J Neurol Neurosci ©
13 (3) 2022 : 001-07 • RESEARCH ARTICLE

Recurrence of acute migraine following ubrogepant and diclofenac buffered solution combination therapy- An observational study

James A Charles*, Nicole Suttora
Holy Name Medical Center, Montclair University, New Jersey, USA

SUMMARY

Objective: To analyze the need for a repeat dose following administration of a single fixed combination dose of ubrogepant 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: Ubrogepant 100 mg tabs and diclofenac potassium buffered solution 50 mg 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 24 hrs. 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 re-dosing , (CI 95% (0.7, 1.0), and 9% had pain relief with no need for re-dosing (CI 95% (-0.02, 0.2), and 4% had no pain relief or freedom and no response to re-dosing (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 24 hrs.

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

Keywords: Urbrogepant; Diclofenac; Combination.

Address for correspondence:

James A Charles
Holy Name Medical Center, Montclair University, New Jersey, USA
E-mail: jcharlesmd@jamesacharlesmd.com

Word count: 1772 **Tables:** 01 **Figures:** 00 **References:** 9

Received: 13.02.2022, Manuscript No. ipjnn-22-12518; **Editor assigned:** 15.02.2022, PreQC No. P-12518; **Reviewed:** 22.03.2022, QC No. Q-12518; **Revised:** 24.03.2022, Manuscript No. R-12518; **Published:** 31.03.2022

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]. Ubrogepant 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 ubrogepant, and 15% require a rescue medication [3]. Diclofenac potassium buffered solution via dissolvable powder is a cox 1-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 ubrogepant and diclofenac buffered solution.

METHODS

The entire study cohort consisted of 23 patient's 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 nsaids or gepants. Patients were permitted to use any preventative as monotherapy or combination therapy.

Each patient was instructed to use a fixed dose combination urbrogepant 100 mg tablet with diclofenac 50 mg 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 24 hrs. 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 2 hrs 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 re-dosing , (CI 95% (0.7, 1.0), and 9% had pain relief with no need for re-dosing (CI 95% (-0.02, 0.2), and 4% had no pain relief or freedom and no response to re-dosing (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 24 hrs. Patients were permitted to use UBR/DlCb for recurrent migraine attacks and the response did not differ from our recorded first response. None of the participants noted adverse effects (**Tab. 1.**).

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 2 hrs required a repeat dose of UBR/DICb or rescue therapy. This effect was sustained through 24 hrs 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/DlCb 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 requires re-dosing 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 urbrogepant 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 urbrogepant 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 urbrogepant 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 urbrogepant causes a delay of the t max of urbrogepant to 3 hrs and decreased bioavailability of urbrogepant by 24% [8]. However, there is no change in the PK of naproxen and urbrogepant when used in combination [9].

Tab. 1. Second dose of UBR/DICb for the next 24 hrs.

Age/Sex (n=23)	Diagnosis*	Adverse Effects	2 hr Pain + MBS Freedom	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 Aura	0	Yes	-	No
35/F	EM w Aura	0	Yes	-	No

An observation not part of the re-dosing 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 needs 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 re-dosing 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 re-dosing 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 re-dosing or rescue in 2 hrs and sustained over 24 hrs 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. **Steiner TJ, Stovner LJ, Jensen R, et al.** Migraine remains second among the world's causes of disability, and first among young women: Findings from the GBD2019. *J Headache Pain*. 2020;21:137.
2. **Martolletti P, Schwedt TJ, Lanter-Minet M, et al.** My Migraine Voice survey: A global study of disease burden among individuals with migraine for whom preventive treatments have failed. *J Headache Pain*. 2018;19:115.
3. **Tfelt-Hansen P, Pascual J, Ramadan N, et al.** Guidelines for controlled trials of drugs in migraine: (3rd Edn). A guide for investigators. *Cephalalgia*. 2012;32:6-38.
4. **Diener HC, Montagna P, Gacs G, et al.** 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*. 2006;26(5):537-547.
5. **Lipton RB, Fanning KM, Serrano D, et al.** Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurol*. 2015;84(7): 688-695.
6. **Dodick DW, Lipton RB, Ailani J, et al.** Urbrogepant for the Treatment of Migraine. *New England J Med*. 2019;381(23):2230-2241.
7. **Brandes J, Kudrow D, Stark SR, et al.** Sumatriptan-Naproxen for acute treatment of migraine: A randomized trial. *JAMA*. 2007;297(13):1443-1454.
8. **Jakate A, Boinpally R, Butler M, et al.** Evaluation of the pharmacokinetic interaction of urbrogepant co-administered with sumatriptan and of the safety of urbrogepant with triptans. *Headache*. 2020; 60(7):1340-1350.
9. **Jakate A, Boinpally R, Butler M, et al.** Evaluation of the pharmacokinetic interaction and safety of urbrogepant co-administered with acetaminophen or non-steroidal anti-inflammatory drugs: A randomized trial. *Cephalalgia*. 2020;3:1-10.