

## Research Article

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## Recurrence of Acute Migraine Following Ubrogapant and Diclofenac Buffered Solution Combination Therapy-An Observational Study

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**ABSTRACT**

**Objective:** To analyze the need for a repeat dose following administration of a single fixed combination dose of ubrogapant and diclofenac potassium buffered solution for an acute migraine attack,

**Background:** A relapse after pain freedom/relief from a migraine abortive is an acute treatment failure. Reduction of acute disability and prevention of chronification is dependent on effective, rapid, complete abortive treatment without adverse effects.

**Methods:** Ubrogapant 100 mg tabs and diclofenac potassium buffered solution 50mg powder (UBR/DICb) are both FDA approved for acute migraine therapy. Twenty-three subjects, 22 female, 1 male with episodic or chronic migraine with and without aura were instructed take both agents within 15 minutes of the migraine attack. Pain freedom and pain relief at 2 hrs. were recorded and need for repeat dose for relapse was the primary efficacy outcome measure for this study. Relief of most bothersome symptoms (MBS)-nausea, photophobia, phonophobia, and adverse effects were also recorded. Observation for need for repeat dosing was extended to 24hrs. Preventives were permitted.

**Results:** Two hours following a single fixed dose of UBR/DICb, 96% of the enrolled study patients were pain free or obtained pain relief with no need for a second dose, and 4% did not respond. Of the 23 patients enrolled in the study, 87% experienced pain freedom with no need for redosing, (CI 95% (0.7, 1.0), and 9% had pain relief with no need for redosing (CI 95% (-0.02, 0.2), and 4% had no pain relief or freedom and no response to redosing (CI 95% (-0.04, 0.12)). Reduction in MBS paralleled pain reduction in our study cohort. None of the responders required a second dose of UBR/DICb for the next 24hrs.

**Conclusions:** At 2 hours, all pain free and pain relief responders to single dose combination ubrogapant and diclofenac buffered solution did not need a repeat dose. Sustained efficacy without redosing necessity is maintained for 24hrs. Single dose combination ubrogapant/diclofenac buffered solution resulted in a significant reduction in need for a second dose than ubrogapant alone from previously published studies. This small observational study will need to be validated in placebo controlled larger studies.

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**Received:** April 11, 2022; **Accepted:** April 14, 2022; **Published:** April 25, 2022**Introduction**

Migraine ranks as the second most disabling disease of the world as measured in years lived with disability [1]. Eighty-seven per cent of patients report their migraine attacks impact either their work, private, or social lives and half stated that migraine attacks impacted all 3 domains [2]. Headache is the most disabling feature of migraine., Nausea, photophobia, and phonophobia are the most bothersome symptoms (MBS). The International Headache Society currently and in previous versions has deemed recurrence of headache or MBS as a therapeutic failure [3]. Ubrogapant is an oral gepant was approved by the FDA as an effective abortive for acute migraine with and without aura. Forty percent of patients require a second dose of ubrogapant, and 15% require a rescue medication [3]. Diclofenac potassium buffered solution via dissolvable powder is a cox1-cox 2 non- steroidal anti-inflammatory agent that is also FDA approved for the acute treatment of migraine. In one study, 15.5% of acute migraine patients had migraine recurrence

following a single dose of diclofenac potassium buffered solution [4]. This study was undertaken to analyze the need for repeat dosing following treatment of a migraine attack with combination ubrogapant and diclofenac buffered solution.

**Methods**

The entire study cohort consisted of 23 patients ages 18 through 65 mostly- female and 1 male. Patients with episodic and chronic migraine with and without aura were included. All patients failed at least one prior abortive.

Patients were excluded if they were pregnant, had active cardiovascular disease, active gastritis or peptic ulcer disease or known hypersensitivity to nsais or gepants. Patients were permitted to use any preventative as monotherapy or combination therapy.

Each patient was instructed to use a fixed dose combination ubrogapant 100mg tablet with diclofenac 50mg buffered powder in 4 oz of water (UBR/DICb within 15 minutes of the onset of headache. Pain freedom and pain relief at 2 hrs. were recorded and need for repeat dose for relapse was the primary efficacy outcome measure for this study. Relief of most bothersome symptoms (MBS)-nausea, photophobia, phonophobia, and adverse effects were also recorded. Observation for need for repeat dosing was extended to 24hrs. Since MBS intensity was parallel to headache in all the subjects when present, MBS was not stratified for sub analysis. Need for a repeat dose for headache at 2hrs and extension observation to 24 hrs. remained the goal of this study.

## Results

Two hours following a single fixed dose of UBR/DICb, 96% of the enrolled study patients were pain free or obtained pain relief with no need for a second dose, and 4% did not respond. Of the 23 patients enrolled in the study, 87% experienced pain freedom with no need for redosing, (CI 95% (0.7, 1.0), and 9% had pain relief with no need for redosing (CI 95% (-0.02, 0.2), and 4% had no pain relief or freedom and no response to redosing (CI 95% (-0.04, 0.12)). Reduction in MBS paralleled pain reduction in our study cohort. None of the responders required a second dose of UBR/DICb for the next 24hrs. Patients were permitted to use UBR/DICb for recurrent migraine attacks and the response did not differ from our recorded first response. None of the participants noted adverse effects (Table).

**Table**

| Age/S ex (n=23) | Diagnosis * | Adverse Effects | 2hr pain + MBS free dom | 2 hr pain+ MBS relief | Second dose or Rescue treatment |
|-----------------|-------------|-----------------|-------------------------|-----------------------|---------------------------------|
| 70/F            | CM w Aura   | 0               | Yes                     |                       | No                              |
| 42/M            | CM w Aura   | 0               |                         | Yes                   | No                              |
| 42/F            | EM w Aura   | 0               | Yes                     |                       | No                              |
| 62/F            | CM w Aura   | 0               | Yes                     |                       | No                              |
| 44/F            | EM w Aura   | 0               | Yes                     |                       | No                              |
| 26/F            | EM w Aura   | 0               | Yes                     |                       | No                              |
| 51/F            | CM wo Aura  | 0               | Yes                     |                       | No                              |
| 63/F            | EM wo Aura  | 0               | Yes                     |                       | No                              |
| 39/F            | CM w Aura   | 0               | Yes                     |                       | No                              |
| 37/F            | Em w Aura   | 0               | Yes                     |                       | No                              |
| 31/F            | CM w Aura   | 0               | No                      | No                    |                                 |
| 40/F            | CM wo Aura  | 0               | Yes                     |                       | No                              |
| 22/F            | CM w Aura   | 0               |                         | Yes                   | No                              |
| 39/F            | EM w Aura   | 0               | Yes                     |                       | No                              |
| 34/F            | EM w Aura   | 0               | Yes                     |                       | No                              |
| 24/F            | EM w Aura   | 0               | Yes                     |                       | No                              |
| 43/F            | EM w Aura   | 0               | Yes                     |                       | No                              |
| 43/F            | CM w Aura   | 0               | Yes                     |                       | No                              |
| 36/F            | CM w Aura   | 0               | Yes                     |                       | No                              |
| 50/F            | EM w Aura   | 0               | Yes                     |                       | No                              |
| 41/F            | EM w Aura   | 0               | Yes                     |                       | No                              |

|      |              |   |     |    |  |
|------|--------------|---|-----|----|--|
| 18/F | CM w<br>Aura | 0 | Yes | No |  |
| 35/F | EM w<br>Aura | 0 | Yes | No |  |

• CM=Chronic Migraine EM= Episodic Migraine # MBS= Most Bothersome Symptom, nausea, photophobia, phonophobia which paralleled pain

## Discussion

Except for one patient who had no response to UBR/DICb, none of the responders as defined as pain free or with pain relief at 2hrs required a repeat dose of UBR/DICb or rescue therapy. This effect was sustained through 24hrs after the migraine attack provided the patients took UBR/DICb within 15 minutes of headache onset. There were no adverse effects. Patients were permitted to use UBR/DICb for recurrent migraine attacks separated by 24 hrs and had the same response as our recorded first migraine attack. MBS paralleled the response to headache and no patient require redosing strictly for MBS.

Two-hour pain-free response is recommended by the International Headache Society as a primary end point in migraine clinical trials [3]. Sustained pain-free response, defined as the percentage of patients' pain-free at two hours with no relapse for the next 48 hours. Complete effective migraine abortive relief is necessary not only for functionality but to prevent chronification of migraine [5]. A second dose of ubrogepant is needed in 40% of cases to abort a migraine attack with ubrelvy monotherapy which translates to a 40% acute treatment failure [6].

Combination therapy affords the patient a multimechanistic advantage. Combination therapy with a triptan and nsaid is more effective than either agent alone for abortive migraine therapy [7]. This led to the FDA approval of Treximet® (naproxen/ sumatriptan) for abortive migraine treatment. However, the t max of sumatriptan is 2.5 hrs., and naproxen is 2 hrs. The t max of ubrogepant is 1.5 hrs. and diclofenac potassium buffered solution is 15 mins making this combination more likely to abort a migraine headache. The half-life of ubrogepant is 6 hrs. which explains the 40% need for a repeat dose in mono therapy studies. Although the half-life of DICb is 2 hrs., we postulate that the 15-minute t max and the blocking of conversion of cyclooxygenase to prostaglandin leads to faster complete termination of the attack without need for a second dose.

Combining a triptan with ubrogepant causes a delay of the t max of ubrogepant to 3 hrs. and decreased bioavailability of ubrogepant by 24% [8]. However, there is no change in the PK of naproxen and ubrogepant when used in combination [9].

An observation not part of the redosing analysis goal of this study deserve special attention: the initial and sustained pain relief rate of 87% pain free and 9% pain freedom is atypically high for a migraine trial. The placebo-controlled trial with 1672 patients of ubrogepant reported lower pain freedom of 21% at 2 hours for the 100 mg group [6]. This effect is either due to the combined multimechanistic effects of ubrogepant and diclofenac buffered solution which need to be studied in a large clinical trial, or possibly a statistical aberration given the small sample size of this study.

Obviously, the limitation of our study is it is a small observational series with a lack of an active or placebo comparator. Our focus was need for redosing or rescue therapy. Also, our study is not powered to compare safety and efficacy of URB/DICb with other abortive agents alone or in combination. Another limitation is not observing the patients need for redosing beyond 24 hrs.

## Conclusion

Our observational study has demonstrated combination maximum dose of ubrogepant with diclofenac potassium buffered solution in the abortive therapy of migraine resulted in no requirement for redosing or rescue in 2hrs and sustained over 24hrs in our responder cohort which was the majority of our patients. There were no adverse effects. Response to most bothersome symptoms was similar to pain relief and freedom. Larger studies would be needed to validate our findings and to determine if combination UBR/DICb is superior to other monotherapy abortive agents.

## References

1. TJ Steiner, Stovner R, Jensen D, Uluduz Z, Katsarava, et al. (2020) Migraine remains second among the world's causes of disability, and first among young women: findings from the GBD2019 J Headache Pain 21: 137.
2. Paolo Martelletti, Todd J Schwedt, Michel Lanteri-Minet, Rebeca Quintana, Veruska Carboni, et al. (2018) My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. J Headache Pain 19: 115.
3. Peer T felt-Hansen, Julio Pascual, Nabih Ramadan, Carl Dahlöf, Domenico D'Amico, et al. (2011) Guidelines for controlled trials of drugs in migraine: Third edition. A guide for investigators. Cephalalgia 32: 6-38.
4. H-C Diene, P Montagna, G Gács, P Lyczak, G Schumann, et al. (2006) Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. Cephalalgia 26: 537-547.
5. Richard B Lipton, Kristina M Fanning, Daniel Serrano, Michael L Reed, Roger Cady, et al. (2015) Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. NEUROLOGY 84: 688-695.
6. Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, et al. (2019) Ubrogepant for the Treatment of Migraine. NEJM 381: 2230-2241.
7. Brandes J, Kudrow D, Stark S (2007) Sumatriptan-Naproxen for Acute Treatment of Migraine-a randomized trial 297: 1443-1454.
8. Jakate A, Boinpally R, Butler M (2020) Evaluation of the pharmacokinetic interaction of ubrogepant co-administered with sumatriptan and of the safety of ubrogepant with triptans. HEADACHE 60: 1340-1350.
9. Jakate A, Boinpally R, Butler M, Lu K, McGeeney D, et al. (2020) Evaluation of the pharmacokinetic interaction and safety of ubrogepant co-administered with acetaminophen or nonsteroidal anti-inflammatory drugs: A randomized trial. Cephalalgia 11: 270-277.

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