A Prospective, Randomized Trial of Intravenous Prochlorperazine Versus Subcutaneous Sumatriptan in Acute Migraine Therapy in the Emergency Department

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Study objective: Intravenous (IV) prochlorperazine with diphenhydramine is superior to subcutaneous sumatriptan in the treatment of migraine patients presenting to the emergency department (ED).

Methods: In this randomized, double-blind, placebo-controlled trial, after providing written informed consent, patients presenting to the ED with a chief complaint of migraine received a 500-mL bolus of IV saline solution and either 10 mg prochlorperazine with 12.5 mg diphenhydramine IV plus saline solution placebo subcutaneously or saline solution placebo IV plus 6 mg sumatriptan subcutaneously. Pain intensity was assessed with 100-mm visual analog scales (visual analog scale at baseline and every 20 minutes for 80 minutes). The primary outcome was change in pain intensity from baseline to 80 minutes or time of ED discharge if subjects remained in the ED for fewer than 80 minutes after treatment. Sedation and nausea were assessed every 20 minutes with visual analog scale scales, and subjects were contacted within 72 hours to assess headache recurrence.

Results: Sixty-eight subjects entered the trial, with complete data for 66 subjects. Baseline pain scores were similar for the prochlorperazine/diphenhydramine and sumatriptan groups (76 versus 71 mm). Mean reductions in pain intensity at 80 minutes or time of ED discharge were 73 mm for the prochlorperazine/diphenhydramine group and 50 mm for those receiving sumatriptan (mean difference 23 mm; 95% confidence interval 11 to 36 mm). Sedation, nausea, and headache recurrence rates were similar.

Conclusion: IV prochlorperazine with diphenhydramine is superior to subcutaneous sumatriptan in the treatment of migraine. [Ann Emerg Med. 2009;xx:xxx.]

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INTRODUCTION

Background

Intravenous (IV) prochlorperazine is safe and effective in migraine abortive therapy.[1-5] It is often given in conjunction with diphenhydramine to minimize the risk of akathisia.[6] Subcutaneously injected sumatriptan has also been found to be a safe and effective migraine remedy.[7-11]

Previous peer-reviewed data have not compared these modalities in the doses and routes typically used in US EDs.[12-15] One study, published in abstract form only, reported prochlorperazine to be superior.[16] However, this study provides limited guidance because of its small sample size (only 24 subjects) and the paucity of data provided in the abstract. The lack of prospective data makes the formation of sound treatment guidelines problematic and forces clinicians to rely primarily on anecdotal experience.

Importance

Migraine headache is a common and debilitating medical condition, accounting for 2.2% of all US emergency department (ED) visits.[17] Approximately 5% of US ED patients list headache or migraine among the top 3 reasons for their visit.[18]

Goals of This Investigation

Our hypothesis was that IV prochlorperazine (Compazine, Bedford Labs, Bedford, OH) with diphenhydramine (Hospira, Lake Forest, IL) would be superior to subcutaneous sumatriptan (Imitrex, GlaxoSmithKline, Philadelphia, PA) in migraine abortive therapy in ED patients.

The primary outcome measure was the mean change in pain intensity 80 minutes after treatment (or at ED discharge, if

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Editor's Capsule Summary

What is already known on this topic

Prochlorperazine and sumatriptan are commonly used to treat acute migraine; however, little evidence exists to support the use of one agent over the other.

What question this study addressed

This 68-patient randomized controlled trial compared the efficacy and adverse effect profiles of intravenous prochlorperazine administered with diphenhydramine (to prevent akathisia) and subcutaneous sumatriptan in the emergency department treatment of migraine.

What this study adds to our knowledge

Prochlorperazine was superior to sumatriptan in relieving pain, whereas adverse effects (nausea and sedation) were similar.

How this might change clinical practice

This study supports the use of prochlorperazine with diphenhydramine over sumatriptan for adults with acute migraine.

earlier than 80 minutes), as measured by a visual analog scale. A difference between the groups of 13 mm or greater was considered a priori to be clinically important.[19,20]

MATERIALS AND METHODS

Study Design

This was a prospective, randomized, double-blind, placebo-controlled study of ED patients with migraine. This study was in accord with the Standards of the Committee of Human Experimentation and was approved by the local institutional review board.

Setting

The setting was a US Department of Defense tertiary care ED with an annual census of 65,000 patients.

Selection of Participants

Consecutive patients between 18 and 50 years of age, with a history of migraine and for whom this was a typical migraine headache, were evaluated by the enrolling physician for involvement in this study. A list of modified International Headache Society criteria for migraine (Figure 1) was used by the physician to confirm the diagnosis of migraine before enrollment. The study took place between October 2006 and March 2007. Exclusion criteria included hypersensitivity to study drugs; history of coronary artery or peripheral vascular disease; diastolic blood pressure greater than 100 mm Hg; pregnancy; use of an ergotamine derivative, triptan, or

At least 2 of the following
- Unilateral location
- Thobbing character
- Worsening pain with routine activity
- Moderate to severe intensity

At least one of the following features:
- Nausea and/or vomiting
- Photophobia and/or phonophobia

Figure 1. Modified International Headache Society criteria for migraine.[24]

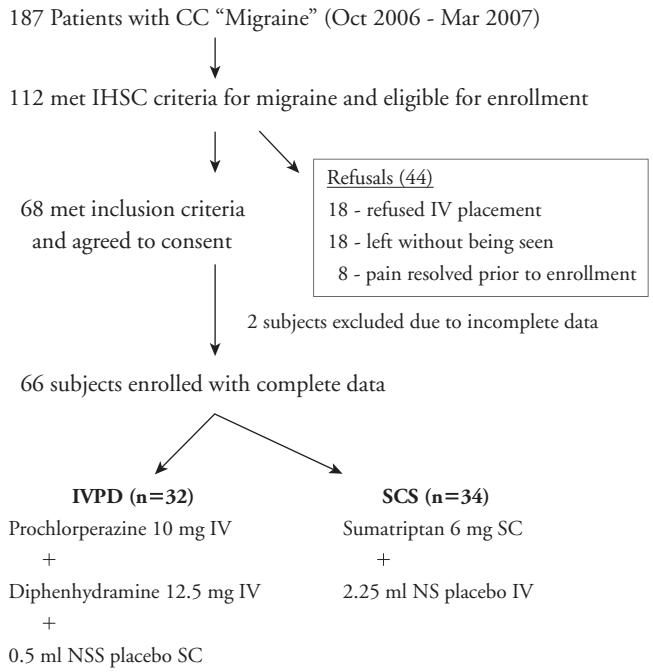

Figure 2. Subject flow chart. *IHSC*, International Headache Society criteria; *IVPD*, intravenous prochlorperazine and diphenhydramine; *SCS*, subcutaneous sumatriptan.

dopamine-blocking antiemetic within the past 24 hours; hepatic impairment; history of nonmelanoma cancer; temperature greater than 38°C (100.5°F); or any atypical headache requiring further evaluation.

All subjects provided written informed consent. Randomization occurred in the pharmacy department, with a random number generator program.

Interventions

Once randomized, each subject received a 500-mL bolus of saline solution and either 10 mg IV prochlorperazine plus 12.5 mg IV diphenhydramine during 2 minutes (combined in one syringe) plus 0.5 mL subcutaneous saline solution placebo (IV prochlorperazine with diphenhydramine) or a

Table. Baseline data and demographic information.

Subject Descriptor	IV Prochlorperazine With Diphenhydramine, n=31	Subcutaneous Sumatriptan, n=35
Women (%)	19 (61)	23 (66)
Mean age, y (SD; 95% CI)	31 (10; 26–36)	28 (6; 25–31)
Mean visual analog scale for pain at time zero (SD; 95% CI)	76 mm (17; 70–82)	71 mm (22; 64–78)
Mean duration of headache before arrival, days (SD; 95% CI)	2.7 (3.3; 1.4–4.1)	1.7 (2.2; 0.8–2.6)
Mean No. of migraines/mo (SD; 95% CI)	5 (6; 2–7)	3 (3; 2–4)
Use of other prescriptions in previous 24 h (acetaminophen, nonsteroidal antiinflammatory drug, Midrin, Fioricet, opioid) (%)	16 (50)	15 (43)
Family history of migraine (%)	9 (29)	11 (31)

2.25-mL saline solution placebo IV during 2 minutes plus 6 mg subcutaneous sumatriptan (Figure 2). Syringes containing drug and placebo were prepared by the pharmacy. The volumes and appearance of the syringes, whether containing drug or placebo, were identical.

Methods of Measurement

Pain was assessed at baseline and 20-minute intervals for 80 minutes. A new, unhatched visual analog scale sheet (0 to 100 mm) was used for each assessment. At no time was any subject, investigator, or caregiver aware of the study arm assignment. Subjects were permitted to leave the ED before the 80-minute mark if their pain was minimal and they requested discharge.

Sedation and nausea were measured on new, unhatched visual analog scale sheets at baseline and each 20-minute interval. At these times, the patient was also asked about the development of any restlessness, anxiety (ie, akathisia), or chest pain.

Telephone follow-up was attempted within 72 hours to assess headache recurrence, defined as a headache necessitating an unscheduled return to a health care provider.

Outcome Measures

The primary outcome measure was the mean change in pain intensity from baseline to 80 minutes (or at ED discharge, if earlier than 80 minutes), as assessed by the visual analog scale, with a difference between the groups of 13 mm or greater considered a priori to be clinically important. In addition, differences in mean degree of nausea and sedation as measured by visual analog scale were assessed.

Primary Data Analysis

A total of 62 subjects was needed (31 per group) to detect the prespecified minimally clinically importance difference of 13 mm between the groups with 80% power. Pain intensity differences from baseline to 80 minutes or ED discharge were compared with a *t* test. If a subject departed before 80 minutes, his or her final recorded visual analog scale score was simply carried forward.

Statistical software used included PASS (Power Analysis and Sample Size, version 2000), SPSS (Statistical Package for the Social Sciences, version 15), and NCSS (Number Cruncher for the Social Sciences).

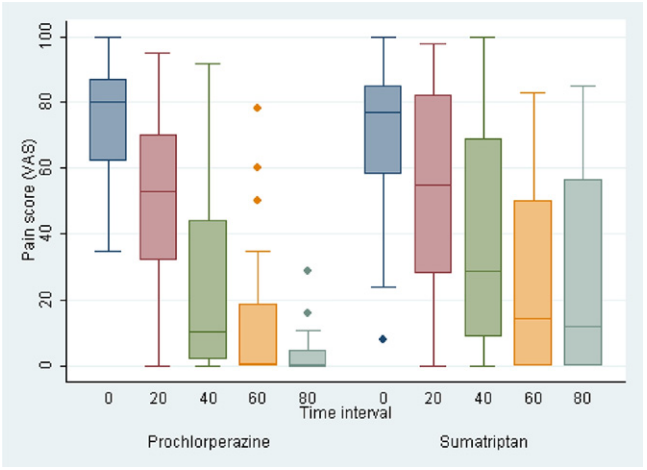

Figure 3. Box-and-whisker plots of visual analog scale pain intensity scores over time.

RESULTS

One hundred eighty-seven patients presented with a chief complaint of migraine during the study period, October 2006 to March 2007. Sixty-eight met the inclusion criteria and were enrolled. Sixty-six completed the study. Incomplete data were found for 1 subject in each group, and they were each excluded from analysis. Because subjects were permitted to depart the ED when they felt ready, only 51 stayed the full 80 minutes. Of those not enrolled, the reasons were that they did not want an IV placed, left without being seen, or were feeling better (Figure 2).

Analysis indicated that data were normally distributed and homogeneous. Data from the 66 subjects were analyzed. There were no important differences between the groups at baseline. These included visual analog scale pain scores at time zero, sex, age, duration of headache, average number of migraines per month, use of other pain medications at home before the ED visit, and family history of migraine (Table). Although both regimens were effective, subjects in the prochlorperazine group exhibited a greater overall improvement in pain compared with those in the sumatriptan group. The mean decrease in pain

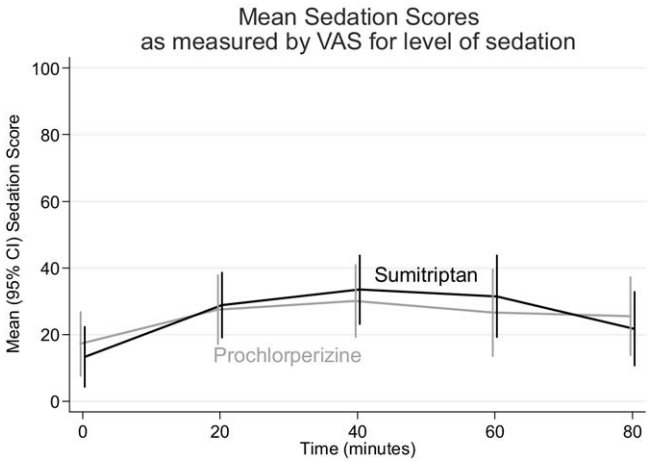

Figure 4. Mean sedation scores as measured by visual analog scale for level of sedation.

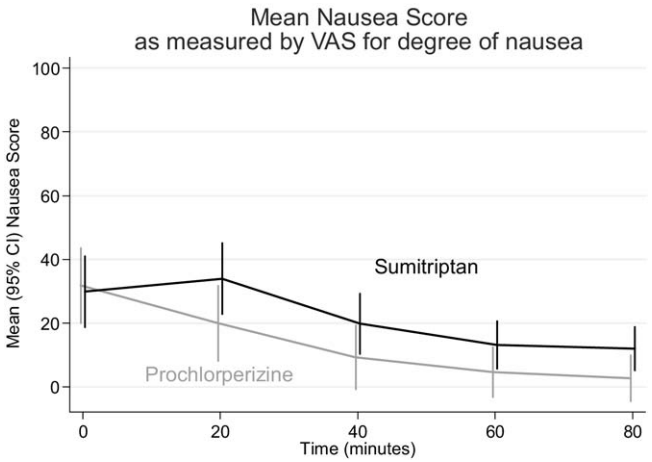

Figure 5. Mean nausea score as measured by visual analog scale for degree of nausea.

intensity in the IV prochlorperazine with diphenhydramine group was 73 mm compared with 50 mm in the subcutaneous sumatriptan group (difference=23 mm; 95% confidence interval [CI] 11 to 36 mm). The reference points used for this calculation were time zero and the final time for which a pain score was recorded before discharge. Box-and-whisker plots of pain intensity from baseline to 80 minutes are presented in Figure 3.

Sedation and nausea scores were similar at baseline. There was no important difference in the increase in mean sedation scores at discharge (IV prochlorperazine with diphenhydramine 11 mm; subcutaneous sumatriptan 10 mm; mean difference 1 mm; 95% CI –15 to 18 mm). With respect to the decrease in nausea in each study arm, the IV prochlorperazine with diphenhydramine group appeared to have greater relief, but this was not statistically significant (IV prochlorperazine with diphenhydramine –30 mm; subcutaneous sumatriptan –18 mm; mean difference –12 mm; 95% CI –24 to 0.5 mm) (Figures 4 and 5). Although 9 of the 32 subjects in the IV prochlorperazine with diphenhydramine group did respond yes when asked whether they felt any restlessness, none requested additional anticholinergic therapy. None of those in the subcutaneous sumatriptan group reported chest discomfort. The presence or absence of cutaneous allodynia was not assessed as a marker of nonresponse to sumatriptan.[21]

Follow-up telephone calls were successfully obtained for 40 of the 66 patients (61%). Of those, 43% in the IV prochlorperazine with diphenhydramine group and 63% in the subcutaneous sumatriptan group reported a return of some degree of headache (difference=20%; 95% CI –31% to 60%). No subjects reported a headache recurrence significant enough to bring them back to the ED or any health care provider. None of the 26 subjects who were unable to be contacted returned to the ED (part of a closed Department of Defense system) for treatment in that period.

LIMITATIONS

Thirty-nine percent of subjects were unable to be contacted by telephone within 72 hours. Although this is a relatively poor follow-up rate, the ED where this study took place is part of a closed Department of Defense network and is the only Department of Defense ED in the region. None of the 22 subjects who were unable to be reached for follow-up returned to the ED in that 72-hour period.

DISCUSSION

To our knowledge, this is the first prospective trial of adult ED patients with typical migraine comparing 2 commonly used pharmacologic agents at standard doses. A strength of this study, in addition to its prospective, controlled, randomized, blinded format, is that it enrolled only patients who met the International Headache Society criteria for migraine. Both drugs were found to be effective treatments for migraine. Prochlorperazine with diphenhydramine, however, is superior. It resulted in a more rapid and greater overall reduction in pain, which was accomplished without significant adverse effects or adverse drug reactions.

Phenothiazines, the group to which prochlorperazine belongs, are powerful antagonists of the neurotransmitter dopamine in the basal ganglia and limbic system. This effect seems to change pain perception, as well as have antipsychotic properties. They are also potent antiemetics through their effect on the chemoreceptor trigger zone. In addition, they are antagonists at α-adrenergic, muscarinic cholinergic, histaminic, and serotonergic receptors. The mechanism by which phenothiazines act in migraine is uncertain. It is likely related to the cumulative effect of its activity at the various receptors detailed above, as well as at the chemoreceptor trigger zone.[3,22,23]

Sumatriptan is a specific and selective serotonin agonist at the 5-HT1B/1D receptor. It has no activity at the other serotonin receptor subtypes (7 major subclasses of serotonin

receptors—classes 1 though 7—are now recognized). It is likely that the 5-HT1B/1D agonist activity is the primary mechanism of the therapeutic effect of this drug. As a result, triptans have 3 potential mechanisms of action: cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second-order neurons of the trigeminocervical complex.[24] It was surprising that no subjects in the subcutaneous sumatriptan group complained of chest pain, which may be a result of the way the question was phrased: "Do you have any chest pain?" Perhaps a more appropriate question might have been, "Do you have any discomfort in your chest or shoulders?" Having no patients report this adverse effect likely helped preserve our blinding.

It would have been optimal to keep all subjects in the ED for the entire 80-minute observation period. However, it was not thought to be reasonable to ask a subject who had become free of pain to stay longer in the ED for complete data collection, nor would it have been practical for patient flow through the ED. Experience dictates that, once aborted, migraines do not quickly recur. It is logical that those subjects discharged at 20, 40, or 60 minutes were unlikely to have a recurrent headache in the following hour. Had they not been discharged early, their subsequent visual analog scale scores presumably would not have altered the outcome.

This study was not intended as a formal cost-benefit analysis. However, cost is an important consideration. At the time of the study, the cost to the Department of Defense of 6 mg of injectable sumatriptan was $34.78 compared with a total of $2.78 for 10 mg of prochlorperazine and 12.5 mg of diphenhydramine. Even including the fixed cost and time for placing a peripheral IV (estimated at $12.60),[25] the IV prochlorperazine with diphenhydramine route is not only more efficient and more effective but also less expensive.

In conclusion, both regimens were effective. However, IV prochlorperazine with diphenhydramine was superior to subcutaneous sumatriptan in the abortive therapy of migraine headache in the ED, without statistically significant differences in adverse effects.

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