SCIENTIFIC SECTION

Family Practice

Adverse neurologic effects of metoclopramide

J. DAVID GRIMES,* MD, FRCP[C]
MOHAMED N. HASSAN,† MB, CH B, FRCP[C]
DAVID N. PRESTON,* MD, FRCP[C]

The incidence of drug-induced extrapyramidal disorders is increasing.[1] It is well known that neuroleptics may induce parkinsonism and tardive dyskinesia.[1,2] Metoclopramide hydrochloride, a nonphenothiazine compound, is frequently prescribed for a number of conditions, including nausea, vomiting, flatulent dyspepsia, gastroesophageal reflux and delayed gastric emptying.[3,4] Soon after metoclopramide became available its use became associated with a small risk of acute dystonic reactions.[5] Initially it was felt that the drug did not induce or exacerbate the more chronic types of extrapyramidal disorders.[6,7]

We studied a large group of patients with Parkinson's disease and other movement disorders who attended the Parkinson's disease clinic of the Ottawa Civic Hospital. We began to notice a frequent association between the long-term use of metoclopramide and a parkinsonian syndrome that was often followed by tardive dyskinesia when this treatment was stopped. We report our experience with 18 patients having both acute and chronic metoclopramide-induced disorders seen over a 2-year period.

Observations

We observed three types of extrapyramidal disorders in 18 patients being treated with metoclopramide (Table I).

Acute dystonic reactions

Four patients, all women between 53 and 55 years of age, experienced acute dystonic reactions consisting of gross spasmodic deviation of the eyes and head to one side, with hyperextension of the neck. They had been taking 20 to 40 mg of metoclopramide orally each day for periods of 1 to 10 days (average 5 days). When treatment with metoclopramide was stopped the dystonic movements ceased spontaneously within 12 to 24 hours in three of the patients. The other patient, who had chronic renal failure, required treatment with benztropine mesylate, 1 mg every 4 hours, for 16 hours before the abnormal movements ceased.

Illustrative case: A 55-year-old woman with hiatus hernia and reflux esophagitis was treated with metoclopramide, 10 mg four times a day. After 3 days of treatment she experienced gross twisting and jerking movements of her neck to the right side. The dose of metoclopramide was reduced to 5 mg four times a day, but the abnormal movements persisted for another 2 days. The drug was discontinued and the dystonic movements ceased spontaneously within 24 hours.

Parkinsonism

Parkinsonism, characterized by tremor, rigidity and bradykinesia, developed in 12 patients, 8 men and 4 women, aged 59 to 73 years. They had been receiving 15 to 40 mg of metoclopramide orally each day for periods of 2 weeks to 4 years (average 8.7 months).

In 10 of the 12 patients the disorder had been misdiagnosed as classic Parkinson's disease, and 6 had already been treated with levodopa for periods of 3 months to 2 years.

Metoclopramide hydrochloride is now commonly prescribed for a variety of gastrointestinal disorders. Over a 2-year period 18 patients with neurologic disorders induced by metoclopramide were assessed at the Parkinson's disease clinic of the Ottawa Civic Hospital. During metoclopramide therapy acute transient dystonic reactions were seen in 4 patients, and parkinsonism, which was frequently misdiagnosed and treated as classic Parkinson's disease, was seen in 12 patients. After treatment with metoclopramide was stopped, tardive dyskinesia appeared in seven patients and has persisted for up to 15 months in three patients. Parkinsonism and tardive dyskinesia occurred in older patients undergoing long-term therapy with metoclopramide. This experience, therefore, suggests that such treatment, especially in older patients, should be avoided.

From the Parkinson's disease clinic, division of neurology, Ottawa Civic Hospital and the University of Ottawa

*Assistant professor of medicine (neurology)
†Senior resident in neurology

Presented in part at the 15th Canadian Congress of Neurological Sciences, Ottawa, June 20, 1980

Reprint requests to: Dr. J. David Grimes, 1081 Carling Ave., Ste. 304, Ottawa, Ont. K1Y 4G2

When the metoclopramide was discontinued the parkinsonism cleared completely within 3 weeks in nine patients and within 4 months in one patient. The remaining two patients showed marked improvement at the time of follow-up but still showed features of parkinsonism; they probably had pre-existing mild classic Parkinson's disease, which was exacerbated by metoclopramide therapy.

Illustrative case: A 73-year-old man received metoclopramide, 10 mg twice a day, for 3 years for recurring nausea and vomiting of uncertain cause. One year after treatment was begun, parkinsonism developed. He was treated for 2 years with antiparkinsonian medications (levodopa, procyclidine hydrochloride and amantadine hydrochloride), without any significant improvement. When seen at the Parkinson's disease clinic he exhibited bradykinesia, bilateral resting tremor and dyskinetic mouth movements. When the metoclopramide and antiparkinsonian medications were discontinued the bradykinesia and tremor cleared within 2 weeks. The mouth movements, which are typical of tardive dyskinesia, worsened temporarily, but completely resolved in 2 weeks.

Tardive dyskinesia

In seven patients, four men and three women aged 65 to 76 years, who had been taking 20 to 40 mg of metoclopramide orally each day for periods of 14 months to 4 years, orobuccolingual dyskinetic movements developed when the metoclopramide was discontinued. This group included 5 of the 12 patients with parkinsonism. The other two patients had had no symptoms or signs of extrapyramidal dysfunction; the metoclopramide was discontinued because their gastrointestinal symptoms had lessened.

In four of the patients the abnormal involuntary movements ceased within 3 weeks after the end of metoclopramide treatment. In the remaining three patients dyskinetic facial and tongue movements were still present 15 months later; two patients obtained mild to moderate improvement with lecithin granules, 30 g/d, and in one patient haloperidol decreased the dyskinesia but worsened the parkinsonism and was therefore discontinued.

Illustrative case: A 72-year-old man had been taking metoclopramide, 10 mg twice a day, for 3 years for reflux esophagitis. One year after the start of metoclopramide therapy parkinsonism developed, characterized by rigidity, tremor and a tendency to run forward and fall. The metoclopramide was continued and he started taking levodopa–carbidopa (Sinemet); this regimen was followed for 2 years. The parkinsonism decreased slightly with Sinemet therapy, but he then began to have orobuccolingual dyskinetic movements associated with abnormal diaphragmatic movements that produced loud and most distressing involuntary grunting. The parkinsonism cleared completely within a few weeks after the metoclopramide and Sinemet were discontinued. However, 15 months after the metoclopramide was discontinued prominent orobuccolingual movements and the grunting were still present.

Discussion

Neuroleptic drugs, such as chlorpromazine and haloperidol, block central dopaminergic receptors and thus may induce parkinsonism. Prolonged blockade can result in receptor supersensitivity and tardive dyskinesia, usually after the drug has been discontinued. Metoclopramide, a chlorbenzamide derivative, initially appeared to be free of these effects, and it was postulated that it may have impaired access to central dopaminergic systems.[6] Subsequent studies,[8,9] however, clearly showed that metoclopramide blocks central dopaminergic receptors and can induce the same biochemical and behavioural changes as neuroleptics.

The incidence of acute dystonic reactions in patients taking metoclopramide is estimated at 1%.[5] Such patients present with combinations of neck pain, torticollis, retrocollis, ocular deviation and trimus. Children[10] and adults[11,12] have been affected, and initial erroneous diagnoses have included tetanus[11] and hysteria.[12] Fever,[13] which has been reported in some patients with metoclopramide-induced dystonia, could add to the diagnostic confusion by suggesting meningeal irritation.

Metoclopramide clearance is impaired in renal failure,[14] and this may increase the risk of acute dystonic reactions. Therefore, it has been suggested that the dose of metoclopramide be reduced by at least 60% in patients with severe renal impairment.[14]

Table I—Adverse neurologic effects of metoclopramide in 18 patients

Effect	Average age (yr) of patients	Dose (mg/d) of metoclopramide	Duration of treatment	Outcome
Acute dystonic reaction during treatment (n = 4)	54	20–40	1–10 d	Spontaneous clearance in 24 h in 3†
Parkinsonian syndrome during treatment (n = 12)	67	15–40	2 wk–4 yr	Clearance in 3 to 4 mo in 10; marked improvement in 2
Tardive dyskinesia after treatment was stopped (n = 7)*	72	20–40	14 mo–4 yr	Residual signs in 3 at 15 mo

*The seven patients include five of the patients with parkinsonism.
†The other patient, who had chronic renal failure, required treatment with benztropine mesylate for clearance of the abnormal movements.

Metoclopramide was initially felt to be safe for use in patients with Parkinson's disease.[6,7] After trials of a few weeks in such patients it was concluded that 30 mg/d of metoclopramide did not significantly worsen the parkinsonism and could be helpful in the management of levodopa-induced nausea and vomiting.

However, in our experience drug-induced parkinsonism seems to be the most frequent chronic neurologic problem related to long-term metoclopramide therapy. This disorder was seen in 12 of the 18 patients in our series and appeared to be more common in the older patients.

The first case of tardive dyskinesia occurring after the end of long-term metoclopramide therapy was reported in 1978.[15] A 48-year-old man had taken up to 80 mg/d of metoclopramide for 10 years. Severe orofacial dyskinesia developed whenever the metoclopramide was discontinued; when the drug was given again the involuntary movements ceased.

Subsequently three other patients were reported to have both parkinsonism and tardive dyskinesia after 1 to 5 years of metoclopramide therapy.[16] When the drug was discontinued the parkinsonism cleared within 3 months in one patient, but features of parkinsonism were still present 6 and 9 months later in the other two patients. The tardive dyskinesia was transient in two of the three patients, but one patient still had involuntary movements 9 months after the end of metoclopramide therapy.

A common problem in our experience has been that in a number of patients the parkinsonian syndrome has been diagnosed and treated as classic Parkinson's disease. At the time of referral 10 of our 12 patients with features of parkinsonism were considered to have Parkinson's disease and 6 were already receiving levodopa, though with minimal therapeutic effect. A careful drug history should be taken from all patients presenting with features of parkinsonism. If metoclopramide or a similar dopaminergic blocking agent is being used it should be discontinued and the patient observed for several weeks before any antiparkinsonian therapy is instituted.

Chronic, possibly irreversible, tardive dyskinesia is the most serious adverse effect we have encountered. It usually occurs after therapy with metoclopramide is stopped, but, as with neuroleptics, tardive dyskinesia develops only after many months to several years of therapy.[16] At present, the treatment of tardive dyskinesia is unsatisfactory. However, modest improvement may be obtained with lecithin.[17,18]

Conclusion

Our findings indicate that metoclopramide therapy may lead to several neurologic complications. Acute dystonic reactions may appear soon after metoclopramide therapy is started, but they clear promptly when it is stopped. Reversible parkinsonism may develop after weeks to months of metoclopramide therapy and may be mistaken for classic Parkinson's disease. After months to years of metoclopramide therapy potentially irreversible tardive dyskinesia may occur when the drug is discontinued.

Metoclopramide is intended for short-term use;[3] long-term therapy, especially in older patients, should be avoided. Its use also appears to be contraindicated in patients with Parkinson's disease. Because of its tendency to produce both acute and chronic movement disorders, metoclopramide should be used with the same caution and respect as neuroleptics.

We thank Dr. W. Grant Thompson, chief, division of gastroenterology, Ottawa Civic Hospital, for his valuable criticisms of the manuscript.

References

1. Critchley EMR: Drug-induced neurological disease. *Br Med J* 1979; 1: 862–865
2. Carpenter WT, Rey AC, Stephens JH: Covert dyskinesia in ambulatory schizophrenia. *Lancet* 1980; 2: 212–213
3. Thompson WG: *The Irritable Gut: Functional Disorders of the Alimentary Canal*, Univ Park, Baltimore, 1979; 169
4. Schulze-Delrieu K: Metoclopramide. *Gastroenterology* 1979; 77: 768–779
5. Robinson OPW: Metoclopramide: side-effects and safety. *Postgrad Med J* 1973; 49 (July): 77–80
6. Tarsy D, Parkes JD, Marsden CD: Metoclopramide and pimozide in Parkinson's disease and levodopa-induced dyskinesias. *J Neurol Neurosurg Psychiatry* 1975; 38: 331–335
7. Bateman DN, Kahn C, Legg NJ, Reid JL: Metoclopramide in Parkinson's disease. *Clin Pharmacol Ther* 1978; 24: 459–464
8. Stanley M, Rotrosen J, Lautin A, Wazer D, Gershon S: Tardive dyskinesia and metoclopramide (C). *Lancet* 1979; 2: 1190
9. Ahtee L: Inhibition by apomorphine of the metoclopramide-induced catalepsy and increase in striatal homovanillic acid content. *Br J Pharmacol* 1975; 55: 381–385
10. Casteels-Van Daele M, Jaeken J, van der Schueren P, Zimmerman A, van den Bon P: Dystonic reactions in children caused by metoclopramide. *Arch Dis Child* 1970; 45: 130–133
11. Cochlin DL: Dystonic reactions due to metoclopramide and phenothiazines resembling tetanus. *Br J Clin Pract* 1974; 28: 201–202
12. Daneshmend TK, Manning AP: Metoclopramide induced dystonic reactions misdiagnosed as hysteria. *Br J Clin Pract* 1978; 32: 334–335
13. Wandless I, Evans JG, Jackson M: Fever associated with metoclopramide-induced dystonia. *Lancet* 1980; 1: 1255–1256
14. Bateman DN, Gokal R: Metoclopramide in renal failure (C). Ibid: 982
15. Lavy S, Melamed E, Penchas S: Tardive dyskinesia associated with metoclopramide. *Br Med J* 1978; 1: 77–78
16. Kataria M, Traub M, Marsden CD: Extrapyramidal side-effects of metoclopramide (C). *Lancet* 1978; 2: 1254–1255
17. Ehrensing RH: Tardive dyskinesia. *Arch Intern Med* 1978; 138: 1261–1264
18. Growdon JH, Gelenberg AJ, Doller J, Hirsch MJ, Wurtman RJ: Lecithin can suppress tardive dyskinesia. *N Engl J Med* 1978; 298: 1029–1030

"Indigestion"

The longer I live, the more I am convinced that the apothecary is of more importance than Seneca; and that half the unhappiness in the world proceeds from little stoppages, from a duct choked up, from food pressing in the wrong place, from a vext duodenum, or an agitated pylorus.

— Sydney Smith (1771–1845)