 minutes post-treatment.

This is the second study to show that 50 mg diclofenac potassium for oral solution is more effective than placebo for the acute treatment of migraine.

In previous reports, 50 mg of diclofenac potassium powder dissolved in water demonstrated analgesic effects as early as 15 minutes following treatment, whereas diclofenac potassium tablets demonstrated improvements over placebo at 60 minutes post-treatment (14). Diclofenac potassium powder also was significantly more effective than diclofenac potassium 50 mg tablets in the percent of subjects achieving a two-hour pain-free response following treatment of moderate or severe headache. Both formulations of diclofenac potassium were significantly more effective compared to placebo in achieving a two-hour pain-free response.

The apparent difference in the efficacy of diclofenac potassium for oral solution compared to diclofenac tablets may be attributable to differences in pharmacokinetic properties. The rapid absorption rate of diclofenac potassium powder is evidenced by a time to maximum plasma concentration (T_{max}) of approximately 15 minutes compared to a T_{max} of 2.3 hours for diclofenac sodium tablets (16,17). The dissociation of diclofenac anion from potassium is more rapid than the dissociation from sodium, a likely explanation for differences in both pharmacokinetics and efficacy (16,17). Direct comparisons of T_{max} plasma levels between oral formulations show a T_{max} at 15 minutes for diclofenac potassium for oral solution compared to 30 minutes for the standard oral tablet (16). Additionally, the maximum plasma concentration (C_{max}) for diclofenac potassium for oral solution was measured as 1618 ng/ml compared to 1160 ng/ml for the diclofenac tablets (16). Collectively, these studies suggest a rapid oral absorption rate for the diclofenac potassium for oral solution formulation.

Though the rapid absorption of 50 mg diclofenac potassium for oral solution likely provides a benefit in efficacy, it also highlights the need for an assessment of tolerability and the onset of adverse events. Herein, the incidence of overall adverse events attributed to study medication was low with 57 events reported by 343 subjects (16.6%) treated with diclofenac potassium for oral solution compared to 39 events reported in 347 subjects (11.2%) treated with placebo. The most common treatment–attributable event was nausea (4.6% diclofenac potassium for oral solution vs. 3.5% placebo). The majority of events were mild to moderate in severity and transient in duration. As with all NSAIDs, there is a risk of gastrointenstinal side effects, which could become more prominent with repeated use. This risk may be partially mitigated by the relative COX-2 selectivity of diclofenac and the infrequent pattern of episodic use in persons with migraine. These results suggest that 50 mg buffered diclofenac potassium for oral solution is a well-tolerated acute migraine therapy. This formulation may be a consideration in patients who do not tolerate other acute migraine medications or experience triptan-related side effects (18).

In a prior comparator study using diclofenac tablets (19), the incidence of treatment-related adverse events was 18% for placebo, 15% for diclofenac potassium 50 mg, 12% for diclofenac potassium 100 mg and 31% for sumatriptan 100 mg tablets. Despite the differences in formulation, the rates of adverse events in the present study and in this previous report are consistent and collectively suggest that diclofenac potassium is well tolerated as an acute treatment for migraine.

Clinical studies show good tolerability and clear analgesic effects of diclofenac sodium for treating several different pain conditions including dental pain, ankle pain and migraine, among others (7–11). Animals studies further demonstrate that diclofenac potassium exhibits anti-inflammatory and antipyretic activities in animal models, which may be mediated by its inhibition of prostaglandin synthesis (6,17). The analgesic and anti-inflammatory effects specific to migraine may be due to proposed inhibitory effects of NSAIDs on peripheral trigeminal neurons as well as central neurons. A number of recent studies demonstrate that NSAIDs inhibit peripheral and central effects on trigeminovascular neurons that are potentially involved in migraine (20–22). Inhibiting analgesic pathways centrally and peripherally believed to be activated in migraine by using an orally administered NSAID that demonstrates plasma levels as early as five minutes following dosing may offer clear treatment advantages for some patients. Additional studies are needed that specifically assess the efficacy of diclofenac potassium in preventing or treating central sensitization in patients with migraine.

Additional studies are also needed that assess the efficacy of diclofenac potassium for oral solution given when migraine pain is mild and/or early in the course of the attack before onset of cutaneous allodynia. In addition, the benefits of re-dosing for persistent or recurrent migraine should be studied. Although statistical significance was achieved relative to placebo at 30 minutes following treatment, additional prospective studies (with onset of pain relief as a primary endpoint, perhaps using time-to-event methods) are needed to specifically assess when the actual onset of efficacy occurs. Subjects with a history of vomiting 20% of the time during migraine attacks or more were usually so incapacitated as to require bed rest during the attack were also excluded. These exclusion criteria do not limit the statistical conclusion validity of the results but they do limit generalizability. Our findings pertain only to migraine sufferers who do not usually require bed rest and who do not vomit more than 20% of the time. Finally, as migraine sufferers treat multiple attacks,

within person consistency of treatment should be assessed (23,24).

In summary, this study provides additional evidence to the efficacy and tolerability of powdered diclofenac potassium for the acute treatment of migraine. The benefit of this formulation is the rapid onset of pain relief with oral therapy. Although there are several NSAIDs available for the acute treatment of migraine (25–29), we predict that diclofenac potassium powder will be most useful in patients for whom an NSAID is the desired treatment when rapid relief is a priority.

Sponsorship

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Participating investigators

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