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Terminating Migraine-Associated Allodynia Using Oral Suspension Diclofenac: A Prospective Non-Randomized Drug Trial

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Triptan-resistant migraine attacks are typically associated with cephalic allodynia that begin hours before time of treatment.^{1,2} Such attacks appear to be compounded by sensitization of second-order spinal trigeminovascular neurons^{1,3,4} lacking the 5HT1d receptors⁵ and consequently the ability to become a direct target for triptan action.⁶ In adults, the development and maintenance of cutaneous allodynia is thought to involve the functionally distinct early and late phases.⁷ Whereas in the early phase (also called the developmental phase), the activity of the sensitize trigeminovascular neurons tend to depend on the incoming nociceptive signals, in the late phase (also called the established phase), their activity becomes independent of the incoming nociceptive signals.⁸ Because triptans' main site of action in the dorsal horn is presynaptic, they are well-positioned to interfere with the transmission of nociceptive signals from the peripheral to the central trigeminovascular neurons.⁶ This allows triptans to be highly effective in reversing allodynia and sensitization as long as the excitability of the central trigeminovascular neurons remains driven by incoming signals from the meninges, but not after they have developed autonomous activity.

Editor's comment

This letter to the editor was originally submitted as a research submission. As it is an open-label unregistered trial it would violate journal policy to accept it in that form. I am publishing this as a letter to the editor due to the level of interest it generated among reviewers and in the hopes that a future double-blind placebo-controlled registered study will follow.

Thomas N. Ward MDs

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¹ Accordingly, to maximize treatment efficacy, patients are routinely instructed to resort to triptan therapy immediately after onset of headache, rather than hours later.

In many headache centers and emergency rooms, allodynic patients who missed the critical window for effective triptan therapy, are often rendered pain-free using intravenous infusion of the non-steroidal anti-inflammatory drug ketorolac^{9–11} – an approach supported clinically by reports that intravenous ketorolac, a COX1/COX2 inhibitor, provides a rescue therapy for allodynic patients who missed the critical period for triptan therapy,¹² and scientifically by studies showing that intravenous administration of both ketorolac and naproxen reverse already established central sensitization.^{12,13}

Because parenteral COX-1/COX-2 inhibitors are administered intravenously or intramuscularly, which usually requires a patient to travel to a clinical care center, uses of parenteral COX-1/COX-2 inhibitors are impractical as routine migraine therapy. The need to develop effective oral formulations of COX-1/COX-2 inhibitors with comparable bioavailability to the spinal cord is apparent. The current study was design to determine whether an oral suspension of the COX-1/COX-2 inhibitor diclofenac can reverse cutaneous allodynia.

METHODS

Patient Selection

The Beth Israel Deaconess Medical Center (BIDMC) committee on clinical investigations approved this prospective, non-randomized, open label treatment study and all participants provided written informed consent. For its nature, design and scope, the study was not registered. Included in the study were 18-to 56-year-old patients who met the criteria of the International Headache Classification Committee for migraine (The International Classification of Headache Disorders: 3rd edition – ICHD beta),¹⁴ had 2–14 migraine attacks each month, and were able to travel to BIDMC for 2 visits, one time without a migraine and one time during a migraine. Patients using or not using migraine prophylactic medications were allowed in the study. Excluded from this study were patients with chronic migraine, peripheral nervous system injuries, and those using chronic opioids.

Experimental Protocol

Forty-eight patients were screened between April 2015 and May 2016. Twentyseven of them fulfilled inclusion/exclusion criteria, provided informed consent, and consequently enrolled in the study. Once enrolled, they were designated to visit the clinical research center at BIDMC twice. In visit 1, which took place when the patients were migraine-free >3 days, they were interviewed for migraine history and accompanied symptoms, and tested for their baseline/interictal skin sensitivity. The interview included the following items: family history; migraine history (age of onset and number of years with migraine); past and present medication use; attack frequency, duration and headache intensity; and associated neurological symptoms (aura, nausea, vomiting, photophobia, phonophobia).

In visit 2, which took place at the beginning of an acute migraine attack (that started >3 days after any prior migraine symptoms) before any abortive medication was taken to relieve the

attack, patients were asked to describe their headache location and characteristics, associated symptoms, time of attack onset, and headache intensity. The time of onset was defined as the time at which the headache began. Headache intensity was rated on a number rating scale ranging from 0 (no pain) to 10 (worst pain). Their skin sensitivity was then measured as per visit 1, only this time it was measured during an attack; once before and once 2 hours after treatment with diclofenac potassium 50 mg. Pain rating was documented at 30, 60, 90, and 120 minutes after treatment.

Quantitative Sensory Testing of Skin Sensitivity

Skin sensitivity was measured using quantitative sensory testing (QST) according to the method of limits^{15,16} as described before.³ Briefly, to determine thermal pain thresholds, we attached a 30 × 30 mm thermode (TSA-2001; Medoc, Ramat-Yishai, Israel) to the periorbital skin at the site of the headache, and the skin was allowed to adapt to 32°C for 3 minutes. Then, the skin was cooled down or warmed up at a rate of 1°C/second until the patient felt pain and stopped the stimulus by pressing a button. Cold and heat thresholds were each calculated as the mean of 3 repetitions (10-second interstimulus interval). Mechanical pain threshold to skin indentation was determined incrementally using calibrated monofilaments (Stoelting, Kiel, WI, USA); the threshold was set at the smallest force that evoked pain in two of three trials. During these tests, patients were supine in a dimly lit room, unable to view the changes in temperature or magnitude of mechanical stimuli on computer monitor.

Changes in skin sensitivity were determined by comparing corresponding pain thresholds obtained in the absence of migraine to pain thresholds obtained during migraine first before and then after treatment with oral suspension diclofenac. The skin was considered allodynic if pain threshold was between 32 and 428C for heat, 32 and 188C for cold, and less than 100 g for skin indentation. The rationale for using these values is that in healthy subjects, pain thresholds to heat, cold, and mechanical skin stimuli range between 42 and 47°C, 32 and 18°C, and 100 to 300 g, respectively. A patient was considered allodynic if during attack one or more modalities met the criteria for allodynia. Changes in skin sensitivity took into consideration previous findings showing that during migraine, pain threshold to heat and cold decrease by 3–5°C, and by 2 VFH monofilaments for mechanical pain.³

Data Collection and Statistical Analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at BIDMC. Research electronic data capture (REDCap) is a secure, web-based application designed to support data capture for research studies.¹⁷ Data analysis was performed using StatPlus (AnalystSoft, Walnut, CA, USA) and STATA 12.1 (StataCorp, College Station, TX, USA).^{18,19} Changes in pain scores and mean pain threshold were analyzed using Tukey's HSD/Friedman two-way analysis of variance. Level of significance was set at .05.

RESULTS

Of the 27 enrolled patients, 24 completed visit 1, and 14 of those who completed visit 1 also completed visit 2. All participants were female and 79% were non-Hispanic white. The

characteristics of the patients who completed both visits are summarized in the Table. Compared to patients who returned for visit 2 (during a migraine), patients who did not return for visit 2 during the 12 months of the study were similar in age, sex, and years with migraine. However, compared to patients who returned for visit 2, patients who did not return reported fewer migraine attacks per month on average (7.3 vs 4.5 attacks/month), longer lasting migraines if untreated (34 hours vs 45 hours), and described prior migraine attacks being less likely to be associated with nausea before head pain began (57% vs 30%), and more likely to have associated aura (29% vs 60%).

Treatment Effects on Pain

All 14 patients who completed the study exhibited changes in their skin sensitivity during migraine and therefore were classified as allodynic. Of those, 4 were treated 1 hour after onset of headache (early group) and 10 were treated >3 hours (range = 3–10 hours, mean 5.6 hours) after headache onset (late group). Of the 4 patients treated 1 hour after pain onset, 1 was rendered pain free, 2 experienced >75%, and 1 experienced 50% reduction in headache severity (Fig. 1A,B). Of the 10 patients treated >3 hours after pain onset, 4 were rendered pain free within 2 hours of treatment, and the remaining 6 patients experienced >75% ($n = 2$), 50–74% ($n = 2$), and 30–49% ($n = 2$) reduction in headache intensity within 2 hours of treatment (Fig. 1C,D). As shown in Figure 1E, the pain decreased linearly between 30 and 120 minutes after treatment.

Treatment Effects on Cutaneous Allodynia

In the absence of migraine, pain thresholds to heat, cold, and mechanical skin stimuli (Figs. 2–4, blue bars) were above 42°C, below 18°C and above 100 g. At the time of treatment, 6 patients were exhibiting allodynia for 3 modalities, 4 for 2 modalities, 3 for 1 modality and the QST values of 1 patient (although lower than baseline values) did not fulfill criteria for allodynia (Figs. 2–4, red bars). Modality-wise, mechanical, cold, and heat allodynia were present in 10, 9, and 10 patients, respectively. Two hours after treatment with diclofenac, 6 patients exhibited allodynia for 1 modality, 2 for 2 modalities, and none exhibited allodynia for 3 modalities (Figs. 2–4, green bars). Modality-wise, post-treatment mechanical, cold, and heat allodynia were present in 6, 1, and 3 patients, respectively; a drop of nearly 65% (29 vs 10) in the incidence of allodynia (Figs. 2–4, red vs green bars).

Our small sample size did not allow assessment of differences in reversal of allodynia by early vs late treatment with diclofenac, and therefore, pain threshold means presented are for all 14 patients. Mechanical pain threshold (mean $\pm$ SE) decreased from 251.4 ± 18.8 g at baseline (ie, interictally), to 52.3 ± 16.8 g during the untreated migraine ($P = .0003$), and then increased to 122.8 ± 22.8 g after treatment ($P = .016$) (Fig. 2). Cold pain threshold (increased in absolute value = enhanced sensitivity) decreased from $11.0 \pm 0.95^\circ\text{C}$ at baseline (ie, interictally), to $19.0 \pm 1.7^\circ\text{C}$ during the untreated migraine ($P = .0003$), and then increased (reduced sensitivity) to $15.6 \pm 1.3^\circ\text{C}$ after treatment ($P = .03$) (Fig. 3). Heat pain threshold decreased from $44.9 \pm 0.72^\circ\text{C}$ at baseline (ie, interictally), to $40.1 \pm 0.77^\circ\text{C}$ during the untreated migraine ($P = .0003$), and then increased to $43.2 \pm 0.90^\circ\text{C}$ after treatment ($n = 14$, $P = .002$) (Fig. 4).

Treatment Effect on Pain and Allodynia

In the 2 non-responders (ie, those whose headache intensity decreased by <50%) – both treated late – mechanical, cold, and heat allodynia were not reversed by the diclofenac treatment (when developed). In the 3 responders whose headache intensity dropped by 50–74%, mechanical allodynia was reversed in 2 late treatment cases, and not reversed in 1 early treatment case; cold allodynia was reversed in 1 late treatment case, not reversed in 1 early treatment case, and did not develop in the third (a late treatment case); heat allodynia was reversed in all 3 cases (2 late and 1 early treatment). In the 4 responders whose headache intensity decreased by >75%, mechanical allodynia was reversed in 3 cases (1 early and 2 later treatment), and was not reversed in 1 early treatment case; cold allodynia was reversed in 3 cases (2 early and 1 late treatment) and not reversed in 1 late treatment case; heat allodynia was reversed in 2 cases (1 early and 1 later treatment), not reversed in 1 late treatment case, and in 1 case the allodynia, which was present in the interictal phase, remained unchanged after the (early) treatment. In the 5 complete responders (ie, those whose headache intensity decreased to 0), mechanical allodynia was reversed in all cases, cold allodynia was reversed in the 3/3 cases (1 early and 2 late treatment) where it developed (2 late treatment patients did not develop cold allodynia), and heat allodynia was reversed in 2 late treatment cases, not reversed in 1 early treatment case, and in 2 cases (both in the later treatment group) it did not develop.

DISCUSSION

We showed previously that patients who develop allodynia during migraine are most likely to become pain-free when using triptans within 1 hour from onset of headache,² that treatment with triptans is far less effective when administered several hours after onset of headache,² that late intravenous infusion of ketorolac terminates migraine and reverses an already-established allodynia in patients,¹² and that late intravenous administration of naproxen reverses central sensitization that no longer depends on pain signals that come from the meninges in second-order trigeminovascular neurons in the spinal trigeminal nucleus.¹³ The present study is first to show that non-parantral administration of a COX1/COX2 inhibitor provides a rescue therapy for allodynic patients who missed the critical period for triptans therapy. We report here that both early and late administration of diclofenac, an oral suspension of the COX1/COX2 inhibitor, reduced allodynia by 65%, and terminated the headache completely (pain-free) or partially (>50% reduction in pain) in 5 (36%) and 7 (50%) of the 14 studied patients, respectively. Because periorbital allodynia is mediated by sensitization of central trigeminovascular neurons in the medullary dorsal horn,^{4,20} we theorize that oral suspension diclofenac reached a level of concentration in the dorsal horn that is sufficient for the suppression of central sensitization during migraine.

Although encouraging, the results of the present study are based on a small case series and a study designed to explore if oral suspension diclofenac reverses activity-independent (ie, established) central sensitization rather than determine drug efficacy. Diclofenac effects on the headache (efficacy data) must be interpreted with great caution as they lack the placebo arm and as such cannot replace the already established efficacy reported earlier in the placebo-controlled randomized trials.^{21,22}

Relevant to the main question of this study is the concept that migraine-induced allodynia is mediated by central sensitization that depends on incoming peripheral pain signals in early, but not late phases of the attack. In the late phases, the continuous barrage of incoming pain signals eventually sensitizes the central trigeminovascular neurons to the extent that they develop their own spontaneous activity and their ongoing firing becomes partially independent of the incoming pain signals.^{1,2} At this stage, it is reasonable to expect that drugs that alter the molecular environment in the dorsal horn may be able to inhibit their firing, whereas drugs lacking the ability to bind to these sensitize neurons, such as the triptans,⁵ or alter their environment may not.

The scientific rationale for using COX1/COX2 inhibitors to reverse established allodynia and central sensitization consist of several sets of data. In animal models of migraine, intravenous administration of ketorolac and naproxen contravened both the induction (when given early) and maintenance (when given late) of sensitization in trigeminovascular neurons of the spinal trigeminal nucleus.^{12,13} In other animal models of pain, nociceptor activation stimulated spinal glia cells,^{23,24} upregulated COX2 transcription^{25,26} and increase prostaglandins production in the dorsal horn,^{27,28} where they bind pre-synaptically to the central terminals of primary afferents, and postsynaptically to central nociceptive neurons.²⁹ Presynaptically, prostaglandins facilitate glutamate release from C-fiber terminals,^{30,31} whereas post-synaptically, they preserve the depolarizing (inward) current.³² Therapeutically, it is therefore reasonable to propose that decreased level of prostaglandins would reduce neurotransmitter release from the primary afferents nociceptors^{30,31,33–35} and diminish hyperexcitability of the central nociceptive neurons^{36,37} in the dorsal horn.

Considering the strength of the scientific data described above, it is now widely accepted that hours after the onset of pain, local prostaglandin release from activated spinal neurons and glia is essential for the maintenance of sensitization.^{38–40} This notion defines the ballpark at which COX1/COX2 inhibitors act to terminate allodynia and central sensitization if they cross the blood brain barrier and reach the dorsal horn at a concentration that is high enough to attenuate spinal prostaglandins production. To the best of our knowledge, this is the first study to show that a non-parenteral COX1/ COX2 inhibitor can reverse migraine-associated established allodynia.

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Fig. 1.—

Diclofenac effects on headache intensity in allodynic migraine patients. (A) Headache intensity score recorded before (red) and 2 hours after (green) *early* treatment with diclofenac in 4 allodynic patients. (B) Effects of *early* diclofenac treatment on mean $\pm$ SEM headache intensity. (C) Headache intensity scores recorded before (red) and after (green) *late* treatment with diclofenac in 10 allodynic patients. (D) Effects of *late* diclofenac treatment on mean $\pm$ SEM headache intensity. (E) Histograms showing mean $\pm$ SEM headache intensity scores recorded before, 30, 60, 90, and 120 minutes after treatment with diclofenac (n = 14). *P* values for 30, 60, 90 and 120 minutes are .003, .001, .001, .001, respectively. Inset shows all 14 individual cases. Note the consistency of the progressive decline in pain scores.

Fig. 2.—

Diclofenac effects on mechanical allodynia. (A) Mechanical pain threshold recorded first interictally (blue), and then ictally, before (red) and 2 hours (green) after early diclofenac treatment of 4 patients. (B) Mean $\pm$ SEM mechanical pain threshold recorded after early treatment. (C) Mechanical pain threshold recorded first interictally (blue), and then ictally, before (red) and 2 hours (green) after late diclofenac treatment of 10 patients. (D) Mean $\pm$ SEM mechanical pain threshold recorded after late treatment. (E) Mean $\pm$ SEM mechanical pain threshold representing all 14 study cases. Beige area indicates allodynia zone. Note that diclofenac treatment reversed mechanical allodynia in the majority of cases.

Fig. 3.—

Diclofenac effects on cold allodynia. (A) Cold pain threshold recorded first interictally (blue), and then ictally, before (red) and 2 hours (green) after *early* diclofenac treatment of 4 patients. (B) Mean $\pm$ SEM cold pain threshold recorded after *early* treatment. (C) Cold pain threshold recorded first interictally (blue), and then ictally, before (red) and 2 hours (green) after *late* diclofenac treatment of 10 patients. (D) Mean $\pm$ SEM cold pain threshold recorded after *late* treatment. (E) Mean $\pm$ SEM cold pain threshold representing all 14 study cases. Beige area indicates allodynia zone. Note that diclofenac treatment reversed cold allodynia in the majority of cases

Fig. 4.—

Diclofenac effects on heat allodynia. (A) Heat pain threshold recorded first interictally (blue), and then ictally, before (red) and 2 hours (green) after *early* diclofenac treatment of 4 patients. (B) Mean $\pm$ SEM heat pain threshold recorded after *early* treatment. (C) Heat pain threshold recorded first interictally (blue), and then ictally, before (red) and 2 hours (green) after *late* diclofenac treatment of 10 patients. (D) Mean $\pm$ SEM heat pain threshold recorded after *late* treatment. (E) Mean $\pm$ SEM heat pain threshold representing all 14 study cases. Beige area indicates allodynia zone. Note that diclofenac treatment reversed heat allodynia in the majority of cases.

Table 1.—

Participant Characteristics

Participant ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age (years)	37	55	24	18	47	46	50	23	56	38	49	38	52	22
Age migraine began	20	18	22	15	18	10	8	17	6	12	19	15	50	6
Migraine attacks/month	2	6	14	3	12	4	5	14	2	2	3	10	2	12
Migraine characteristics														
HTT6 disability score	57	61	66	54	60	69	52	65	74	68	65	68	65	71
Duration–treated (hours)	4	12	3	6	8	1	1	2	24	12	3	48	1	8
Duration–untreated (hours)	4	24	72	6	24	48	24	24	72	48	5	72	48	8
Pain intensity (0–10) *	28	80	57	60	40	60	48	40	80	50	75	70	76	75
Aura		✓			✓					✓		✓		
Unilateral location	✓	✓				✓	✓	✓	✓	✓	✓	✓		
Pulsating	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	
Worsens with activity		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Nausea/vomiting		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Photophobia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Phonophobia	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓

*
0 = no pain; 10 = pain as bad as it can be.