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PATIENTS WITHOUT BASELINE NAUSEA RESPOND BEST TO MT100 FOR PAIN RELIEF: EVIDENCE FOR A ROLE OF DOPAMINE IN MIGRAINE?

John R. Plachetka, PharmD; Susan E Spruill, MS; W. James Alexander, MD, MPH
POZEN, Inc., Chapel Hill, NC

BACKGROUND

Migraine

Migraine causes a heterogeneous spectrum of symptoms and for an individual patient, the occurrence of any of the associated symptoms of migraine–nausea, photophobia and/or phonophobia–may vary for separate attacks. Nausea is the least frequently reported associated symptom of migraine and in one survey of migraineurs, nausea did not accompany migraine in approximately 50% of migraine attacks (1).

Migraine without nausea is recognized as distinct within the diagnostic criteria of migraine (2).

Additional treatment options are needed for patients whose migraine attacks are inadequately treated with over-the-counter medications, simple analgesics and some prescription drugs.

Naproxen sodium

Naproxen sodium, an NSAID analgesic with an extended duration of action, has been shown to have efficacy as a single agent in migraine (3).

Metoclopramide

The efficacy of the dopamine antagonist metoclopramide in the parenteral treatment of migraine has been established in individual studies and by a meta-analysis of randomized controlled trials (4, 5, 6, 7).

One mechanism of action of metoclopramide in migraine may be through inhibition of dopamine hypersensitivity that may occur in migraine (8, 9).

The pharmacologic action of metoclopramide to facilitate the absorption of analgesics of the NSAID class during a migraine attack has been shown in small studies (10, 11).

MT100

MT100 is a fixed combination of naproxen sodium 500mg and metoclopramide 16mg in a uniquely formulated tablet.

OBJECTIVES

To compare the efficacy of MT100 with the efficacy of naproxen sodium 500mg in migraine attacks with and without nausea at the time of treatment as a measure of the contribution of metoclopramide in the acute treatment of each type of migraine.

METHODS

Two double-blind, randomized, single-attack studies were conducted in the US, comparing MT100, naproxen sodium 500mg alone, and metoclopramide 16mg alone for the acute treatment of migraine with headache of moderate to severe intensity. Study protocols were approved by Institutional Review Boards. Study A enrolled 1067 subjects at 39 sites; Study B enrolled 2627 subjects at 74 sites.

Cochran-Mantel-Haenszel tests and ordered logistic regression were used to analyze the relationship between migraine treatment responses and clinical variables. Prospectively planned analyses included assessment of migraine pain responses by presence or absence of nausea (of any severity) at the time of treatment. A retrospective analysis of data from Study B assessed the relationship between severity of nausea at time of treatment of the migraine attack and the degree of migraine pain response. A Mantel-Haenszel test for trend was employed in analyses of these data from Study B.

RESULTS

Table 1: Pain Responses in Migraine Attacks Without Nausea

	MT100	Naproxen sodium	Metoclopramide
Study A (n=571)			
Pain Response at 2 hr	50.7 %	45.3 %	33.6 %
Sustained Pain Response at 24 hr*	38.4 %	28.5 %	19.1 %
Study B (n=853)			
Pain Response at 2 hr†	54.6 %	47.2 %	37.0 %
Sustained Pain Response at 24 hr**	36.7 %	26.7 %	16.1 %

* p = 0.009; MT100 vs. naproxen sodium, ordered logistic regression
** p = 0.004; MT100 vs. naproxen sodium, ordered logistic regression
† p = 0.056; MT100 vs. naproxen sodium; Cochran-Mantel-Haenszel test

Table 2: Pain Responses in Migraine Attacks With Nausea

	MT100	Naproxen sodium	Metoclopramide
Study A (n=492)			
Pain Response at 2 hr	45.3 %	48.2 %	35.0%
Sustained Pain Response at 24 hr*	32.3 %	31.5 %	20.4 %
Study B (n=1760)			
Pain Response at 2 hr†	47.2 %	46.5%	36.3 %
Sustained Pain Response at 24 hr**	29.6 %	28.5 %	20.0 %

* p = 0.796; MT100 vs. naproxen sodium, ordered logistic regression
** p = 0.622; MT100 vs. naproxen sodium, ordered logistic regression
† p = 0.468; MT100 vs. naproxen sodium; Cochran-Mantel-Haenszel test

Table 3: 2 Hour Pain Response for All Treatment Groups in Study B by Severity of Nausea with Migraine Attack

Baseline nausea severity	MT100	Naproxen sodium	Metoclopramide
No nausea	54.6 %	47.2 %	37.0 %
Mild nausea	50.3 %	48.9 %	38.0 %
Moderate or Severe nausea	43.0 %	42.5 %	33.8 %
M.H. Chi-square*	7.671	1.062	0.312
p value	0.0056	0.3027	0.5764

* Mantel-Haenszel Chi-square test for trend

Table 4: Sustained Pain Response at 24 hours for All Treatment Groups in Study B by Severity of Nausea with Migraine Attack

Baseline nausea severity	MT100	Naproxen sodium	Metoclopramide
No nausea	36.7 %	26.7 %	16.1 %
Mild nausea	31.7 %	29.2 %	21.9 %
Moderate or Severe nausea	26.0 %	27.4 %	16.9 %
M.H. Chi-square*	7.736	0.077	0.066
p value	0.0054	0.7810	0.7970

* Mantel-Haenszel Chi-square test for trend

Table 5: Percent of Subjects with Specific Adverse Event Occurrence by Treatment Group and Nausea Status

	Migraine Without Nausea			Migraine With Nausea		
Event	MT100	Naproxen sodium	Meto-clopramide	MT100	Naproxen sodium	Meto-clopramide
Any Event						
Study A	16 %	13 %	11 %	18 %	11 %	18 %
Study B	24 %	17 %	20 %	27 %	23 %	31 %
Somnolence						
Study A	3 %	<1 %	<1 %	2 %	<1 %	3 %
Study B	6 %	1 %	4 %	6 %	2 %	6 %
Diarrhea						
Study A	2 %	<1 %	2 %	2 %	2 %	3 %
Study B	4 %	1 %	2 %	4 %	1 %	5 %

CONCLUSIONS

- MT100 is significantly superior to naproxen sodium alone in the acute treatment of migraine attacks without nausea.
- The mechanism of the better pain responses with MT100 treatment is likely due to coordinated release of metoclopramide from MT100 and resultant gastrokinesis leading to enhanced early absorption of naproxen sodium.
- Metoclopramide 16mg alone was comparatively less effective in the relief of moderate to severe headache of migraine.
- When nausea accompanies a migraine attack, the severity of nausea may be related to the magnitude of the expected treatment benefit of MT100.

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