CLINICAL REVIEW

Metoclopramide-Associated Tardive Dyskinesia

An Analysis of 67 Cases

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Objective: To summarize information regarding the frequency, risk factors, clinical characteristics, treatment, and course of metoclopramide hydrochloride–associated tardive dyskinesia obtained from an analysis of 67 case reports.

Data Sources: All the case reports of metoclopramide-associated tardive dyskinesia involving human patients in the literature in English obtained by using *Index Medicus* and *Med-Search*. The indexing terms used were as follows: metoclopramide, tardive dyskinesia, dyskinesia, parkinsonism, and extrapyramidal side effects.

Study Selection: For a patient to be included, the main published research criteria had to be met based on the information provided. These criteria included exposure to metoclopramide for at least 30 days before the onset of dyskinesia. Fifty-two patients met these criteria.

Data Extraction: One author independently extracted the data.

Data Synthesis: The incidence and prevalence of tardive dyskinesia associated with metoclopramide have not been well studied. The mean (±SD) length of treatment with metoclopramide before the onset of symptoms was 20±15 months. The most common location of the dyskinetic movements was the face (28 [60%] of 47) followed by the tongue (21 [45%] of 47). In 15 (71%) of 21 patients on whom long-term follow-up was provided, the symptoms were still present 6 months or more after discontinuation of metoclopramide.

Conclusions: Persistent tardive dyskinesia is a serious potential side effect associated with metoclopramide treatment.

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Tardive dyskinesia (TD), an involuntary movement disorder that may appear after several months of treatment with antipsychotic drugs, is characterized by a variable combination of orofacial dyskinesia, chorea, athetosis, dystonia, tics, stereotypies, and facial grimacing, and may be transient or persistent.[1] The most widely described triad of symptoms is sucking and smacking movements of the lips, pulling of the cheeks with tongue thrusting or rolling, and lateral jaw movements.[2] Several factors have made TD a serious problem. First, the reported prevalence of TD has increased progressively since 1960 and is currently about 24% among patients treated with neuroleptic drugs.[3,4] Second, in approximately 60% of patients with TD, the disorder persists for longer than 3 months, even after the neuroleptic treatment has been discontinued.[5] Third, there are no well-established, effective treatments for TD,[6] although some success has been reported with tetrabenazine, a dopamine-depleting drug available only with an investigative new drug application.[7] Last, there is a growing number of court cases against clinicians and hospitals filed by patients with TD.[8]

Although metoclopramide hydrochloride has been in clinical use for over two decades, its pharmacologic actions are complex and still not completely understood. It is known that among its other actions, metoclopramide is a dopamine receptor blocker and has some antipsychotic activity. Like other drugs that are known to be dopamine receptor blockers, metoclopramide has been associated with extrapyramidal side effects including TD. We reviewed the literature in English and found 21 articles containing 67 cases of metoclopramide-associated dyskinesia. We pro-

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vide herein an overview of what is known about metoclopramide-associated TD, and summarize pertinent information from an analysis of the 52 cases that met our inclusion criteria.

METOCLOPRAMIDE

Metoclopramide was first introduced into clinical use in France[9] and in 1967, it became available for clinical use in the United Kingdom[10] as an antiemetic in a wide range of situations. Metoclopramide did not become available in the United States until 1979.[11] According to Wyeth-Ayerst Laboratories (Philadelphia, Pa), the company that up until May 1990 had exclusive rights to the manufacture and sale of the drug in the United States, the mean number of single units (capsules or tablets) sold to drug stores and hospitals in the United States per year from 1987 to 1989 was 1 470 066 (personal communication, Wyeth-Ayerst Laboratories Medical Services Division, 1990). In May 1990, the drug became available in generic form. It is projected that in 1990, 73.2% of the metoclopramide prescriptions written in the United States will be by physicians in family practice (28%), internal medicine (26.8%), or general practice physicians (10.8%), or gastroenterologists (7.6%) (written communication, IMS America, December 5, 1991).

Metoclopramide is generally classified as a specific D_2 dopamine receptor blocker.[12] There is evidence, however, that it also acts on dopamine autoreceptors.[13] Metoclopramide can be administered orally, intramuscularly, and intravenously. In patients other than those receiving chemotherapy for cancer, the usual dose for any route of administration is 10 mg three or four times daily before meals or before symptoms are likely to occur

Metoclopramide treats vomiting associated with narcotic analgesia, radiation therapy, and pregnancy as well as or better than phenothiazine antiemetics. It diminishes postoperative vomiting when it is given near the end of surgery, and is superior to placebo in a variety of gastrointestinal disorders associated with delayed gastric emptying,[14] such as gastroesophageal reflux, gastric stasis following vagotomy, and diabetic gastroparesis. A few studies suggest that a dose of 60 mg/d may facilitate healing of local inflammation.[15] Metoclopramide provides symptomatic improvement in diabetic gastroparesis, although objective improvement has been difficult to demonstrate.[14] Metoclopramide is equal to or superior to anticholinergic drugs, phenothiazine antiemetics, and antacids in the treatment of dyspepsia. No evidence exists to support that metoclopramide promotes healing of peptic ulcer.[14]

Initial studies using relatively small doses of metoclopramide failed to demonstrate that it had significant tranquilizing or antipsychotic activity,[16,17] but now there is some evidence showing that it is an effective antipsychotic drug when administered in 500- to 1000-mg doses.[18-20] The effect of metoclopramide on in vivo dopamine turnover suggests that its potency as an antipsychotic drug on a milligram per kilogram basis may be similar to that of chlorpromazine.[18] Stanley et al[19,20] successfully treated psychotic symptoms in eight patients with chronic schizophrenia using metoclopramide.

The reported frequency of extrapyramidal side effects associated with metoclopramide varies from 1%[21] to 5%[22] to 9%[14] to 25%.[16] Acute dystonic reactions are the most common type of extrapyramidal side effect associated with metoclopramide. The approximate frequency of dystonic reactions is 0.2% when a dose of 30 to 40 mg/d is used. In patients receiving markedly higher doses, the rate of dystonic reactions is considerably higher. For example, in young patients receiving chemotherapy for cancer, the frequency of dystonic reactions is 25% or greater if dystonia prophylaxis (eg, intravenous diphenhydramine) is not administered.

Parkinsonian side effects also occur but the frequency is unknown.[23] Bateman et al[24] reported 20 cases of metoclopramide-induced parkinsonism. In seven cases, the parkinsonian side effects appeared within 7 days of treatment, and in seven other cases, the symptoms appeared after 28 days. In two of these latter cases, the symptoms appeared after 5 years of treatment, which makes their association with metoclopramide treatment rather tenuous.

MATERIALS AND METHODS

We searched the literature in English for studies of the frequency of metoclopramide-associated TD and found only a few such studies. We found no systematic studies of TD in patients treated with metoclopramide. Because of this, we included all the studies that provided information on frequency regardless of the quality of the methods used or of the manner of reporting results. We also searched the literature for case reports of metoclopramide-associated TD. We found 21 articles containing information on 67 patients with metoclopramide-associated dyskinesia. We also found an article by Board[11] with summary data from 26 cases of involuntary movement disorders "consonant with TD" that were reported to the A. H. Robins Co (Richmond, Va) in the first 5 years during which metoclopramide was available in the United States. We did not include these data in our analysis because we could not determine which of these cases were previously described in the published case reports.

To be included in our analysis, a patient had to meet the main TD diagnosis criteria of Schooler and Kane[25] and Jeste and Wyatt[3] (based on the description provided), except for the criterion regarding the minimum length of exposure. We decreased this requirement to 1 month based on the definition of TD proposed in the *DSM-IV Sourcebook*.[3] A minimum duration of exposure of

1 month is necessary to avoid including acute and subacute dyskinesias that are clearly not "tardive" or late-onset.[2] In addition, patients could not have a history of another movement disorder.

Fifty-two cases met these criteria. Of the patients included in the study, exposure to metoclopramide was documented to be 3 months or more in 47, between 1 and 3 months in two, and was undocumented before the onset of TD in three cases. To decrease the likelihood of bias, we report findings from all 52 included cases (group 3) and findings from only the 47 case reports with documented exposure to metoclopramide of more than 3 months (group 1). For purposes of discussion, patients with less than 3 months' exposure to metoclopramide and patients with undocumented exposure before the onset of symptoms are referred to as group 2 patients. Only one of 52 patients had a history of previous exposure to neuroleptic drugs. This was a patient in group 2 who had received 10 mg of trifluoperazine hydrochloride twice a day for an unspecified length of time for treatment of an episode of depression that occurred 2½ years before treatment with metoclopramide.[25]

Fifteen of the original 67 were excluded. We excluded four cases because the symptoms of dyskinesia appeared within the first 30 days of treatment with metoclopramide.[27-30] Ten case reports that did not contain enough information to determine whether the cases met inclusion and exclusion criteria were excluded.[24,31] We attempted to contact the authors of the reports to obtain the missing information but our efforts did not yield any additional information. We excluded one case because written communication with the author revealed that the dyskinesia resolved "within 1 hour of its onset."[12]

Ten of the articles contained case reports that clearly met criteria for inclusion in the analysis but, nonetheless, contained cases with missing data. We attempted to contact the authors of these articles to obtain the missing data. Grimes et al[32] reported 12 cases with only mean values for the entire group. For the purposes of our analysis, we used the mean values as if they were the specific values for each of these cases. Two cases reported by Miller and Jankovic[33] did not include information about the length of exposure; however, we assumed that the researchers who made these diagnoses were aware of the criteria regarding minimum required length of exposure and we included these two cases. It should be noted that Miller and Jankovic[33] reported maximum daily metoclopramide dose. The authors of all the other case reports included in our analysis reported daily doses, mean daily doses, or dose ranges. When dosage ranges were given, we used the midpoint value of the range to calculate the mean daily dose for our sample.

RESULTS

Our results are summarized in the **Table**.[34-36]

FREQUENCY

To our knowledge, the incidence and prevalence of TD associated with metoclopramide have not been studied. Indo and Ando[28] found 10 cases of metoclopramide-induced parkinsonism among 282 cases of parkinsonism treated during a 10-year period from 1970 through 1979 at a hospital in Gifu, Japan, and noted that four of these patients had dyskinesia. They did not provide information on the size of the population from which these cases were identified. Wiholm et al[37] found 11 cases of TD associated with metoclopramide that had been reported to the Swedish Adverse Drug Reactions Advisory Committee from 1977 to 1981. Using total drug sales and prescription statistics, these authors calculated the incidence of TD during treatment with metoclopramide to be one in 2000 to 2800 treatment years. Bateman et al[24] found four cases recorded in an adverse reactions register in the United Kingdom during a 15-year period when an estimated 15.9 million prescriptions had been written. Miller and Jankovic[33] assessed 16 metoclopramide-treated patients with dyskinesia who had been selected from a database of 3000 patients with various extrapyramidal disorders seen from 1977 through June 1989. The most common movement disorder in this group was TD, observed in 10 patients. The frequency of metoclopramide-associated TD has not been well studied. Ganzini et al[38] recently reported a study of 51 patients treated with metoclopramide for a mean of 2.5 years. Twenty-four of these patients had diabetes. In the diabetic group, 42% met research criteria for TD. In the group without diabetes, 19% met criteria for TD. We did not find any study of the prevalence of TD in large cohorts of metoclopramide-treated patients.

RISK FACTORS

Wiholm et al[37] found that the incidence of TD with long-term metoclopramide use in patients aged 70 years or older was greater than one in 1000. This incidence was two to three times higher than that in a group representing all the patients treated with metoclopramide. These authors concluded that long-term metoclopramide treatment was associated with a significant risk of developing TD, especially among the elderly.

The mean (±SD) age of the patients in group 3 was 70±10 years. The mean age of patients in groups 1 and 2 were 70±10 and 71±13, respectively. Group 1 was composed of 24 women, 10 men, and 13 patients whose gender was not specified. Group 2 was composed of five women. In group 3, the female-male ratio was approximately 3:1. Sixteen of the 47 patients in group 1 and two of the five patients in group 2 had parkinsonian symptoms along with TD. Four patients in group 1 and one patient in group 2 were described as having diabetes. Although depression has been pro-

Case Reports of Metoclopramide-Associated Tardive Dyskinesia (TD)

Source, y	No. of Cases	Mean Age (Range), y	Sex, M/F/ Uncertain	Mean Dose (Range), mg/d	Mean Length (Range) of Use Prior to TD	TD Localization*	TD Status After Metoclopramide Withdrawal at Last Follow-up, mo†
Kataria et al,[19] 1978	3	75 (66-84)	0/3	28 (15-40)	34 (12-66)	J, Tr (n=2); J, Lp (n=1)	R 0.75, P 9, P 6
Law et al,[20] 1978	1	48	1/0	20-40 (6 y) 80 (4 y)	72	F, J, Lp, To	
Grimes et al,[3] 1982‡	12	72	?	29	26	F, Lp, To	R 0.75 (3), P 18 (8)
Indo and Ando,[38] 1982	3	67 (64-71)	1/1/1	30	15 (6-27)	Lp; Lp, To; J	R 0.75, P 0.75, R 3
Shearer et al,[39] 1984	1	50	1/0	30	4	Tr	R 27
Wilhoit R et al,[1] 1984	11	76 (69-86)	0/11	31 (10-60)	17 (4-44)	F, J, To (n=2); F, J, To, Tr (n=9)	P 17, P 2, R ?
Beaudoin and Fontaine,[40] 1986	1	74	0/1	30-60	?	J, To	P 6
Breitbart,[41] 1986	1	45	1/0	2 mg/kg	11	F, J, Lp, Lm, Tr	P 3
Lazzara et al,[42] 1986	1	83	0/1	30	8	F, J, To	P 1
Patel and Louis,[24] 1986	1	84	0/1	?	8	Lp, To	P 6
Sirota et al,[43] 1986	1	65	0/1	30	2	F	R 0.25
Sarma et al,[44] 1987	1	66	1/0	30-40	12	F, Lm, Lp, To, Tr	P 36
Yamamoto et al,[45] 1987	1	81	1/0	30	9	Lp, To	P 0.32
Miller and Jankovic,[46] 1989§	11	68 (53-85)	2/9	33 (20-40)	18 (2.5-48)	F, Lp (n=9); ? (n=2)	?
Lang,[47] 1990	1	74	0/1	30	4	F, To	P 27
Sewell et al,[48]	2	46	2/0	40 (30-60)	11.5 (11-12)	J, Lp, To	P 18, P3

*J indicates jaw; Tr, trunk; Lp, lips; F, face; To, tongue; and Lm, limbs.
†P indicates persistence of symptoms, and R, complete resolution of symptoms at time of latest reported follow-up.
‡Authors reported mean values from 12 cases of metoclopramide-associated TD. Numbers in parentheses indicate sample sizes studied for TD status at follow-up.
§Authors did not specify exact number of months but used the word "several."
‖Authors reported maximum (not mean) metoclopramide doses.

posed as a risk factor for antipsychotic drug-induced TD,[39] only two case reports of metoclopramide-associated TD (one each in groups 1 and 2) specified the presence or history of depression.[20,40] Metoclopramide was prescribed for a number of different indications and five patients had two indications for metoclopramide. The indications for metoclopramide treatment were nausea and vomiting (n=10); esophageal reflux/esophagitis (n=5); hiatal hernia (n=4); diabetic gastroparesis (n=3); epigastric discomfort (n=2); ulcer (n=2); anorexia (n=2); chronic gastritis (n=2); diverticulitis (n=1); ileus (n=1); partial gastrectomy (n=1); and unspecified (n=24).

CLINICAL CHARACTERISTICS

Thirty-one of the 52 case reports analyzed described the temporal relationship between the treatment with metoclopramide and the onset of TD symptoms. In 25 cases (81%), the TD symptoms developed during treatment with metoclopramide and in six (19%), the symptoms developed after treatment was discontinued. In group 1, 23 patients (79%) developed symtoms during treatment and six (21%) after treatment was discontinued. This information was reported for only two of the five patients in group 2, both of whom developed TD symptoms during treatment. The mean length of treatment with metoclopramide before the onset of TD symptoms for the 49 cases for which this information was provided was 20±15 months and the mean daily dose was 32±7 mg. In patients in group 1, mean treatment duration was 20±15 months and mean daily dose was 33±10 mg. In 20 (38%; 18 from group 1 and two from group 2) of 52 cases, parkinsonian symptoms were reponed to coexist with TD.

In 47 (44 from group 1 and three from group 2) of the 52 case reports, the topographic location of the dyskinetic movements was described. All but five cases had dyskinetic movements affecting more than one region. The most common location of the dyskinetic movements was the face (n=28), followed by the tongue (n=21), the lips (n=19), the jaw (n=19), the trunk (n=9), and the limbs (n=3). Three patients had movements affecting the eyelids.[37,41,52] Three had movements affecting the pelvic region,[43,44] of whom one had contractions of the anal and vaginal musculature.[43] Two patients had diaphragmatic dyskinesia[42,44] and one of these resulted in severe breathing and swallowing difficulties.[42] The **Figure** compares the topographic localization of metoclopramide-associated TD with that of TD induced by traditional antipsychotic agents.

TREATMENT AND COURSE

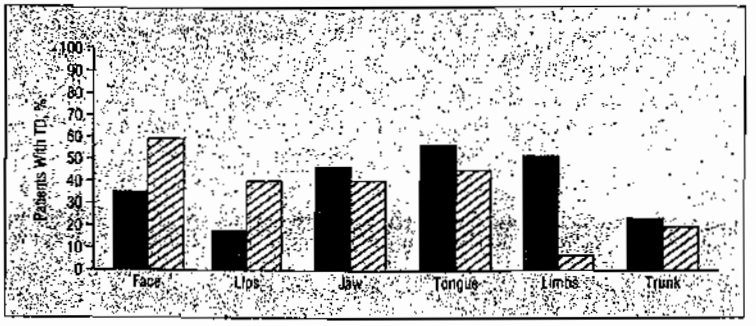
In all 52 cases, treatment was ultimately discontinued once the pos-

sible causative relationship between metoclopramide and TD was recognized. Thirty-two case reports (30 in group 1 and two in group 2) included information regarding the course of the TD symptoms after withdrawal of the drug. Twenty-one of these provided information 6 months or longer after onset of TD and 11 either did not specify the length of the follow-up or had a follow-up of less than 6 months. The mean follow-up provided for all cases for which this information was available was 16±6.5 months, with a range of 6 to 27 months. It is noteworthy that 15 (71%) of the 21 case reports with follow-up information at 6 months or more had persistent TD.

In five group 1 cases and in one group 2 case, the TD symptoms were noted to have resolved completely at some point during the first 6 months after discontinuation of metoclopramide. The mean duration until the resolution of the symptoms for all case reports that included this information was 2.0±2.2 months and the range was 1 week to 6 months.

In the remaining 11 case reports that included follow-up information, 10 patients were described as having persistent TD symptoms and in one patient the symptoms were reported to resolve. The duration of follow-up was not specified in two of the 10 patients with persistent TD and in the one in whom the symptoms did not resolve. In the remaining eight patients, the follow-up period reported was less than 6 months. The mean follow-up for these eight was 1.4±1.4 months and the range was 6 days to 4 months.

One patient in group 1 was described as achieving significant improvement with treatment with choline; however, the dose and duration of treatment were not specified.[43] Another patient[28] in group 1 was treated with levodopa and benserazide; 1 week later, the tremor diminished but the authors did not comment on whether these medications decreased the symptoms of dyskinesia. Grimes et al[32] reported that in three of 12 patients (all group 1) with TD, the dyskinetic movements resolved within 3 weeks after the termination of metoclopramide treatment. One patient died, and in the remaining eight, the movements persisted between 6 and 36 months (mean, 18 months). In addition, the authors reported that two patients had mild to moderate improvement in TD with treatment with 30 g of lecithin granules per day, and in one patient, treatment with haloperidol decreased the TD but worsened parkinsonian symptoms.[32] Another patient[41] (group 1) initially treated with anticholinergic drugs that made the movements more pronounced, was then treated with diazepam, which led to moderate improvement but the symptoms persisted until the patient died of cancer 3 months later. Another patient (group 2) experienced great improvement in facial dyskinesia 1 day after receiving treatment with diphenhydramine hydrochloride.[43] One patient[42] (group 1) receiving "carbidopa/levodopa" (25 mg/100 mg) at the time the TD symptoms developed, continued receiving this medication unchanged with the addition of 2 mg of trihexyphenidyl hydrochloride twice a day. One month later, the patient's TD symptoms were much worse. Both medications were discontinued and treatment with 5 mg of diazepam four times daily, 0.1 mg of reserpine four times daily, and 0.5 mg of clonazepam every 4 hours was begun. The patient improved several months later, but grimacing and blepharospasm persisted.



Topographic distribution of tardive dyskinesia (TD) in patients with metoclopramide-associated TD (hatched bars) vs patients with TD associated with traditional antipsychotic medications (solid bars). Percentages for patients with TD associated with traditional antipsychotic use were from an analysis by Jesta and Wyatt,[5] who calculated and reported mean values using percentages obtained from five studies of the localization of dyskinetic movements. Although the topographic distribution of TD associated with metoclopramide resembles that associated with traditional antipsychotic drugs, one apparent difference is the lower frequency of limb dyskinesia in cases of metoclopramide-associated TD.

COMMENT

One of the limitations of a review based on case report analysis is the variable omission of pertinent information. Other limitations of this review are the modest sample size of 52 cases and the fact that few of the case reports included the systematic application of published criteria to diagnose TD.

On the other hand, to our knowledge this is the largest review of metoclopramide-associated TD and there have been no published prospective studies. In addition, we systematically tried to apply published criteria for the diagnosis of TD and excluded cases that did not meet those criteria. Our survey does not prove that a causal relationship exists between treatment with metoclopramide and the development of TD. To obtain direct evidence, a prospective study needs to be conducted comparing the frequency of dyskinesia in a group of patients whose only exposure to neuroleptic drugs has been treatment with metoclopramide, with a group of well-matched control patients never exposed to metoclopra-

mide or any other neuroleptic medication. Such a study will need to take into account the rate of spontaneous dyskinesia[46] and the impact of other possible causes of dyskinesia.

(71%) of the 21 case reports with follow-up information at 6 months or more had persistent TD.

The results of our literature review are of interest for several reasons. Although the findings here do not provide direct evidence that metoclopramide causes TD they do provide highly suggestive indirect evidence. This evidence takes three forms: (1) the number of published case reports; (2) the known pharmacologic similarities between metoclopramide and the traditional antipsychotic medications; and (3) the similarities we found between the syndrome of TD associated with metoclopramide and that caused by the traditional antipsychotic agents.

We found 52 case reports in the literature in English of metoclopramide-associated TD that met our selection criteria. This may be too large a number to be simply a coincidence. There have been more case reports of TD associated with metoclopramide treatment than with any other class of medication except the traditional antipsychotic drugs. Furthermore, in 47% of the cases that we analyzed, TD symptoms were reported to persist for at least 6 months. To our knowledge, except for neuroleptic drugs, no other drugs produce persistent dyskinesia.[5]

Metoclopramide shares a number of characteristics with the commonly used antipsychotic drugs: (1) it blocks dopamine receptors[12]; (2) it has tranquilizing and antipsychotic effects[18-20]; and (3) the rate extrapyramidal side effects associated with metoclopramide, although not as high as with traditional antipsychotic drugs, is much higher than with other psychotropic medications.

The syndrome of TD in patients treated with metoclopramide resembles that seen in patients treated with traditional antipsychotic medications. The mean length of metoclopramide treatment prior to the onset of dyskinesia was 20 months, clearly indicating the "tardive" nature of the movement disorder. The abnormal movements observed in the 52 cases of metoclopramide-associated TD are phenomenologically similar to the antipsychotic drug–induced TD.[47] In 15 (47%) of the 32 cases that provided long-term follow-up information, TD was still present after 6 months. This is similar to the proportion of patients in whom symptoms of TD persist after exposure to traditional antipsychotic drugs.[48] In all cases, the TD symptoms developed either during treatment or within a few weeks of discontinuation. In addition, many of the patients who developed TD while taking metoclopramide experienced temporary worsening immediately after discontinuation of the treatment,[44,49,50] a phenomenon often seen after traditional neuroleptic treatment withdrawal. Last, anticholinergic medications worsened symptoms[41] but resumption of treatment with metoclopramide[37,49] or initiation of treatment with a traditional antipsychotic[37,51] improved symptoms. Thus, there are striking similarities between TD associated with metoclopramide and that induced by antipsychotic drugs. Nonetheless, the comparison presented in the Figure suggests that metoclopramide-associated TD may have at least one difference from antipsychotic drug-induced TD. Specifically, TD associated with metoclopramide may more frequently involve the face and lips and less frequently the limbs than that associated with antipsychotic drugs.

There are a number of reasons why studying metoclopramide-associated TD is important: (1) our review suggests that the syndrome may be persistent; (2) it can lead to serious complications such as respiratory compromise[42]; (3) it appears to be relatively resistant to treatment just like the TD associated with traditional antipsychotic treatment; (4) metoclopramide is a rather commonly used medication and therefore a significant number of patients may be at risk; and (5) the frequency of TD associated with metoclopramide is probably underestimated. Although few of the authors of case reports of metoclopramide-associated TD provided quantitative data regarding TD severity, the descriptions provided and the distress and complications reported suggest that the overall severity of the cases in our analysis was high. It is likely that reports of only the more severe cases of TD were published. It is known that a majority of the cases of antipsychotic drug–induced TD are mild. If the literature on TD associated with traditional antipsychotic drugs is any guide, there may be a large number of cases of mild TD associated with metoclopramide.

It should also be noted that reports on frequency that obtained data from adverse drug reaction registers are limited by the rate of reporting of adverse drug reactions. What percentage of adverse drug reactions are actually reported is not known, but certainly it is reasonable to assume that this percentage is not high.

Determining the frequency of metoclopramide-associated TD requires accurate recognition of TD. In a letter to the editor in 1983, Casey[52] alerted physicians to the drug's potential for neurologic side effects including TD. Until recently, however, TD has been a medication side effect almost exclusively diagnosed in psychiatric settings. Just as psychiatrists were initially slow to recognize and diagnose TD during the period following the first description of TD,[48] clinicians outside of the

psychiatric field currently may be somewhat less likely to recognize TD, especially when it is mild. The fact that patients with TD frequently are completely unaware of it until it has been brought to their attention by someone else probably also decreases the likelihood that TD will be diagnosed promptly.

The published literature suggests that TD is more frequent in older patients and in women.[53] Several groups of investigators have reported a frequent coexistence of TD and parkinsonism[54,55] with some indicating that neuroleptic drug–induced parkinsonism may be a risk factor for TD.[56,57] In addition, a recently published controlled study by Ganzini et al[58] suggests that diabetes mellitus may be a risk factor for TD. Our results suggest that these risk factors could also characterize metoclopramide-associated TD.

It is not known how the risk of metoclopramide-associated TD compares with the risk of TD from other antipsychotic drugs. Except for patients undergoing chemotherapy, most patients receiving metoclopramide generally receive doses much lower than those required to treat psychosis, which suggests that the risk for these patients may be lower. On the other hand, metoclopramide is often used for long periods in patients who might have a higher frequency of putative TD risk factors such as advanced age and diabetes. In addition, it is unclear why there are so few cases in the literature of TD associated with prochlorperazine maleate than with metoclopramide when, except for patients receiving chemotherapy for cancer, both are often prescribed at doses much lower than those required to treat psychosis. It is possible that metoclopramide is more likely to produce TD than other drugs that block dopamine. Until recently, TD was not associated with medications used outside of the practice of psychiatry. The case reports summarized above suggest that TD is no longer an iatrogenic disorder unique to psychiatry.

RECOMMENDATIONS

Our review suggests a number of clinical recommendations: (1) metoclopramide should be used with caution in patients who are at high risk of developing TD, eg, elderly or diabetic patients; (2) patients who require metoclopramide should be monitored at regular intervals for signs of TD; (3) if signs of TD appear, even if they are very mild, metoclopramide should be discontinued, if feasible.

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Practice Commentary

Metoclopramide, an effective drug in the treatment of emesis and gastrointestinal disturbances, is frequently prescribed by generalists. Seventy-one percent of all prescriptions are written by family physicians, internists, and general practitioners, and it is commonly used in our practice. Sewell and Jeste remind us of potentially serious side effects of the drug. It is important to note that the risk for TD increases with the duration of therapy and with age and that the incidence is higher in diabetics. It is discouraging that many cases were permanent. As practitioners, we can minimize the risk by carefully selecting patients, especially among the elderly, and limiting the duration of therapy. We should all be aware of the mild forms of TD, including those visible to the examiner but unrecognized by the patient, and discontinue the treatment if feasible when the symptoms appear.

This study again illustrates how poorly we understand the risks and benefits of many of our interventions. In spite of an exhaustive literature search and conscientious efforts on the part of the authors to obtain missing data, the incidence, prevalence, and duration of metoclopramide-induced TD is still poorly understood because of the limitations of the studies reviewed and the small sample size.

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