ORIGINAL INVESTIGATION

The Prevalence of Metoclopramide-Induced Tardive Dyskinesia and Acute Extrapyramidal Movement Disorders

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Background: Metoclopramide hydrochloride, a neuroleptic dopamine receptor antagonist used to treat gastric ailments, is reported to cause extrapyramidal movement disorders. The goals of this study were (1) to determine the prevalence and severity of tardive dyskinesia and acute extrapyramidal movement syndromes including akathisia, acute dystonia, and drug-induced parkinsonism in metoclopramide-treated patients and (2) to compare the prevalence and severity of tardive dyskinesia in metoclopramide-treated diabetics and nondiabetics.

Methods: From a list of metoclopramide-treated patients received from the Portland (Ore) Veterans Affairs Medical Center pharmacy, 53 patients met inclusion criteria and 51 (96%) agreed to participate. Controls consisted of a convenience sample drawn from the Portland Veterans Affairs Medical Center Outpatient Clinic who were matched to subjects on age (±10 years), gender, and presence or absence of diabetes. Of 61 potential controls contacted, 51 (84%) agreed to participate. Metoclopramide-treated subjects and controls were seen by a rater who was "blind" to all diagnoses and treatments. The rater performed a standardized examination used to elicit signs and symptoms of tardive dyskinesia and acute extrapyramidal movement syndromes.

Results: The relative risk for tardive dyskinesia was 1.67 (95% confidence interval, 0.93 to 2.97), and the relative risk for drug-induced parkinsonism was 4.0 (95% confidence interval, 1.5 to 10.5). Metoclopramide-treated patients had significantly greater severity of tardive dyskinesia, drug-induced parkinsonism, and subjective akathisia than controls. Use of metoclopramide was associated with impairment in ambulation and increased use of benzodiazepines. Metoclopramide-treated diabetics had significantly greater severity of tardive dyskinesia than metoclopramide-treated nondiabetics.

Conclusions: Metoclopramide use is associated with a significantly increased prevalence and severity of several extrapyramidal movement disorders.

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METOCLOPRAMIDE hydrochloride is a neuroleptic dopamine receptor antagonist commonly used to treat diabetic gastroparesis, esophageal reflux, and chemotherapy-induced nausea.[1] It has been anecdotally reported to cause all of the extrapyramidal movement syndromes (EPSs) associated with neuroleptic medications.[2-5] Acute EPSs, which occur within hours to weeks in the course of treatment with neuroleptics, include drug-induced parkinsonism, akathisia, dystonia, and, rarely, neuroleptic malignant syndrome. Drug-induced parkinsonism, a syndrome indistinguishable from idiopathic Parkinson's disease, increases in prevalence with both age and drug dose. It may be the most common neuroleptic-induced EPS in old age.[2] Akathisia, a syndrome of subjective or motor restlessness, causes considerable discomfort and may be misinterpreted by patients and physicians as anxiety.[6] Dystonia, a cramplike muscular contraction most often occurring in the head, neck, or face, is common in young patients treated with high-potency neuroleptics but is rare in the elderly.[6] These early-onset neurologic syndromes may cause significant morbidity but remit with discontinuation of the neuroleptic.[6]

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SUBJECTS AND METHODS

SUBJECTS

A list of all patients who had received a prescription for metoclopramide between May and August 1991 was obtained from the Portland (Ore) Veterans Affairs Medical Center pharmacy. Patients were excluded who were prescribed less than 20 mg/d of metoclopramide hydrochloride, were only prescribed metoclopramide on an as-needed basis, or were prescribed metoclopramide for less than 3 months. Attempts were made to contact the remaining 119 metoclopramide users by telephone or letter. Fifty-five had discontinued taking metoclopramide, six could not be contacted or lived a significant distance from the Portland Veterans Affairs Medical Center, two subjects were excluded for a record of threatening behavior to health care professionals, and three were excluded for current or past use of a neuroleptic other than metoclopramide for more than 2 months. Of 53 eligible subjects, 51 agreed to participate (96%).

Control subjects were drawn from patients recorded on appointment lists of general medical and endocrinology clinics at the Portland Veterans Affairs Medical Center after the patient's current medication records were reviewed for neuroleptic and hypoglycemic use. Each metoclopramide-treated subject was matched with a control for gender, age (±10 years), and presence or absence of diabetes mellitus. Sixty-eight potential control subjects were contacted. Seven were excluded because of previous neuroleptic exposure of greater than 2 months. Of the remaining 61 potential subjects, 51 (84%) agreed to participate.

Other exclusion criteria at the onset of the study were presence of neurologic illnesses known to cause movement disorders, such as Huntington's chorea, Wilson's disease, or idiopathic Parkinson's disease; presence of medical illnesses such as hyperthyroidism or hypoparathyroidism that may be associated with dyskinesias; or use of dopaminergic agonists.[10] However, no subject was excluded because of these criteria. Patients with cerebrovascular disease were not excluded.

For the purposes of this study, subjects treated with an oral hypoglycemic or insulin were assumed to have diabetes mellitus. Subjects not treated with hypoglycemics were classified as diabetic if they had a fasting plasma glucose level greater than 7.8 mmol/L (>141 mg/dL), or any random plasma glucose level greater than 11.1 mmol/L (>200 mg/dL)[10] or a glycosylated hemoglobin (HbA_{1c}) value greater than 0.062 g/L (reference range, 0.045 to 0.061 g/L). Five metoclopramide-treated subjects were not classifiable using this scheme to dichotomize subjects into diabetic or nondiabetic groups. All available medical data on these subjects were submitted to a diabetologist (A.L.M), who classified them as diabetic (n=3) or nondiabetic (n=2). The diabetologist was "blind" to the results of the movement examinations. Nondiabetic subjects had a random plasma glucose level less than 6.1 mmol/L (<110 mg/dL) and a HbA_{1c} level within the reference range and received no hypoglycemic agents.

ASSESSMENT AND PROCEDURES

The Abnormal Involuntary Movement Scale (AIMS) was used to measure tardive dyskinesia.[17] The AIMS rates signs of tardive dyskinesia over a five-point scale (from 0 (no abnormal movements) to 4 (severe abnormal movements). Rated body parts include face, jaw, lips, tongue, trunk, upper extremities, and lower extremities. The sum of all item scores determines the total severity score (maximum, 28). Both persistence of abnormal movements through the examination period and severity of movements contributed to higher scores. Using accepted diagnostic criteria, tardive dyskinesia was classified as probable if a subject scored either a rating of moderate severity (≥3) or more in any body part or a rating of mild severity (≥2) in two or more body parts.[18] Control subjects who met this case definition of tardive dyskinesia were more appropriately denoted as having spontaneous dyskinesia.

Metoclopramide-induced parkinsonism was measured with the St Hans Neurologic Rating Scale.[19] This scale measures common signs of parkinsonism over a seven-point (0 to 6) scale of severity. Rated signs include diminished facial expression and mobility, bradykinesia, tremor, stooped posture, diminished arm swing, shuffling gait, and excess salivation. A global score on a 0 to 6 scale of severity was also determined. The global score takes into account severity of parkinsonian signs, number of parkinsonian signs, and overall level of disability. Case definitions for the presence or absence of drug-induced parkinsonism are not well established, and the syndrome is best understood as presenting on a con-

Tardive dyskinesia is an EPS that appears after several months of neuroleptic treatment. This syndrome is characterized by involuntary choreoathetoid movements in the face (tongue protrusions, chewing movements, lip smacking, and facial grimacing) and writhing, choreoathetotic or tic-like movements of the limbs and trunk. Tardive dyskinesia is often disfiguring and is potentially irreversible, as there is no effective treatment.[10]

Increasing age is the most important risk factor for development of tardive dyskinesia.[10,11] Female gender, affective disorder, anticholinergic medication use, and increasing dose and duration of neuroleptic treatment have also been implicated.[10] Despite intuitive appeal, it has been difficult to demonstrate that the presence of a preexisting brain disease, such as dementia, predisposes neuroleptic-treated patients to tardive dyskinesia.[10] Recently, a study from this center using a controlled, blindly rated design demonstrated that neuroleptic-treated diabetics had a significantly higher prevalence and severity of tardive dyskinesia than neuroleptic-treated nondiabetic controls when matched for age, gender, psychiatric diagnosis, dose, and duration of neuroleptic treatment.[11]

Metoclopramide is equipotent to chlorpromazine in dopamine receptor blocking affinity.[1] The daily dose of

tinuum. Although scores of 2 or greater are interpreted as mildly abnormal and consistent with the earliest signs of drug-induced parkinsonism in young patients, these criteria are overly sensitive to age-related changes in the elderly in posture, gait, and movement, which are multifactorial in origin and not clearly attributable to basal ganglia disease.[7] For the purposes of determining prevalence, a global score of 3 or higher was used to determine prevalence of drug-induced parkinsonism.

The St Hans scale also allows rating of objective measures of facial or limb dystonia and measures of akathisia, including subjective akathisia (subject's report of inner restlessness) and objective akathisia (observed restlessness such as marching in place). A score of 2 or higher on subjective or objective akathisia was considered diagnostic of akathisia. Cognitive function was assessed with the Folstein-McHugh Mini-Mental State examination (MMSE).[20]

Other information obtained from the subject and the medical record included length of treatment with metoclopramide, metoclopramide dosage, and presence or absence of the following common chronic illnesses: cerebrovascular disease, atherosclerotic heart disease, congestive heart failure, renal disease, thyroid disease, autoimmune disease, hypertension, seizure disorder, ulcer disease, chronic obstructive pulmonary disease, degenerative joint disease, and current alcoholism. Presence or absence of the following classes of medications was noted: calcium channel blockers, diuretics, β-blockers, other antihypertensives, lipid-lowering agents, antiarrhythmics, digoxin, thyroid medications, oral corticosteroids, nonsteroidal anti-inflammatory agents, β-agonists, theophylline, anticonvulsants, benzodiazepines, antidepressants, and centrally acting anticholinergics. Data collected on diabetics included history of diabetic complications (retinopathy, neuropathy, nephropathy) by chart review, diabetic treatment (diet control, oral hypoglycemic, insulin), number of years with recognized diabetes, history of hypoglycemic episodes, and hospitalizations for hyperglycemia or hypoglycemia. Each subject underwent a blood test to determine plasma glucose and HbA_{1c} levels.

Each subject was seen once by a rater who was blind to all diagnoses, diabetic status, and medications, including metoclopramide. All subjects were evaluated by a single rater who performed a standardized examination[19] to elicit signs and symptoms of acute EPS and tardive dyskinesia.

In 30 subjects seen by the blind rater and the principal investigator, agreement on presence or absence of tardive dyskinesia as determined by κ statistic was κ=.67,[21] and the correlation between the two raters in the AIMS summed score was r=.89 (Pearson's test). Agreement on presence or absence of drug-induced parkinsonism was κ= 63. Correlation between the raters on St Hans parkinsonism summed score was r=.90 (Pearson's test).

DATA ANALYSIS

The main effects of metoclopramide and diabetes on acute EPS and tardive dyskinesia were examined using a multivariate analyses of variance. All comparisons of metoclopramide-treated subjects with non–metoclopramide-treated controls were paired and comparisons of diabetics and nondiabetics were unpaired. The assumption of homogeneity of covariance matrices was checked using Box's M statistic for the multivariate analyses.[22]

For other comparisons, metoclopramide-treated subjects were compared with non–metoclopramide-treated controls using paired statistics: McNemar's test (or dichotomous variables (Fisher's Exact Test when appropriate) and paired *t* test for continuous variables. Metoclopramide-treated diabetics were compared with metoclopramide-treated nondiabetics using Pearson's χ^2 for dichotomous variables (Fisher's Exact Test when appropriate) and unpaired *t* test for continuous variables.[23] Homogeneity of variance was examined using the Bartlett-Box statistic for univariate tests.[22]

The magnitude of tardive dyskinesia and drug-induced parkinsonism was expressed as relative risk with 95% confidence intervals (CIs).[23] Pearson's *r* was used for correlational analyses, with Bonferroni's correction for multiple comparisons. Hierarchical regression analysis was used to partition the variance in tardive dyskinesia among demographic, medication, and disease variables. Polynomial regression was used to estimate missing data when necessary.[24] The α value was set at .05. Type I error was controlled by examining hypotheses hierarchically. A priori hypotheses regarding main effects of diabetes and metoclopramide treatment on tardive dyskinesia and drug-induced parkinsonism were tested without correction beyond that afforded by the multivariate analysis of variance technique. Subsequent exploratory analyses were corrected, as needed, using the Bonferroni inequality.[24]

metoclopramide hydrochloride (approximately 40 mg/d) is, on average, only 10% of the usual daily dose of chlorpromazine. However, metoclopramide is frequently prescribed to older, chronically medically ill, often diabetic patients, who may be more sensitive to drug-induced EPS.

Descriptive reports of metoclopramide-induced acute EPS and tardive dyskinesia have originated from movement disorder clinics and adverse drug reaction registries. Unfortunately, descriptions from these resources do not allow for accurate estimation of the prevalence of EPS. Because patients are referred to movement disorder clinics, severe cases of EPS are overrepresented. On the other hand, adverse drug reaction registries underestimate the true incidence of EPS because of substantial underreporting.[14] Despite the absence of prevalence studies, the manufacturer's product labeling reports the incidence of all metoclopramide-induced EPSs at 0.2%.[15] Our clinical experience suggests that the true prevalence of metoclopramide-induced EPSs is substantially higher than reported by the manufacturer. We designed a study using blind assessments to compare the prevalence of acute EPS and tardive dyskinesia in metoclopramide-treated patients with controls matched for age, gender, and the presence or absence of diabetes mellitus. In addition, we hypothe-

sized that the prevalence of tardive dyskinesia would be higher in metoclopramide-treated diabetics than in metoclopramide-treated nondiabetics.

RESULTS

Table 1 compares the characteristics of metoclopramide-treated subjects and controls. Consistent with a veteran population, the subjects were predominantly male and older. The average daily dose of metoclopramide hydrochloride was 31 mg, and the average length of treatment was 2.6 years. Forty-seven percent (n=24) of all metoclopramide users were diabetic. Subjects and controls had, on average, four chronic medical illnesses. Forty controls were followed up in a general medicine clinic as compared with 41 metoclopramide-treated subjects (χ^2=0.81, not significant [NS]). Metoclopramide-treated subjects were more likely than controls to have peptic ulcer disease (McNemar's test, 6.25, $P<.05$) and to take oral corticosteroids (Fisher's Exact Test, $P<.001$), ulcer medications (McNemar's test, 17.64, $P<.001$), benzodiazepines (Fisher's Exact Test, $P<.001$), β-agonists (Fisher's Exact Test, $P<.005$), and theophylline (Fisher's Exact Test, $P<.005$).

Table 1. Comparisons of Metoclopramide-Treated Subjects and Controls*

	Metoclopramide Hydrochloride–Treated Subjects (n=51)	Controls (n=51)
Age, y		
Mean±SD	67.6±10.8	63.8±10.6
Range	42-96	38-83
Gender, No. (%)		
M	50 (98)	50 (98)
F	1 (2)	1 (2)
Mean (±SD) metoclopramide hydrochloride dose, mg/d	31.0±11.0	
Mean (±SD) duration of metoclopramide treatment, y	2.6±2.6	
Diabetic status, No. (%)		
Diabetic	24 (47.1)	24 (47.1)
Nondiabetic	27 (52.9)	27 (52.9)
MMSE† score, mean±SD	25.8±3.1	27.0±3.1‡
No. of chronic illnesses, mean±SD	4.2±1.7	4.0±1.9
AIMS†,TD		
Diagnosis, No. (%)§	15 (29.4)	9 (17.7)‖
Summed score, mean±SD	4.1±2.4	2.9±2.3¶
St Hans psychosis		
Diagnosis, No. (%)#	16 (31.4)	4 (7.8)‖
Summed score, mean±SD	5.6±4.3	4.4±3.41
Global score, mean±SD	2.1±1.0	1.5±0.95
St Hans akathisia		
Diagnosis, No. (%)	6 (11.7)	3 (5.8)
Objective, mean±SD	0.26±0.52	0.12±0.44
Subjective, mean±SD	0.44±0.68	0.20±0.541

*MMSE indicates Folstein-McHugh Mini-Mental State examination[28]; AIMS, Abnormal Involuntary Movement Scale[27]; TD, tardive dyskinesia; and St Hans, St Hans Neurologic Rating Scale[29].
†Paired t test, $P<.05$.
‡McNemar's test, $P=.08$.
§Paired t test, $P<.001$.
‖McNemar's test, $P<.005$.
¶Paired t test, $P<.005$.

TARDIVE DYSKINESIA

Twenty-nine percent (n=15) of metoclopramide users met the case definition of tardive dyskinesia compared with 17.6% (n=9) of nonusers (McNemar's test, 3.0, $P=.08$). The relative risk of developing tardive dyskinesia was 1.67 (95% CI, 0.93 to 2.97). The mean (±SD) AIMS summed score in metoclopramide users was 4.1±2.4, compared with 2.9±2.3 in controls. The multivariate analysis of variance revealed that the main effect of metoclopramide on summed AIMS score was highly significant ($F=11.7$, $P<.001$). There was a trend for the diabetics to have higher AIMS scores using this model ($F=3.5$, $P=.07$), but the interaction between diabetes and metoclopramide treatment was not significant. There was no significant heterogeneity in the group covariance matrices (Box's M=6.0, NS). In metoclopramide-treated subjects, there was no correlation between summed AIMS score and age, cognitive status as measured by the Mini-Mental State examination, or dose and duration of treatment with metoclopramide.

Within the metoclopramide-treated groups, diabetics had significantly higher summed AIMS scores compared with the nondiabetics (t test, $P<.05$) (**Table 2**). The Bartlett-Box test for the heterogeneity of variances was not significant ($F[1,7131]=1.33$, NS). There was a trend for metoclopramide-treated diabetics to have a higher prevalence of tardive dyskinesia than metoclopramide-treated nondiabetics ($\chi^2=3.3$, $P=.07$). There was no significant difference between metoclopramide-treated diabetics and metoclopramide-treated nondiabetics with respect to age, length of metoclopramide treatment, daily dose of metoclopramide, use of centrally acting anticholinergics, or presence of affective disorder. Among the diseases and medications for which we examined, diabetics had more cerebrovascular disease ($\chi^2=4.3$, $P<.05$). However in metoclopramide-treated subjects, no medications or diseases except diabetes were associated with presence or absence of tardive dyskinesia. In the metoclopramide-treated diabetics, there was no significant correlation between summed AIMS score and plasma glucose or HbA_{1c} level, type of diabetes treatment, duration of diabetes, or any recognized diabetic complications.

Examining only the control group, the summed AIMS score of diabetic controls was 3.2±2.4 (SD) compared with 2.6±2.2 (SD) in nondiabetic controls (t test, NS). Six diabetic controls (24%) had spontaneous dyskinesia compared with three nondiabetic controls (11%) (Fisher's Exact Test, NS).

DRUG-INDUCED PARKINSONISM

Thirty-one percent (n=16) of the metoclopramide users met our case definition of drug-induced parkinsonism compared with 7.8% (n=4) of controls (Table 1). The relative risk of parkinsonism was 4.0 (95% CI, 1.5 to 10.5). The **Figure** demonstrates the distribution of global scores of the St Hans scale. Using a multivariate analysis of variance, there was a significant effect of metoclopramide on both global parkinsonism mean scores ($F=13.6$, $P<.001$) and summed parkinsonism mean scores ($F=11.1$, $P<.005$) but no effect of diabetes. A test for heterogeneity of the group covariances matrices (Box's M=3.7) was not significant. There was a significant correlation between age and summed parkinsonism in metoclopramide-treated subjects ($r=.52$, $P<.001$) but not in controls ($r=.33$, NS).

In 16 metoclopramide-treated subjects (31.4%), we were unable to rate gait, posture, and arm swing because of their inability to ambulate or use of a gait-assistive device such as a cane or walker, compared with six control patients (11.8%) ($\chi^2=5.6$, $P<.05$). Inability to obtain these measures was associated with elevated summed parkinsonism scores of other body parts (upper extremity rigidity, increased salivation, bradykinesia, and decreased facial mobility) ($F=10.5$, $P<.005$). The sum of the three missing items was estimated from a regression using a fourth-order polynomial with total parkinsonism score as the dependent variable, thus allowing an estimation of total parkinsonism score for those patients with missing data. Use of this correction did not increase the magnitude of the separation between metoclopramide-treated subjects and controls ($F=0.309$, NS). Inability to test gait-posture-arm swing was not associated with other disease processes except cerebrovascular disease ($\chi^2=4.27$, $P<.05$). However, the effect of metoclopramide on ambulation was still apparent when the effect of cerebrovascular disease was removed (Mantel-Haenszel $\chi^2=5.7$, $P<.05$). There was no effect of diabetes on any measures of parkinsonism, including ambulation status.

AKATHISIA AND DYSTONIA

Complaints of subjective akathisia were significantly higher in the metoclopramide-treated subjects than controls (paired t test, $P<.05$), though the overall prevalence of akathisia was low (Table 1). There was no statistically significant difference between groups in objective measures of akathisia. Metoclopramide users had higher use of benzodiazepine medications than controls (Fisher's Exact Test, $P<.001$). Subjective akathisia complaints were associated with the use of benzodiazepines (Fisher's Exact Test, $P<.001$). Benzodiazepines used by subjects in this study included lorazepam (n=3), triazolam (n=6), clonazepam (n=1), diazepam (n=3), and alprazolam (n=1). Despite the difference between metoclopramide-treated subjects and controls in use of β-agonists and theophylline, there was no association between use of these pulmonary medications or chronic obstructive pulmonary disease, and akathisia or antianxiety medications.

Table 2. Comparison of Metoclopramide-Treated Diabetics and Nondiabetics*

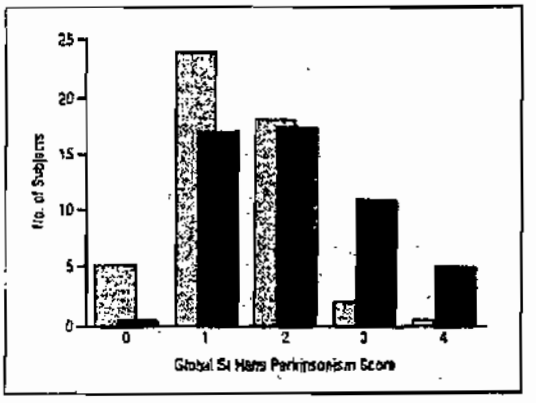
	Diabetics (n=24)	Nondiabetics (n=27)
Mean (±SD) age, y	52 (±10.9	66.5±10.7
Mean (±SD) metoclopramide dose, mg/d	31.7±12.5	30.2±8.7
Mean (±SD) duration of metoclopramide treatment, y	2.5±2.1	2.9±1.9
MMSE score, mean±SD	26.1±3.0	28.4±2.8
No. of chronic illnesses, mean±SD	4.3±1.8	4.8±1.4
St Hans summed parkinsonism score, mean±SD	6.4±3.5	7.0±5.4
AIMS TD		
Diagnosis, No. (%)	10 (42)	5 (19)†
Summed score, mean±SD	1.8±2.6	2.5±7.0‡

*MMSE indicates Folstein-McHugh Mini-Mental State examination[20]; AIMS, Abnormal Involuntary Movement Scale[17]; TD, tardive dyskinesia; and St Hans, St Hans Neurologic Rating Scale.[18]
†$P=.07$, χ^2.
‡$P<.05$, t test.

There were no cases of dystonia in either group. In no case had the presence of any of the motor syndromes measured in this research study been recorded by the clinician in the medical record.

COMMENT

Our results indicate that the prevalence and severity of EPS, including tardive dyskinesia, drug-induced parkinsonism, and subjective akathisia, were significantly increased in a group of chronically medically ill, older, metoclopramide-treated men. These data clearly suggest that both the prevalence and severity of metoclopramide-induced acute EPS and tardive dyskinesia have been underestimated and underrecognized and are approximately 100 times more prevalent than previously reported.[19] Confidence in these findings is supported by certain design features of this study. First, metoclopramide-treated subjects and controls were matched for the most significant risk factors for tardive dyskinesia (age, gender, diabetic status) and drug-induced parkinsonism (age). In addition, there were no differences between subjects and controls in other putative risk factors for tardive dyskinesia, including anticholinergic medications, presence of affective disorder, and dosage and duration of metoclopramide treatment, or in drug-induced parkinsonism, including dosage of metoclopramide. Second, bias was further minimized by blinding raters to diagnoses and medications. Third, extensive medical record review excluded subjects and controls who received other neuroleptic treatments concurrently or in the past. Finally, because of the ability to identify and study most metoclopramide users at our medical center, problems of under-



Distribution of St Hans global parkinsonism scores in 51 metoclopramide-treated subjects (closed bars) and 51 controls (shaded bars). The overall χ^4, 13.7, P<.01.

selection and overselection of cases with EPS were minimized.

The prevalence of tardive dyskinesia in elderly patients who are treated with neuroleptics for mental illness is over 50%, and this disorder does not resolve in 70% of elders even if the neuroleptic is discontinued.[31] Metoclopramide-induced tardive dyskinesia has been described in case series from movement disorder clinics and adverse drug registries. Reports document that the elderly are disproportionately affected by tardive dyskinesia and that the movement disorder persists for months after metoclopramide treatment is discontinued.[4-6] Miller and Jankovic[3] reported that in 12.2% (16) of 131 patients with drug-induced movement disorders, metoclopramide was identified as the cause, and 10 of these patients had tardive dyskinesia. Bateman and colleagues[25] requested information from physicians regarding adverse side effects following new prescriptions of metoclopramide. They attempted to determine the prevalence of "dyskinesia-dystonia." Because they describe this as an acute EPS most likely to occur in younger patients, they appear to be reporting predominantly acute dystonia. The incidence of dyskinesia-dystonia was 1:213 events per prescription. Their method does not take into account the substantial underrecognition of EPS even in high-risk populations. Weiden and colleagues[26] reported that only 10% of subjects on a psychiatric ward who received a research diagnosis of tardive dyskinesia also received a diagnosis of tardive dyskinesia from the treating physician. In the present study, we found no mention of tardive dyskinesia by the primary provider in the medical record in any case identified by the study. Underrecognition of metoclopramide-induced tardive dyskinesia may result from lack of knowledge about the side effects of metoclopramide, failure to observe systematically for tardive dyskinesia, and failure to recognize mild forms of tardive dyskinesia.

Our previous finding[12] of an increased prevalence of tardive dyskinesia associated with diabetes in neuroleptic-treated patients is confirmed by a similar trend found in this study. This higher prevalence cannot be accounted for by other suspected risk factors for tardive dyskinesia, including age, gender, affective disorder, and dosage and duration of metoclopramide treatment, because in metoclopramide-treated patients there was no difference between diabetics and nondiabetics in these risk factors. Pathophysiologic mechanisms for this increased prevalence remain speculative. They may include the effect of hyperglycemia on brain neurotransmitters or may be mediated through increases in microvascular and macrovascular effects of diabetes.[13,27,28] In this study, cerebrovascular disease, although more prevalent in metoclopramide-treated diabetics, was not associated with tardive dyskinesia.

Spontaneous dyskinesias (dyskinesias without known neurologic or medication cause) were found in 24% of diabetic controls and 11% of nondiabetic controls. Waddington[29] calculated a weighted prevalence of spontaneous dyskinesia of 8.9% (n=1584) from six studies using medically ill populations. Three of these studies focused on elderly patients and published prevalences of spontaneous dyskinesias of over 15%. The weighted prevalence of spontaneous dyskinesias in community-living healthy elderly was 1.6% (n=1032). Our finding of higher prevalence of spontaneous dyskinesias may represent a higher degree of medical illness in our population, greater sensitivity of the rating methods, or undetected prior use of neuroleptics by controls.

We also found an increased prevalence and severity of parkinsonian signs in metoclopramide-treated subjects. As with tardive dyskinesia, there was substantial overlap in scores between the subjects and controls. The apparent prevalence (7.8%) of idiopathic parkinsonism in this study is higher than that customarily found (<1%) in community-based prevalence studies.[30] Some specificity was sacrificed because the blind rater was not allowed to distinguish true parkinsonism from age- and other illness-related changes in posture, speed of movement, and gait. Because of careful matching on important variables between metoclopramide-treated subjects and controls, the statistically significant (P<.01) shift to the right (Figure) in severity of parkinsonism scores in metoclopramide-treated subjects is likely attributable to metoclopramide use and suggests that metoclopramide increases parkinsonian symptoms in a clinically meaningful manner. Despite the subtlety of these parkinsonian signs and considerable overlap with age-related abnormalities, it is of great concern that subjects in the present study were more functionally impaired in ambulation than controls. Metoclopramide use, perhaps in combination with age, frailty, and other medical illnesses, may have been the final cumulative "insult" that resulted in loss of the ability to walk independently. Again, clinical nonrecognition of the role of metoclopramide was universal. Because the subjects were elderly and chronically medically ill, clinicians may have attributed impairment in gait to other factors and not suspected the role of metoclopramide.

Akathisia is a syndrome of subjective and motor restlessness. Mild forms are without objective signs, but in more severe cases, patients show an inability to remain seated, shifting in place or pacing. These symptoms may cause considerable distress. Prevalence estimates of akathisia in psychiatrically ill, neuroleptic-treated patients are conservatively placed at 20%.[4] The present study found an association between subjective akathisia and the use of anxiolytic and hypnotic types of benzodiazepines in metoclopramide users. One interpretation of the finding is that mild akathisia was either interpreted as anxiety or resulted in impaired sleep, prompting pharmacologic treatment. Alternatively, anxious or sleepless patients may have more nonspecific gastrointestinal distress, resulting in treatment with metoclopramide.

The lack of drug-induced dystonia is not surprising in this older cohort. Acute dystonia is dose related and more common in younger patients. A retrospective review of dystonia in the elderly found an incidence of 2% in patients over 60 years of age.[9] Because drug-induced dystonia often presents in a dramatic fashion, such as the sudden onset of torticollis or oculogyric crisis, it is rarely overlooked.

CONCLUSION

This study found a higher prevalence and severity of drug-induced parkinsonism and greater severity of tardive dyskinesia and akathisia associated with metoclopramide use than previously reported. Moreover, the use of metoclopramide was associated with considerable morbidity, including impairment in ambulation and increased use of benzodiazepines. Prospective studies may clarify cause-and-effect relationships suggested by this cross-sectional approach. Nevertheless, we suggest that in the elderly, acute EPS and tardive dyskinesia occur at much lower metoclopramide doses than previously believed. Even when mild, these side effects may interfere with a patient's quality of life. The clinician should consider these findings in assessing patient's need for metoclopramide.

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