
Metoclopramide and Tardive Dyskinesia

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Introduction

Metoclopramide (MCP) is a D-2 receptor blocker (Kebabian and Calne 1979), which has been available by prescription in the United States since 1979 for use as an antiemetic in a wide range of situations. One of the common indications for MCP is the treatment of diabetic gastroparesis (Physicians' Desk Reference 1993). A few recent reports suggest that diabetes mellitus may be a risk factor for tardive dyskinesia (TD) (Ganzini et al 1991; Woerner et al 1993). There have been case reports but few systematic studies of MCP-associated TD (Sewell et al 1992; Sewell and Jeste 1992; Ganzini et al 1993).

We present here preliminary results of a clinical study of MCP-associated TD. We wished to study the frequency of dyskinesia in patients with a history of exposure to MCP compared to a non MCP-treated comparison group. We also wished to study localization and course of MCP-associated TD, as well as factors such as the diagnosis of diabetes mellitus which might be associated with an increased risk of TD.

Methods

Subjects

All the study participants were veterans who were receiving medical care at the San Diego VA Medical Center. The inclusion criteria were: no prior exposure to any neuroleptic other than MCP, history of MCP use for 30 days or longer, absence of current

DSM-III-R-diagnosed (APA 1987) alcohol or substance use disorders, and the absence of a preexisting movement disorder such as idiopathic Parkinson's disease. Information regarding the various inclusion and exclusion criteria was obtained directly from the patient in a structured clinical interview with a board-certified psychiatrist (DDS) and from a review of medical and computerized pharmacy records. Comparison subjects were selected from the same clinics and inpatient units with similar age, gender, race, and frequency of diabetes mellitus. All the subjects provided written informed consent at the initial visit. At entry, we obtained pertinent clinical information and the subjects were rated by "blind" raters using the following scales: Mini-Mental State Examination (MMSE) (Folstein et al 1975), modified Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health 1975), Rockland Abbreviated Dyskinesia Rating Scale (Simpson et al 1979), and modified Simpson-Angus' Scale for extrapyramidal symptoms or EPS (Simpson and Angus 1970).

The presence of TD was defined clinically, using the criteria of Schooler and Kane (1982) and Jeste and Wyatt (1982) except that the minimum required length of prior neuroleptic exposure was 1 month (instead of three months) because of the increased susceptibility of older patients to develop TD. Group comparisons on categorical variables were done using Fisher's exact tests of probability, and on continuous variables using Mann-Whitney U-tests or Wilcoxon Rank Sum tests. All statistical tests were two-tailed.

Results

Demographics and Clinical Rating Scales

As expected, there were no differences between the 51 MCP-treated and 35 comparison subjects in terms of age, race, gender or frequency of diabetes mellitus (Table 1.)

Frequency

Fourteen MCP-treated subjects met criteria for TD and four comparison subjects met criteria for spontaneous dyskinesia (i.e., met

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Table 1. Demographic and Clinical Rating Scale Data for MCP-Treated and Comparison Subjects

	MCP-Treated	Comparison	<i>p</i>
<i>n</i>	51	34	
Age in years: Mean (SD)	60 (12)	61 (10)	NS
Gender: percentage male	79%	90%	NS
Race: percentage Caucasian	76%	84%	NS
Percentage with Diabetes Mellitus	45%	43%	NS
Mini-Mental Status Examination score (SD)	28 (2)	28 (2)	NS
Simpson-Angus' rating scale total (SD)	16 (3)	16 (4)	NS
AIMS total (SD)	2.6 (2.6)	1.5 (1.7)	0.03 ^a
Percentage with dyskinesia	27%	12%	0.08 ^b

^a*t*-test (two-tailed).^bFisher Exact test (two-tailed).

Schooler and Kane criteria, except for a lack of neuroleptic treatment history) ($p = 0.08$). None of the MCP-treated and none of the comparison subjects had global AIMS ratings of severe dyskinesia, 2 and 1 had moderate dyskinesia, and 12 and 3 had mild dyskinesia.

Topographical Distribution of the TD

Twelve of the 14 MCP-treated patients had TD affecting more than one region. Dyskinetic movements occurred with equal frequency in the lips ($n = 8$), jaw ($n = 8$), tongue ($n = 8$), and limbs ($n = 8$), followed by face ($n = 3$), and trunk ($n = 2$). Six subjects had only orofacial involvement, two had only limb-truncal movements, and six had both orofacial and limb-truncal movements. The AIMS scores for right and left limbs were similar. All of the subjects with spontaneous dyskinesia had dyskinetic movements affecting more than one region. The topographical distribution of the dyskinetic movements in the patients with spontaneous dyskinesia was: lips ($n = 3$), jaw ($n = 1$), tongue ($n = 1$), limbs ($n = 3$), and trunk ($n = 0$). One of the subjects with spontaneous dyskinesia had only orofacial involvement and three had both orofacial and limb-truncal movements.

Associated Factors

Among the MCP-treated patients, there was no difference between those who developed TD and non TD groups on age (61 ± 11 versus 57 ± 14 years, respectively) or total score on the MMSE (28 ± 2 versus 28 ± 1 , respectively), however, there was a difference in mean total score on the modified Simpson-Angus' Scale for EPS (17 ± 3 versus 15 ± 3 , $p = 0.048$, Wilcoxon Rank Sum test). Nine of the 14 TD patients who were exposed and developed TD and 14 of the 37 non TD patients were diabetic ($p = 0.05$). Among the comparison subjects, there were no demographic differences between those with and without spontaneous TD, however, the sample of patients with spontaneous dyskinesia was very small ($n = 4$).

Course

Five of the 14 TD patients were followed for 10 months. In four patients, MCP was discontinued, yet all four continued to have TD 11 months later. In one patient, MCP was continued and this patient was found to have TD 9 months later. Two of the four patients with spontaneous dyskinesia were followed for an average of nine months and both continued to have spontaneous dyskinesia.

Discussion

This preliminary study is limited by a small sample size, nonetheless, our results along with the recently published results of Ginzini et al (1993) argue for additional systematic research on TD associated with MCP, a commonly used drug. Specifically, we found that MCP-associated TD may be frequent, mild to moderate in severity, and persistent. Published data suggest that elderly women patients may have a higher risk of TD than younger women or men (Yassa and Jeste 1992). Given our small sample size, it is possible that the slightly higher (although not significant) proportion of women in our MCP-treated group could have increased the likelihood of finding a difference in the frequency of TD between the two groups. The frequency of TD in MCP-treated patients (27%) was almost identical to the frequency of TD reported by Yassa and Jeste (1992) in an extensive analysis of studies on the prevalence of TD in patients with psychiatric illness. Our study challenges the notion proposed by some investigators (Owens et al 1982) that TD is merely a symptom of schizophrenia or similar psychiatric illnesses. Like others (Ginzini et al 1993; Woerner et al 1993) we also found that patients with diabetes mellitus who were exposed to MCP were more likely to have TD than nondiabetic MCP-treated patients and that TD was frequently associated with neuroleptic-induced parkinsonism (Jeste and Caligiuri 1993). Age and cognitive status did not appear to be risk factors for MCP-associated TD. MCP-associated TD was similar to antipsychotic-induced TD (Jeste and Wyatt 1982) in terms of predominant orofacial involvement and a tendency for persistence.

We believe that studies of MCP-associated TD will contribute to a better understanding of TD in general. Studying MCP-associated TD offers certain advantages for studying TD in patients with psychiatric illness. For example, many of the patients who develop MCP-associated TD can discontinue MCP because a number of alternative treatments are available and because the consequences associated with discontinuation of MCP are much less severe than those associated with the discontinuation of antipsychotic medication in patients with chronic schizophrenia.

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