DFN-15 effects on migraine with allodynia
February 27th, 2018

DFN-15 effects on migraine with allodynia

Objectives:

1. To determine whether oral administration of DFN-15 (solution of a COX2 inhibitor celecoxib) terminates migraine attacks when given to allodynic patients 3 hours after attack onset.
2. To determine whether mechanical and heat allodynia that develop during acute migraine attacks could be reversed by late (> 3hrs after attack onset) treatment with DFN-15.

Background:

The majority of migraineurs seeking secondary or tertiary medical care develop cutaneous allodynia during the course of migraine (Burstein et al., 2000), a sensory abnormality mediated by sensitization of central trigeminovascular neurons in the spinal trigeminal nucleus (Burstein et al., 1998). Triptan therapy can render allodynic migraineurs pain-free within a narrow window of time (20-120 min) that opens with the onset of pain and closes with the establishment of central sensitization (Burstein et al., 2004). This calls for the development of drugs that can tackle ongoing central sensitization and render allodynic migraineurs pain-free *after* the window for triptan therapy has expired.

Rational for testing a DFN-15:

Several years ago, we (the Burstein group) published a series of papers showing that parenteral administration of ketorolac and indomethacin reverse central sensitization in animals and cutaneous allodynia in episodic migraine patients, and proposed that these actions of the drugs are critical in terminating migraine attacks that are unrelieved by triptan therapy (Jakubowski et al., 2005). The premise behind these studies was that there is an association between headache and inflammation. This association is based on (1) demonstrated efficacy of NSAIDs in treating migraine (Snow et al., 2002), (2) RCT trials showing that the efficacy of oral NSAIDs and oral triptans is equal in treating migraine (Tfelt-Hansen, 2008), (3) epidemiological studies demonstrating the protective role of NSAIDs therapy in preventing patients' transition from episodic to chronic migraine (Bigal et al., 2008; Scher et al., 2010), and (4) the American Academy of Family Physicians, American College of Physicians, and American Society of Internal Medicine guideline recommendation to use NSAIDs as a first-line treatment choice for all migraine attacks (Schroeder, 2003).

Rational for testing DFN-15? In the concluding remarks of our papers on parenteral COX1/COX2 inhibitors we wrote: "Parenteral administration of COX-1/COX-2 inhibitors is impractical in routine migraine therapy as it required that patient travel to

hospitals." We then concluded the following: "To allow patients to treat themselves at home, it will be useful to develop oral formulations of COX-1/COX-2 inhibitors with comparable bioavailability to the spinal cord." DFN-15 is a COX-2 selective NSAID. It is extensively expressed in cells involved in inflammation and is upregulated by bacterial lipopolysaccharides, cytokines, growth factors, and tumor promoters. As such, it is used to treat a variety of conditions associated with pain and inflammation.

Study design:

Overall strategy: This study will be a proof-of-concept study to determine the mechanism of action of DFN-15 on cutaneous allodynia and central sensitization. To achieve our objectives, we will determine the cutaneous pain thresholds (mechanical, heat) and headache severity of episodic migraine patients under 3 different conditions: (a) while pain-free, (b) during migraine predosing, (c) 2 hours after treatment with either DFN-15 or a matching placebo.

Participant selection:
COX-2 inhibitors have been shown to have a lower GI toxicity than other more commonly-used NSAIDS. Although, COX-2 inhibitors can have severe cardiovascular and renal adverse events including, but not limited to: myocardial infarction, stroke, heart failure, and hypertension (Mathew et al., 2011). Therefore, the inclusion/exclusion criteria for this study will be designed to minimize adverse events.

Individuals with episodic migraine will be considered for participation in this study. Primary inclusion criteria will be (1) age 18-64 years old, (2) history of migraine with or without aura, based on the International Classification of Headache Disorders (3rd edition) for at least 3 years, (3) two or more migraine attacks per month on average during the previous year, and (4) ability to communicate in English (in order to understand and follow instructions of testing). Exclusion criteria will include: (1) fifteen or more headache days per month; (2) aspirin or NSAID-induced asthma or allergy; (3) pregnancy and/or lactating; (4) history of coronary artery bypass surgery, heart attack, angina, stroke, serious gastrointestinal bleeding, peptic ulcer disease; or chronic kidney disease; (5) having medical conditions requiring use of diuretics or daily anticoagulants; (6) having severe uncontrolled medical problems or medications that may influence measurements or impair ability to participate in the testing (e.g. daily or frequent use of opiates or barbiturates (>8 days per month), or NSAIDs or other analgesics (>14 days per month); known creatinine > 2.5 md/dl or GFR < 30, severe peripheral neuropathy, dementia, etc.); and (7) having been advised by a health professional not to use COX-2 inhibitors.

Potential participants will be recruited from the Hartford Healthcare Headache Program.

Randomized controlled trial: After screening, which will be performed on a non-migraine day, participants will be randomized in a double-blinded fashion to receive either the active drug (DFN-15) or placebo in a ratio of 4:1. They will be instructed to return to the

clinic during a migraine. At the 'during-migraine' visit, which will begin 3 hours after onset of headache, we will document headache intensity, associated symptoms, and mechanical and heat pain threshold (first) before treatment (at 180 min after onset of headache) and (second) at a 120 min after treatment (5 hours after headache onset). Based on our prior experience studying migraine patients, we plan to screen 100 patients to achieve 50 participants completing the 2 study visits as planned. 80/100 patients will be randomized to receive the active drug and 20/100 patients will receive the placebo. The study will be terminated as soon as the first 40 patients who received the DFN-15 and first 10 patients who received placebo completed visit 2.

Screening visit - In the first appointment we will identify patients who are good candidate to participate in the study and measure their pain thresholds following an initial evaluation. This appointment will allow us to train patients in how the quantitative sensory testing is performed.

'During-migraine" visit – In the second appointment patients' headache intensity, associated symptoms, and mechanical and heat pain thresholds will be tested 180 min after the onset of a migraine headache. Pain threshold will be determined within the referred pain area in the head. These tests will provide the pre-treatment data to be compared later with post-treatment data. Once pain thresholds are established, patients will be treated and their headache intensity, associated symptoms and pain thresholds will be re-examined 120 minutes later.

Quantitative Sensory testing (QST): Testing will be done in a quiet room away from noise and distraction. Patients will be able to choose their most comfortable position (sitting on a chair or lying in bed) during the sensory testing. In each testing session, pain thresholds to hot and mechanical stimulation will be determined in the skin over the site to where the pain is referred to. This site includes most commonly the periorbital and temporal regions. Heat skin stimuli will be delivered through a 30x30 mm^2 thermode (Q-Sense 2016, Medoc) attached to the skin at a constant pressure and their pain thresholds will be determined by using the *Method of Limit*. To determine pain thresholds, the skin will be allowed to adapt to a temperature of 32°C (89.5 ^{o}F) for 5 minutes and then warmed up at a slow rate (1 °C/sec) until pain sensation is perceived, at which moment the subject stops the stimulus by pressing a button on a patient response unit. Heat stimuli will be repeated three times each (with 10 seconds between each test) and the mean of recorded temperatures will be considered threshold. Pain threshold to mechanical stimuli will be determined by using a set of 20 calibrated von Frey hairs (VFH, Stoelting). Each VFH monofilament is assigned a scalar number in an ascending order (1 = *0.0045g*, 2 = *0.023g*, 3 = *0.027g*, 4 = *0.07g*, 5 = *0.16g*, 6 = *0.4g*, 7 = *0.7g*, 8 = *1.2g*, 9 = *1.5g*, 10 = *2.0g*, 11 = *3.6g*, 12 = *5.4g*, 13 = *8.5g*, 14 = *11.7g*, 15 = *15.1g*, 16 = *28.8g*, 17 = *75g*, 18 = *125g*, 19 = *281g*). Because a linear relationship exists between the log force and the ranked number, mechanical pain thresholds are expressed as VFH numbers (#) rather then their forces (g). Each monofilament will be applied to the skin 3 times (for 2 sec and 2 sec in between each application) and the smallest VFH number capable of inducing pain at two out of three trials will be considered threshold. Skin sensitivity will also be determined by recording patient's perception of soft skin brushing,

which is a dynamic mechanical stimulus, as distinguished from the VFH, which is a static mechanical stimulus. The equipment used for quantitative sensory testing has an FDA approval. It is routinely used by neurologists, nurses, and pain specialists throughout the country. It imposes no risk or discomfort, and since it is controlled by the patient, stimuli can be stopped at any time. Each QST will last about 10 minutes.

Patient Safety:

Throughout the treatment and testing the patients will be monitored (vitals, etc.) to ensure their safety. If a member of the control group is in excruciating pain and their migraine is intolerable they will be prescribed a rescue medication. In this case the participant will drop out of the study. The participants will have the option to drop out at any point in the study. At the end of the testing (5 hours after migraine onset), if a participant (from either group) is still symptomatic and in pain, they will have the opportunity to have a rescue medication prescribed by one of the specialists at the Headache Center. In the case that a patient does not respond well to the study treatment they will be monitored for at least 1 hour before leaving the clinic.

Data analysis:

Primary endpoint: There are 2 primary endpoints in this study. The first is reduction in headache intensity after DFN-15 treatment, and the second is reduction in skin sensitivity at 2 hours after DFN-15 treatment.

For reduction in headache intensity, level of pain will be documented at 1 and 2 hours after treatment using a visual analogue scale of 0 (no pain) to 10 (worst pain). Comparisons of these ordinal (repeated) measures will be performed using Friedman two-way analysis of variance followed by Wilcoxon matched-pairs signed-ranks test.

For reduction in skin sensitivity (allodynia), pain thresholds will be determined 2 hours after DFN-15 or placebo treatment. Since the detection of pain thresholds depends on subjective data input, several algorithms have been developed in order to minimize subjective variation, and make the results as objective as possible. These algorithms are incorporated into the software program that controls the thermal and mechanical sensory analyzer (Q-Sense 2016). Changes in skin sensitivity will be determined by comparing corresponding pain thresholds obtained in the pain-free session (baseline) to pain thresholds obtained during migraine, first before (untreated migraine) and then after (treated migraine) treatment with DFN-15 or placebo. In healthy subjects, pain thresholds for heat and mechanical skin stimuli range between 42-47 ^{o}C (107.3-116 ^{o}F) (Lindblom, 1994), and 75-281 g (Strigo et al., 2000), respectively. Using a more stringent criteria, we will consider a patient to be allodynic if her/his pain threshold is below 41 ^{o}C (105.8 ^{o}F) for heat, and below 30 g for skin indentation with the calibrated von Frey hairs. Meeting the criterion for any one of modality will be sufficient to determine that the patient is allodynic at the 'during untreated migraine' testing. For this endpoint, the database will consisted of pain threshold measurements in 50 patients, taken while they are pain-free (baseline), during untreated migraine attack (before DFN-15 or placebo treatment), after treatment with DFN-15 or placebo. Only those patients who completed all 3 testing sessions will be included in the data analysis. The resulting distributions will be tested for normality, and their descriptive statistics computed. The differences

between before and after DFN-15 treatment will be computed on a pair-wise basis. To increase the sensitivity of detecting changes, patients in this study will be compared to themselves (baseline vs. during untreated migraine vs. during treated migraine) rather than to control subjects because the large normative range of pain thresholds reduces the sensitivity of detecting allodynia in reference to the normal range. Differences between pain-free vs. during untreated migraine vs. during treated migraine will be computed on a multiple sample pair-wise basis. Differences in mean pain threshold will be judged (significant or not significant) by using appropriate pair-wise multiple sample comparison (Newman-Keuls, Kruskal-Wallis) tests. Alternatively, repeated measurements of pain thresholds (allodynia) will be analyzed using Friedman two-way analysis of variance. Finally, secondary analyses using the collected data may be done as a part of this study including, but not limited to, the duration and intensity of the headache prior to arrival at the clinic.

The primary outcome measure in the current study is the proportion of patients demonstrating a headache intensity decrease that is greater than 50% (post-treatment compared to pre-treatment). Secondary outcome measures are proportions of patients demonstrating allodynia before and after treatment; allodynia to thermal stimuli is defined as a pain threshold < 41 0C, and to mechanical stimuli as pressure pain threshold of < 30 g.

The primary and secondary outcome measures will be examined using the Z test for comparison of independent proportions and Chi-square (x2) test to assess the categorical association between the group (treatment / placebo) and (i) reduction rate of headache intensity (below / above 50%; primary outcome measure); (ii) proportion of thermally allodynic participants (pain threshold below / above 41 0C; secondary outcome measure); and (iii) proportion of mechanically allodynic participants (pressure pain threshold below / above 30 g; secondary outcome measure).

Power analysis was based on the Z test for comparison of independent proportions. Incorporated were α of 5% (significance level), 1-β error probability of 90% (power), and allocation ratio of 4:1 (treatment:placebo, respectively). Based on previously published data (Burstein et al., Annals of Neurology 2004), the primary outcome measure is expected to be lower in the treatment group; accordingly, power analysis was one-tailed. The primary hypothesis was that post-intervention proportions of patients demonstrating a headache intensity decrease that is greater than 50% in the treatment and placebo groups would be 80% and 30%, respectively. This computation yielded a required number of 9 subjects in the placebo group and 36 patients in the treatment group (critical Z = -1.645). An additional 20% were accounted for potential dropout. Thus, a total of 54 participants (11 placebo, 43 treatment) are to be enrolled in the entire study.

References:

Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. 2008. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48(8):1157-1168.

Burstein R, Collins B, Jakubowski M. 2004. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. Ann Neurol 55(1):19-26.

Burstein R, Yamamura H, Malick A, Strassman AM. 1998. Chemical stimulation of the intracranial dura induces enhanced responses to facial stimulation in brain stem trigeminal neurons. Journal of Neurophysiology 79(2):964-982.

Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. 2000. An association between migraine and cutaneous allodynia. Annals Neurol 47:614-624.

Jakubowski M, Levy D, Goor-Aryeh I, Collins B, Bajwa Z, Burstein R. 2005. Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors. Headache 45(7):850-861.

Mathew S, Devi S G, Prasanth VV, Vinod B. 2011. Efficay and Safety of COX-2 Inhibitors in the Clinical Management of Arthitis: Mini Review. ISRN Pharmacology.

Scher AI, Lipton RB, Stewart WF, Bigal M. 2010. Patterns of medication use by chronic and episodic headache sufferers in the general population: results from the frequent headache epidemiology study. Cephalalgia 30(3):321-328.

Schroeder BM. 2003. AAFP/ACP-ASIM release guidelines on the management and prevention of migraines. American family physician 67(6):1392, 1395-1397.

Snow V, Weiss K, Wall EM, Mottur-Pilson C. 2002. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Annals of internal medicine 137(10):840-849.

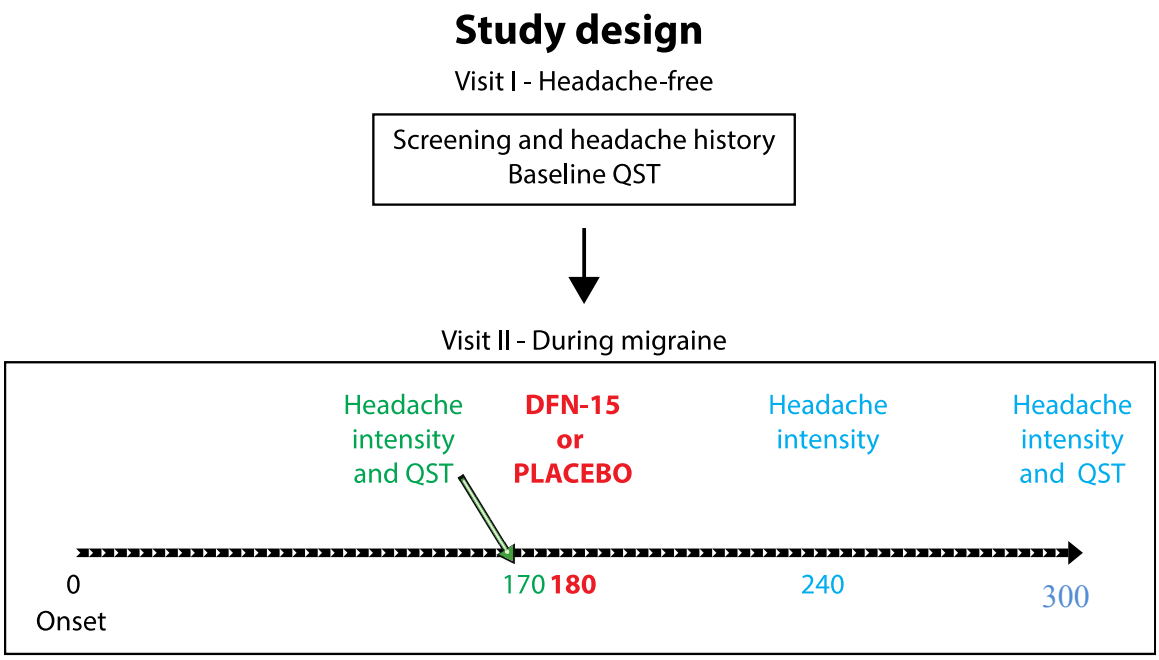
Tfelt-Hansen P. 2008. Triptans vs other drugs for acute migraine. Are there differences in efficacy? A comment. Headache 48(4):601-605.

Harrison JL, Davis KD. 1999. Cold-evoked pain varies with skin type and cooling rate: a psychophysical study in humans. Pain 83(2):123-135.

Lindblom U. 1994. Analysis of abnormal touch, pain, and temperature sensation in patients. In: Boivie J, Hansson P, Lindblom U, editors. Touch, temperature and pain in health and disease: mechanism and assesments. Seattle: IASP press. p 63-84.

Strigo IA, Carli F, Bushnell MC. 2000. Effect of ambient temperature on human pain and temperature perception. Anesthesiology 92(3):699-707.

Flow chart:


Study design
Visit I - Headache-free
Screening and headache history
Baseline QST
Visit II - During migraine
Headache intensity and QST
DFN-15 or PLACEBO
Headache intensity
Headache intensity and QST
0
Onset
170
180
240
300