The Combination of Metoclopramide and/or Caffeine Does Not Improve the Efficacy of Frovatriptan

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Abstract

This study explored the combination of metoclopramide and/or caffeine with Frovatriptan in the acute treatment of migraine to determine if such combinations enhance the efficacy of Frovatriptan alone. The research study was approved by a certified IRB.

Primary Objective
The primary objective of this study was to evaluate the effectiveness of combining metoclopramide (M) and/or caffeine (C) with Frovatriptan (FMC) in the acute treatment of migraine. The primary end point was relief of headache pain (from moderate-severe to mild or no pain, or mild pain to no pain).

Secondary Objectives
Secondary objectives were: a.) 2 hour pain relief comparing FMC vs. FM, FC combined and FM, FC combined vs. Frovatriptan alone (FPBO); b.) comparisons of time to first meaningful relief in 15 minute intervals among all 4 arms; c.) 2, 4, and 24 hour pain-free status among all 4 arms; d.) 24 hour sustained pain-free status among all 4 arms, e.) 2, 4, and 24 hour migraine-free status (absence of migraine related symptoms) among all 4 arms; and f.) disability comparisons at 2, 4, and 24 hours among all 4 arms.

Data were analyzed using Chi-square, ANOVA, McNemar's test, and Kaplan-Meier survival analysis as appropriate using SPSS.

Methods

The study was a randomized, double-blind, crossover, active comparator trial using Frovatriptan + Placebo (FPBO) alone or in combination with Metoclopramide 10 mg (FM) or Caffeine 35 mg (FC) or both (FMC) to study the efficacy of each of the various combinations. Subjects were recruited from Mercy Health Research and the Ryan Headache Center. Subjects served as their own controls with each subject receiving all four combinations of study product in a randomized and double blind fashion across 4 separate migraine attacks. Subjects were instructed to treat at the earliest possible time from onset of migraine. Rescue medication was allowed at 2 hours (using identical attack specific investigational product) and again, if needed, at 4 hours after initial dosing utilizing open-label ibuprofen 800 mg orally. Subjects recorded a detailed diary of their attacks. Treatment combinations were randomized in sequencing such that subjects and investigators were blinded to the actual dosing combination for each attack. The possible treatment sequences were limited to four:

Possible Treatment Sequencing

Attack 1	Attack 2	Attack 3	Attack 4
FMC	FC	FM	FPBO
FC	FM	FPBO	FMC
FM	FPBO	FMC	FC
FPBO	FMC	FC	FM

Results

63 individuals with ICHD-II criteria migraine with or without aura consented to participate in the study (97% female, ages 19-62, years with headache = 20.10 years, mean headaches/month = 4.8). Among those, 46 completed treatment of 4 attacks, while a total of 50 treated three attacks. A total of 198 treated attacks.
Table 1 shows that the 2, 4, & 24 hour pain relief did not differ across treatments arms.

(Table 1) 2, 4, 24 hour Pain Relief

	2hr	4hr	24hr
FPBO	53%	67%	86%
FC	46%	70%	80%
FM	59%	80%	89%
FMC	64%	67%	92%

Response to treatment did not differ significantly between treatment arms regardless of baseline HIT-6, MIDAS or MSQ scores; migraine severity or associated symptoms at the time of dosing. There was no significant difference between treatment arms even when evaluating results among attacks that became pain free, sustained pain free, or even migraine-free. Similarly there was no significant difference when comparing attacks treated with a single dose versus attacks using a second dose or rescue medication.

The groups did not differ in regards to adverse events.

Conclusion

The results of the current findings indicate that adding metoclopramide and/or caffeine to frovatriptan does not enhance the efficacy of frovatriptan alone in treating acute migraine. Though not statistically significant, for the attacks achieving relief with just a single dose of study product, frovatriptan alone was slightly faster than any of the combinations. The results for Frovatriptan alone were comparable to those reported in the pivotal regulatory trials.

It is quite remarkable that regardless of the nature of comparisons, there were no statistically significant differences at any time point for any of the treatment arms for any of the outcomes and variables.

The results of this study suggest that the use of these adjunctive medications for the purpose of enhancing clinical efficacy of a triptan, is unnecessary. Clinicians should purposefully evaluate the potential contributions of such therapies as they may only contribute to increased potential for side effects and drug-drug interactions as well as unnecessarily increase costs of treatment.

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