ORIGINAL ARTICLE

Rate of metoclopramide infusion affects the severity and incidence of akathisia

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Objective: To investigate the effect of the rate of metoclopramide infusion on akathisia incidence, severity, onset of symptoms, and duration in patients with headache, and/or nausea/vomiting in the emergency department (ED) setting.

Methods: Prospective, double blind, randomised clinical study comparing two rates of intravenous infusion of metoclopramide over a period of six months at a tertiary university hospital ED.

Results: A total of 300 patients presented to the ED met the inclusion criteria: 151 (50.3%) with nausea/vomiting, 108 (36%) with headache, and 41 (13.7%) with headache and nausea/vomiting. Of these, 154 patients (51.3%) were given 10 mg metoclopramide as a slow intravenous infusion over 15 minutes plus placebo (SIG group) and 146 patients were given 10 mg metoclopramide intravenous bolus infusion over two minutes plus placebo (BIG group). Nine of the 154 patients in the SIG group (5.8%) had akathisia compared with 36/146 patients (24.7%) in the BIG group ($p < 0.001$, OR 5.273, 95% CI 2.43 to 11.403). Severe akathisia were observed in 13/45 (28.8%). The incidence of severe akathisia was significantly higher in the BIG group (30.5%; 11/36) than in the SIG group (22.2%; 2/9), $p = 0.009$. Metoclopramide successfully relieved the presenting symptom(s) of 137/146 (90.8%) and 139/154 (90.2%) patients in the BIG and SIG groups, respectively.

Conclusions: This study suggests that slowing the rate of infusion of metoclopramide is an effective strategy for reducing the incidence of akathisia in patients with headache, and/or nausea/vomiting in ED.

The term "akathisia" describes a syndrome of objective and subjective motor restlessness manifested as the inability to sit or stand still. Clinically, akathisia can be described as the urge to move the extremities or torso and anxiety with agitation. The movements are typically stereotypical motor patterns such as pacing, body rocking, or foot tapping. Akathisia also occurs in some disorders of the basal ganglia including drug induced movement disorders. It is used to describe the restlessness observed in patients secondary to neuroleptic drug use, typically manifested by excessive voluntary movement. Dopamine blocking agents such as antipsychotics and antiemetics may induce akathisia.¹ However, the phenomenon was observed before the introduction of antipsychotics, and the term "akathisia" was used in 1901 by Ladislav Haskovec, a Czech neurologist.²

Metoclopramide is a benzamide antiemetic drug, frequently used in emergency departments (EDs) in the management of nausea, vomiting, and vascular-type headache.^{3–6} The US Food and Drug Administration has limited its indications to diabetic gastroparesis, oesophageal reflux, gastrointestinal radiography, intestinal intubation, and nausea/vomiting. The literature indicates that there may be a direct relation between serum concentration of metoclopramide and akathisia, and that slow infusion of metoclopramide could reduce the akathisia.^{7, 8} Akathisia can easily be missed by physicians in crowded and busy EDs. If the initial symptoms are underdiagnosed, massive anxiety and agitation can lead to refusal of treatment and patients pulling out their intravenous lines, leaving the ED, and even attempting suicide.^{9–13}

We carried out this study because a literature search (Pub Med accessed on 7 November 2002; keywords: Akathisia, Metoclopramide, Akathisia and metoclopramide, migraine headache and treatment, nausea) revealed a lack of double blind, randomised clinical trials investigating the effects of metoclopramide infusion rates on the incidence of akathisia.

METHODS

Study design

We conducted a prospective, double blind, randomised clinical study to compare the effects of:

- (a) a fast intravenous infusion of metoclopramide over two minutes plus a slow infusion of placebo over 15 minutes
- and
- (b) a slow intravenous infusion of metoclopramide over 15 minutes plus fast infusion of placebo over two minutes

with regard to the incidence, severity, onset of symptoms, and the duration of akathisia. The main outcome measure of our study was the proportion of study participants in each group with akathisia at 60 minutes. The Dokuz Eylul University Hospital Review Board approved the study. All the participants signed an informed consent form before enrolment.

Study population and setting

The study was conducted between July and December 2001 at the Dokuz Eylul University Hospital Emergency Department, which has an annual rate of 36 000 visits. The inclusion criteria were: age 17 years or older and any indication for metoclopramide, such as headache and/or nausea/vomiting. In addition, patients could have been taking other medications (which were otherwise included in the exclusion criteria) for added relief of symptoms. The exclusion criteria were: initial akathisia score 3 or greater, previous organic brain disorder, dementia, severe agitation or anxiety that required rescue medication and did not allow interpretation of akathisia symptoms (severe renal colic, acute myocardial infarction, severe nausea/vomiting, or acute gastrointestinal bleeding), pregnancy, lactation, previous

neurological motor diseases (restless leg syndrome or Parkinson's disease), any contraindication for anticholinergic medications (glaucoma, urinary retention, or bowel obstruction), recent administration of anticholinergic, sedative, antiakathic, antiemetic, antihistaminic, antipsychotic, antispasmodic drugs within the last three days, and antidepressants, lithium, barbiturates, benzodiazepines, other sedative-hypnotics and opioid drugs within the last two weeks.

Study protocol

All patients eligible for the study were randomised to one of two groups:

- BIG—10 mg metoclopramide in an intravenous bolus infusion over two minutes plus placebo (100 ml normal saline in a slow infusion over 15 minutes)
- SIG—10 mg metoclopramide in 100 ml normal saline given as a slow intravenous infusion over 15 minutes plus placebo (2 ml normal saline in a bolus infusion over two minutes)

Akathisia scores were recorded at 0, 5, 15, 30, and 60 minutes according to the Prince Henry Hospital Rating Scale of Akathisia.¹⁴ Patient satisfaction and side effects other than akathisia (allergic reactions, hypotension, hypertension, dystonic reactions, sedation, etc.) were also recorded at the end of 60 minutes.

At 60 minutes we discontinued observation for akathisia and further management of the patients was planned by their primary physician in the ED. Anxiolytic agents or diphenhydramine were prescribed for patients who had akathisia scores greater than 13 (major akathisia) or if a patient requested a rescue medicine regardless of their total score during the study period. The patients' presenting symptom(s) were evaluated after one hour and a 50% reduction in the severity of the symptoms was accepted as successful.

Measures

We used the Prince Henry Hospital Rating Scale of Akathisia (PHH Akathisia Scale) (table 1).¹⁴ The PHH akathisia scale has objective and subjective components rated between 0 and 3 (from absent to severe, respectively). The sum total of the components (global rating) gives the PHH akathisia score: absent (0), mild (1), moderate (2), or severe (3). The objective components were rated by the observer and the subjective components were rated based on the response from the patient to the questions. The data were collected by emergency medicine residents other than the physicians providing treatment in the ED. They were all senior residents (postgraduate year 4) in the hospital's emergency medicine residency programme who had attended a two hour training course in data collection, PHH akathisia scale rating, clinical diagnosis, and management of akathisia, prior to commencement of patient enrolment.

Data analysis

We analysed the data with SPSS 11.0 for Windows; the χ^2 test was used for analysing the demographic characteristics of both groups and the t test was used for categorical data and determination of akathisia incidence. A p value <0.05 was accepted as statistically significant and 95% confidence intervals (CI) for the differences were calculated. With regard to sample size, it was calculated that least 94 patients should be included in each group when 80% power is anticipated with a hypothesis of determination of 10% difference between the akathisia rates ($p^2 - p^1 < 10\%$), at 0.05 level of significance. We included 300 patients (154 SIG and 146 BIG) in our study.

Table 1 The 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 *Biological Psychiatry*, 35,⁴ Sachdev P. A rating scale for acute drug-induced akathisia: development, reliability, and validity, pp. 270–1, Copyright (1994) with permission from Society of Biological Psychiatry.

Global rating (by rater): 0—absent; 1—mild; 2—moderate; 3—severe.

RESULTS

During the six month study period 320 eligible patients with headache and/or nausea/vomiting underwent evaluation for akathisia. Ten patients were excluded from the study because of inadequate records and five patients were excluded as they were taking medications listed in the exclusion criteria. Another five patients were excluded as they left the ED against medical advice.

Of the 300 patients randomised to the BIG and SIG groups, 151 (50.3%) presented to the ED with nausea/vomiting, 108 (36%) with headache, and 41 (13.7%) with headache and nausea/vomiting. The demographic characteristics of the 300 patients are shown in table 2. Characteristics of the BIG and SIG groups were comparable.

In total 45 patients experienced akathisia (table 3). Comparing the two groups, 5.8% (9/154) patients in the SIG group and 24.7% (36/146) patients in the BIG group had akathisia ($p < 0.001$, OR 5.273, 95% CI 2.43 to 11.403).

Forty three patients (14.3%) experienced akathisia in the first 15 minutes after metoclopramide infusions: 24 (8%) in

Table 2 Patient characteristics

	Group*		p value
	BIG (n = 146)	SIG (n = 154)	
Age in years (mean (SD))	42.67 (17.10)	39.94 (16.30)	0.157
Females	115	120	0.859
Weight in kg (mean (SD))	66.99 (12.29)	65.71 (12.92)	0.380
Indication			
Headache	56	52	
Nausea/vomiting	74	77	
Headache+nausea/vomiting	16	25	

*BIG, 10 mg metoclopramide as intravenous bolus infusion over two minutes; SIG, 10 mg metoclopramide as slow intravenous infusion over 15 minutes.

Table 3 Akathisia rates*

Group†	Akathisia (n (%))		Total (n (%))
	No	Yes	
SIG	145 (94.2)	9 (5.8)	154 (100)
BIG	110 (75.3)	36 (24.7)	146 (100)
Total	255 (85.0)	45 (15)	300 (100)

*Fisher's test: $p < 0.001$.

†BIG, 10 mg metoclopramide as intravenous bolus infusion over two minutes; SIG, 10 mg metoclopramide as slow intravenous infusion over 15 minutes.

the first five minutes (of whom two patients (0.6%) were in the SIG group) and 19 (6.3%) between five and 15 minutes (of whom four patients (1.3%) were in the SIG group). One patient (2.2%) had akathisia between 15 and 30 minutes and another patient between 30 and 60 minutes (both patients were in the SIG group). There was no statistically significant association between the infusion rate and time of onset of akathisia (Fisher, $p = 0.071$ and $p = 1.00$, respectively, for incidence of akathisia at 5 minutes and 15 minutes in both groups).

Severe akathisia was observed in 13/45 patients with akathisia (28.8%). The incidence of severe akathisia was significantly higher in the BIG group (30.5%, 11/36) compared with the SIG group (22.2%, 2/9), $p = 0.009$. Sixteen patients experienced moderate akathisia of whom 75% (12/16) were in the BIG group and 15 patients had mild akathisia of whom 86.6% (13/15) were in the BIG group.

Metoclopramide successfully relieved the presenting symptom of 137/146 patients (90.8%) in the BIG group and of 139/154 patients (90.2%) in the SIG group. There was no statistically significant difference between the two groups with regard to relief of presenting symptom(s) (Fisher, $p = 0.272$).

Although 35/45 of the patients with akathisia were female, there was no statistically significant relation between akathisia incidence and sex. There were also no statistically significant relations between akathisia incidence and the other demographic characteristics such as age, weight, previous diseases (diabetes, hypertension) in medical history, smoking, alcohol consumption, history of allergies, and history of medications (calcium channel blocking agents, β receptor blocking agents, H_2 blocking agents, or digoxin). None of the other side effects due to metoclopramide infusion observed in both the groups were statistically significant.

DISCUSSION

Akathisia incidence

Akathisia incidence due to medications varies in the literature.^{8, 15–18} We achieved a significantly lower rate of akathisia by slowing down the rate of infusion of metoclopramide. A recent study reported the akathisia incidence as 3.5% in patients treated with metoclopramide alone.¹⁵ The main purpose of that study was not to investigate the akathisia incidence but to compare the effects of metoclopramide, meperidine, and their combination in the treatment of patients with recent onset primary headache. There was no comparison of rates of infusion of metoclopramide with regard to akathisia, and instead of the akathisia scale the observers used a yes/no questionnaire. In another study, a 12% rate of akathisia incidence was reported with a slow intravenous infusion of 10 mg metoclopramide, but there was no comparison with bolus infusion.¹⁶ Miller and Jankovic stated that study design, form of the preparation, or long term medication use might account for the differences in the reported rates.⁷ It has been suggested that akathisia symptoms may occur just after the intravenous

metoclopramide infusion and resolve quickly. Hence, in the clinical setting, unless clinicians closely observe patients for akathisia, the symptoms may be easily missed or under-diagnosed, especially in a busy ED. In our study we assessed the patients at zero, 5, 15, 30, and 60 minutes in the ED. This gave us the chance to observe closely, early in the treatment, the time of onset of the side effects. However, both the patients who participated in the study and the physicians who enrolled them complained about the study protocol as both groups found the close observation (five times in one hour) difficult.

Severe akathisia

We also found that the incidence of severe akathisia correlated with bolus infusion of metoclopramide ($p = 0.009$). The lower incidence of akathisia reported in previous studies might have been the result of slowing down the infusion rate, as in our study. The mechanism by which akathisia occurs following metoclopramide infusion is still theoretical. Further studies correlating akathisia scores with serum metoclopramide levels may help to identify this mechanism.

We conclude that slow infusion is better and as of now report the lowest akathisia rate (5.4% for slow infusion group, $p < 0.001$) in the literature.

Onset time

The onset time and duration of symptoms of akathisia were shorter than we have reported before.¹⁵ Twelve of the 24 patients who experienced akathisia at five minutes had no symptoms at 30 minutes. In eight of the 19 patients had akathisia at between five and 15 minutes, the symptoms disappeared without any medication at 30 minutes. We could not find any data regarding onset time of akathisia symptoms following intravenous metoclopramide infusion in previous studies. Most of the previous research was conducted in clinical settings other than the ED, and several of these basically investigated the side effects of oral metoclopramide treatment of various durations.^{7, 17, 18} Bateman *et al* found that the incidence of akathisia incidence in patients treated with oral metoclopramide was related to peak plasma concentration of metoclopramide (over 100 ng/dl). They suggested that the route of administration is of major importance when determining the action of this drug.⁸

Efficacy

It has been reported that the most commonly used medications for parenteral treatment of isolated benign headache in EDs in the USA are meperidine (30.0%), ketorolac (21.4%), and prochlorperazine (16.7%).¹⁹ Antiemetics may especially be useful for the resolution of headache and there is a trend suggesting the superiority of antiemetics.^{15, 20} Metoclopramide, which is a benzamide antiemetic, is widely used in EDs in Turkey in the treatment of patients with isolated benign headache and/or nausea and vomiting.¹⁵ A limited number of studies have investigated the incidence of akathisia following metoclopramide infusion in patients with nausea/vomiting and headache.^{15, 16, 18} In a study comparing the efficacy of prochlorperazine with metoclopramide and placebo, Coppola *et al* reported that prochlorperazine had a significantly higher rate of efficacy in patients with migraine-type headache (82%, 46%, and 29%, respectively).⁴ On the other hand, Braude *et al* concluded that intravenous metoclopramide (10 mg) and droperidol (1.25 mg) were significantly better for the control of nausea and vomiting in an unselected ED population than prochlorperazine or intravenous fluids alone.¹⁸ In our study, metoclopramide was an effective agent regardless of the route of administration in patients with nausea (143/151, 94.7%), headache (95/108 patients, 87.9%), and nausea/headache (38/41 patients, 92.7%).

Limitations of the study and future directions

Our study has several limitations. Firstly, although data were collected and the patients rated by different physicians, we did not determine the interrater reliability for both data collection and rating of patients on the PHH akathisia scale. The physicians who recorded the data and rated the patients were trained in data collection, the PHH akathisia scale, clinical diagnosis, and management of akathisia in a two hour course prior to patient enrolment. However, interrater reliability for and validity of the PHH akathisia scale was examined in relation to the Barnes rating scale for akathisia (Barnes scale) in the original study by Sachdev.¹⁴ The kappa coefficient was calculated for each item and the global rating by two raters and all correlations were highly significant ($p < 0.001$). The correlation between the global akathisia ratings on the two scales was significant for both rater 1 (0.84) and rater 2 (0.86) (two tailed t test, $p < 0.01$). Secondly, we used a yes/no questionnaire instead of a visual analogue scale to assess the severity of headache, nausea, and vomiting before and after metoclopramide infusion. Thirdly, we used a multichoice question for determining patient satisfaction rather than ideally a scale. Hence we could not statistically analyse the difference between the groups with regard to patient satisfaction. Finally, the patients were not observed for longer than an hour so we could not record how long the akathisia symptoms lasted and which rescue medications were needed.

These limitations did not directly influence the objective and results of the study. However, they restricted our discussion of patient satisfaction, successful treatment of akathisia, and the efficacy of metoclopramide infusion treatment in patients with headache and/or nausea/vomiting.

CONCLUSIONS

We suggest that slowing the infusion rate of metoclopramide is an effective strategy for reducing the incidence of akathisia in patients with headache and/or nausea/vomiting. Further clinical trials are needed to explain the mechanism of and relation between the incidence of akathisia and metoclopramide infusion rates.

AUTHORS' CONTRIBUTIONS

IP, RA, and MP conceived the study and designed the trial. IP and RA supervised the conduct of the trial and data collection. IP, MC, MP, BE, MG, MS, and SK contributed to data collection. RA and MP provided statistical advice on study design and analysed the data; IP presented the data at the first World Congress of Emergency and Military Contingency Medicine, 3–8 June 2002, Kemer, Turkey. IP, RA, and MP drafted the manuscript. IP and RA revised the manuscript and all authors contributed substantially to its revision. IP takes responsibility for the paper as a whole.

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