Intravenous administration of metoclopramide by 2 min bolus vs 15 min infusion: does it affect the improvement of headache while reducing the side effects?

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Objective: To determine the therapeutic effect (alleviation of vascular type headache) and side effects of a slow intravenous metoclopramide infusion over 15 min compared with those effects of a bolus intravenous metoclopramide infusion over 2 min in the treatment of patients with recent onset vascular type headache.

Material and methods: All adults treated with metoclopramide for vascular type headache were eligible for entry into this clinical randomised double blinded trial. This study compared the effects of two different rates of intravenous infusion of metoclopramide over a period of 13 months at a university hospital emergency department. During the trial, side effects and headache scores were recorded at baseline (0 min), and then at 5, 15, 30 and 60 min. Repeated measures analysis of variance was used to compare the medication's efficacy and side effects.

Results: A total of 120 patients presenting to the emergency department met the inclusion criteria. Of these, 62 patients (51.7%) were given 10 mg metoclopramide as a slow intravenous infusion over 15 min (SIG group) and 58 patients (48.3%) were given 10 mg metoclopramide intravenous bolus infusion over 2 min (BIG group). 17 of the 58 patients in the BIG group (29.3%) and 4 of the 62 patients (6.5%) in the SIG group had akathisia ($p=0.001$). There were no significant differences between the BIG and SIG groups in terms of mean headache scores ($p=0.34$) and no adverse reactions in the study period. Metoclopramide successfully relieved the headache symptom(s) of patients in both the BIG and SIG groups.

Conclusion: Slowing the infusion rate of metoclopramide is an effective strategy for the improvement of headache and reducing the incidence of akathisia in patients with vascular type headache.

Headache, mostly benign, is the chief complaint of 1.7–2.5% of patients admitted to an emergency department.¹ Its treatment is sometimes challenging for emergency physicians. It has been reported that the most commonly used medications for parenteral treatment of isolated benign headache in emergency departments in the USA are meperidine (30.0%), ketorolac (21.4%) and prochlorperazine (16.7%).² Antiemetics may especially be useful for the resolution of headache and recently there has been a move towards these agents.^{3,4} Studies of intravenous metoclopramide reported benefit over placebo and, in one study, a success rate of 67%.⁵

Metoclopramide, a benzamide antiemetic drug, is frequently used in the emergency department for the management of nausea, vomiting and headache. It is postulated to act via central antidopaminergic mechanisms.^{5–8} Metoclopramide mainly exerts its effect by blocking dopaminergic receptors within the chemoreceptor trigger zone, and is thus associated with extrapyramidal findings such as dystonic episodes, parkinsonism, chronic tardive dyskinesia, muscle spasm in the tongue, face, neck or back, and acute akathisia.^{9–10} Akathisia can be defined as a state of mental and motor restlessness. It includes a subjective component that consists of intense feelings of internal discomfort and tension with a compulsive urge to move, as well as an objective component characterised by motor agitation, particularly affecting the legs, resulting in the observable inability to remain still either while sitting or standing.^{11–12} The reported incidence of akathisia is 20–25% after the intravenous administration of 10 mg metoclopramide to unmedicated patients.^{13–15}

The mechanism by which akathisia occurs following metoclopramide infusion is still speculative. The literature indicates

that there may be a direct relationship between serum concentrations of metoclopramide and akathisia. Slowing the infusion rate of metoclopramide is an effective strategy for reducing the incidence of akathisia in patients with headache and/or nausea and vomiting.^{16–17} Another supportive study comparing rates of metoclopramide infusion in a different group of patients was also conducted during an overlapping time period in Turkey, the results of which have been reported elsewhere.¹⁸ The authors of several studies noted that akathisia occurred only in subjects who had peak plasma concentrations of drugs above 100 ng/ml, but was not appreciated at lower peak plasma concentrations.^{19–20}

The aim of this study was to determine the therapeutic effect (alleviation of vascular type headache) and side effects of a slow intravenous metoclopramide infusion over 15 min compared with those effects of a bolus intravenous metoclopramide infusion over 2 min in the treatment of patients with recent onset vascular type headache.

MATERIALS AND METHODS

Study design and procedures

This prospective, randomised, double-blind study was conducted over a 13 month study period between July 2001 and August 2002 after obtaining permission from the Institutional Review Board of Dokuz Eylül University Medical Faculty. The current study was conducted in the emergency department of the university. All consecutive adult patients (≥ 18 years of age) referred to the emergency department with vascular type

Abbreviations: BIG, 2 min bolus group; SIG, 15 min slow infusion group (SIG)

Table 1 Prince Henry Hospital akathisia rating scale**OBJECTIVE RATINGS:** (ratings by observer)**I. Sitting**

1. Semipurposeful/purposeless leg/feet movement	0 1 2 3
2. Semipurposeful hand/arm movements	0 1 2 3
3. Shifting body position in chair	0 1 2 3
4. Inability to remain seated	0 1 2 3

II. Standing

1. Purposeless/semipurposeless leg/feet movements	0 1 2 3
2. Shifting weight from foot-to-foot and/or walking on spot	0 1 2 3
3. Inability to remain standing on one spot (walking or pacing)	0 1 2 3

Sum score**SUBJECTIVE RATINGS:** (three questions were asked)

1. Do you feel restless, or urge to move, especially in the legs?	0 1 2 3
2. Are you unable to keep your legs still?	0 1 2 3
3. Are you unable to remain still, standing or sitting?	0 1 2 3

Key: 0–3: absent, mild, moderate, severe

0—absent

1—mild and present some of time

2—mild and present most of the time or severe and present some of the time

3—severe and present all the time

Sum score**TOTAL SCORE**

*Reprinted from Sachdev P. A rating scale for acute drug-induced akathisia: development, reliability, and validity. *Biol Psychiatry* 1994;**35**:270–1. Copyright (1994) with permission from Society of Biological Psychiatry. Global rating (by rater): 0, absent; 1, mild; 2, moderate; 3, severe.

headache lasting shorter than 7 days were asked to give informed consent for participation in the study. Vascular score criteria established by Belgrade *et al*²¹ and Carleton *et al*²² have long been used to distinguish migraine headache and other types of vascular headache. These criteria are easy to use in emergency circumstances. After excluding patients who refused to participate, all enrolled patients were randomised to one of two predetermined drug administration schemes: 15 min slow infusion group (SIG) or 2 min bolus group (BIG). Excluded from the study were patients with secondary headache, altered mental status, abnormal vital signs, women who were pregnant, those with a history of epilepsy, Parkinson's disease or pheochromocytoma, or any known allergy to the study drugs, and uncooperative individuals.

Diagnostic criteria for vascular headache included aura or anticipation of headache, nausea, vomiting, diarrhoea, anorexia; unilateral headache; photophobia or phonophobia; visual complaints; periodic headache; throbbing headache; childhood onset headache; history of motion sickness; family history of headache; headache triggered by certain foods; and temporal association with menstruation. Prior headaches must have been resolved within 96 h and should not have been associated with any neurologic dysfunction. Patients with four or more positive items from this list were categorised as having vascular headache, as recommended by the vascular score criteria.^{21 22} Emergency physicians responsible for the patients rated each criterion for all patients with the headache.

Data collection

Study personnel were trained before the study. Patients received the SIG or the BIG medication schemes according to their random allocations. Randomisation was achieved by using computer software to generate random numbers. During the intervention, participants were monitored by an oxygen saturation (SpO₂) monitor, an automatic sphygmomanometer (blood pressure), and a rhythm monitor (heart rate and rhythms). One researcher blinded to patient allocation observed the whole procedure and recorded the headache scores. Patients in both groups received two types of medication in a similar manner (for example, all patients in SIG received bolus

infusion as placebo and all patients in BIG received bolus infusion as placebo), thus ensuring double blinding. Headache scores were recorded at 0, 5, 15, 30 and 60 min on a numeric pain scale of 1 to 10.²³

All other medications required during the study were recorded. During the study, pulse rate, systolic blood pressure, diastolic blood pressure, respiration rate and oxygen saturation (SpO₂) were recorded at baseline (0 min), and 15, 30 and 60 min. Akathisia and other adverse reactions such as allergic reactions, sedation, hypotension, hypertension and dystonic reactions were also recorded during the study. The Prince Henry Hospital rating scale of akathisia^{24 25} was used to measure the level of akathisia^{19 26} (table 1).

Data analysis

SPSS 10.0 for Windows (SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis. Data were summarised as median, mean (SD) and n (%); χ^2 and t tests were used for comparisons. Repeated measure analysis of variance (ANOVA) was used for the analysis of repeating data. Kruskal–Wallis was used for sensitivity analyses where appropriate. Values of $p < 0.05$ were significant.

RESULTS

One hundred and twenty participants were randomised into two groups according to the type of metoclopramide administration during the 13 month study period (fig 1). Of these 120, 97 (81%) were female; the mean (SD) age was 41.3 (12.9) years in the BIG and 41.7 (10.7) years in the SIG. There were no significant differences between the groups in terms of patient sociodemographic characteristics; however, there was a significant difference in diastolic blood pressure between the groups at baseline ($p = 0.03$) (table 2).

At 0, 5, 15, 30 and 60 min the median pain scores were 8, 7, 4, 2, 1 in the BIG and 8, 7, 5, 2, 1 in the SIG, respectively (all $p > 0.05$). There was no significant difference between the BIG and the SIG in terms of mean pain scores during the study ($p = 0.34$) (fig 2). Slowing the infusion rate did not change the improvement in headache.

On the other hand, a significant difference in akathisia incidence was observed between the groups: 17 (29.3%) in the BIG and 4 (6.5%) in the SIG ($p = 0.001$). Slowing the infusion rate reduced the incidence of akathisia. There was no significant difference between the groups in terms of side effects; the incidence of sedation was 13 (22.4%) in the BIG and 7 (11.3%) in the SIG ($p = 0.10$). One patient in each group had hypotension. Mean vital findings did not differ between the groups during the study (fig 3).

DISCUSSION

The current study compared two different intravenous bolus infusions of metoclopramide for the treatment of vascular type headache. The rate of metoclopramide infusions did not change its efficacy in the treatment of headache. Nevertheless, akathisia due to metoclopramide was mainly detected in the BIG.

Most patients visiting emergency departments because of headache are diagnosed with acute primary headache.⁴ Even though most headache syndromes are benign, their treatment is sometimes challenging for the emergency physician. Currently, metoclopramide is widely used by emergency physicians in Turkey for the treatment of patients with isolated benign headache and/or nausea and vomiting. In a study comparing the analgesic effects of metoclopramide, pethidine, a combination of metoclopramide + pethidine, and placebo in the treatment of adult patients with acute primary vascular and tension type headache admitted to the emergency department,

Figure 1 Patients enrolled by treatment groups. ED, emergency department.

Cicek *et al*⁴ reported that metoclopramide was a much more effective analgesic than pethidine in both vascular and tension type headache in patients with acute primary headache episodes. However, in another study comparing the efficacy of prochlorperazine with metoclopramide and placebo, Coppola *et al*⁶ reported that prochlorperazine had a significantly higher rate of efficacy in patients with migraine type headache (82%, 46%, and 29%, respectively). Numerous other investigations on the effects of metoclopramide on migraine episodes have also been studied.^{5-8, 21, 27-34} Some studies even showed that metoclopramide is effective in benign vascular type headache as a single agent.^{5, 7, 27, 28} In contrast, two other studies argued that metoclopramide failed to provide significant relief in migraine headache.^{6, 29}

At present, no data are available on the effect of administration techniques of metoclopramide on vascular type headache. In our study, metoclopramide was an effective agent regardless of the rate of administration in patients with vascular type headache. Headache scores were reduced in the first 15 min in both groups and all patients' headaches improved significantly in the first 30 min. However, an increase in side effects, especially akathisia, was observed in the BIG compared with the SIG.

The incidence of akathisia caused by metoclopramide varies in the literature.^{4, 13-15, 17, 18, 35, 36} In a study of the effect of metoclopramide on prolactin and aldosterone, the incidence of akathisia was 25% after receiving 10 mg of metoclopramide intravenously.¹³ For intravenous 10 mg bolus doses of metoclopramide, the incidence of restlessness seems to range from 20–25%.^{13, 14} The speed of administration seems to be an important factor in determining the incidence of akathisia induced by metoclopramide.^{14, 37} A limited number of studies have investigated the incidence of akathisia following metoclopramide infusion in patients with nausea/vomiting and headache.^{4, 18, 35} In our study, akathisia was detected in 17

Table 2 Distribution of the baseline characteristics between the study groups

Variables	Medication		p Value*
	BIG (n = 58)	SIG (n = 62)	
Gender (%)			0.38
Male n = 23 (19)	13 (56.5)	10 (43.5)	
Female n = 97 (81)	45 (46.4)	52 (53.6)	
Age (years)†	41.3 (12.9)	41.7 (10.7)	0.85
Weight (kg)†	67.1 (10.8)	69.8 (11.8)	0.20
Headache score†	8.2 (1.7)	8.1 (1.7)	0.34
Respiratory rate (beats/min)†	16.84 (1.9)	17.05 (1.92)	0.094
Pulse rate†	80.95 (11.24)	82.77 (10.35)	0.45
SBP (mm Hg)†	126.8 (21.5)	129.2 (20.6)	0.32
DBP (mm Hg)†	76.2 (12.8)	81.7 (12.1)	0.03
Body temperature (°C)†	36.2 (0.4)	36.2 (0.5)	0.91

BIG, bolus infusion group; DBP, diastolic blood pressure; SBP, systolic blood pressure; SIG, slow infusion group.

*p values from χ^2 and t tests.

†Mean (SD).

(29.3%) patients treated with metoclopramide in the BIG and in 4 (6.5%) patients treated with metoclopramide in the SIG. Other adverse reactions such as sedation were also detected more frequently in the BIG than in the SIG. In another study, a 12% incidence rate of akathisia was reported with a slow intravenous infusion of 10 mg metoclopramide, but there was no comparison with a bolus infusion.³⁵ In a study comparing two infusion rates of metoclopramide in the treatment of headache and/or nausea and vomiting in the emergency department, Parlak *et al*¹⁸ reported that nine out of 154 patients in the SIG (5.8%) had akathisia compared with 36/146 patients (24.7%) in the BIG ($p = 0.001$). They concluded that slow infusion of metoclopramide could reduce the rate of akathisia.

In conclusion, we suggest that even though slowing the infusion rate of metoclopramide does not affect the improvement of headache, it is an effective strategy for reducing the incidence of akathisia and other side effects in patients with vascular type headache.

Limitations

One limitation of this study is the high turnover of patients in our emergency department. The subjects in our study were not observed for longer than 1 h, so no records were made of how long the akathisia symptoms lasted and which rescue medications were used. Four subjects did not complete the whole

Figure 2 Mean headache scores by the study groups during the study.

Figure 3 Mean vital findings in the two study groups (slow infusion vs. bolus infusion): (A) respiratory rate; (B) systolic blood pressure (mm Hg); (C) diastolic blood pressure (mm Hg); (D) pulse rate (beats/min).

process because of personal reasons such as being “late for the work” and having “to pick up children from day care”. Although loss of subjects may increase the chance of bias, there was no direct evidence that these limitations influenced the objectivity and results of the study. Due to the fact that the headache scale used in this study is ordinal, this could raise the question of appropriateness of parametric tests in the analysis. However, we also completed sensitivity analysis using non-parametric tests (Kruskal–Wallis) in order to confirm our previous findings.

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