

Clinical Differences Between Metoclopramide- and Antipsychotic-Induced Tardive Dyskinesias

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ABSTRACT: A patient with tardive dyskinesia dominated by pelvic thrusting movements is described. A retrospective review of the clinical features documented in patients with metoclopramide- and antipsychotic-induced tardive dyskinesias seen over a six year period demonstrated that the occurrence of pronounced pelvic thrusting and respiratory dyskinesias were significantly more common in the metoclopramide treated group. The occurrence of bucco-linguo-masticatory movements, limb stereotypies or chorea, and mild truncal or abdominal rocking were not significantly different between the two groups. None of the tardive dystonia patients had metoclopramide as the causative agent. These findings will require confirmation in larger, better matched patient populations. Whether the differences relate to different pharmacologic profiles of drug action, patient populations exposed, or other factors, remains to be elucidated.

RÉSUMÉ: Différences cliniques entre les dyskinésies tardives induites par le métoclopramide et les antipsychotiques Nous décrivons le cas d'un patient présentant des dyskinésies tardives dont l'élément principal consistait en des mouvements de projection du bassin. Une revue rétrospective des manifestations cliniques observées chez les patients présentant des dyskinésies tardives induites par le métoclopramide et les antipsychotiques et ayant consulté sur une période de six ans, a démontré que l'apparition de mouvements marqués de projection du bassin et de dyskinésies respiratoires était significativement plus fréquente dans le groupe recevant du métoclopramide. L'apparition de mouvements bucco-linguo-masticatoires, de stéréotypies ou de chorée des membres et d'un léger bercement du tronc ou de l'abdomen n'était pas significativement différente chez les deux groupes. Le métoclopramide n'était l'agent causal chez aucun des patients présentant une dystonie tardive. Ces observations demandent confirmation dans des populations de patients plus grandes et mieux appariées. Il reste à déterminer si les différences observées ont trait à des profils pharmacologiques différents de l'activité de ces médicaments, à des différences entre les populations de patients exposés ou à d'autres facteurs.

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All of the so-called "extrapyramidal" side effects of neuroleptic drugs have now been reported with metoclopramide. To date, there is little to suggest that the characteristics of these side effects differ from those seen with more typical neuroleptics. One exception may be the reported higher incidence of acute dystonic reactions in females treated with metoclopramide¹ in contrast to the well-recognized predisposition of young males to this complication with antipsychotic drugs.² The first case of tardive dyskinesia due to metoclopramide was reported in 1978.³ Since then, a number of cases have been mentioned in the literature.^{1,4-24} There has been no evidence presented to date suggesting that the clinical manifestations of tardive dyskinesia due to metoclopramide differ in any way from those due to neuroleptic drugs. The recent review of a patient with metoclopramide-induced tardive dyskinesia dominated by pelvic thrusting movements ("copulatory dyskinesias" a term adopted from reference 4) prompted a retrospective analysis of the clinical features of tardive syndromes seen over the last six years. The

results of this survey suggest that some clinical differences do exist between the tardive syndromes caused by metoclopramide and antipsychotics.

CASE REPORT

This 74-year-old woman had been treated with metoclopramide 10 mg tid for a one year period for symptoms of a hiatus hernia. Her past history included diabetes controlled by diet, distant cervical spine injury, mastectomy for carcinoma of the breast, and herpes zoster involving the left leg. Eight months prior to her first assessment, she had the subacute development of pelvic rocking movements which interfered with her ability to lie, sit or stand still. She also noted some general slowing of activity and softening of her voice. She denied any other neurological symptoms.

On examination, she had a masked facies, mild limb and axial rigidity, marked bradykinesia and poor postural stability. There were repetitive, at times rhythmic, movements occurring approximately once per second involving bilateral quadriceps and tensor fasciae latae synchronously with paraspinous muscles. Contractions of adductor magnus and biceps femoris alternated with those in quadriceps. These move-

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Table 1: Patient Details and Clinical Features of Tardive Dyskinesias**

	Metoclopramide	Antipsychotics	
n	9	33	
Sex F/M	8/1	20/13	NS
Age (range)	75.2 (72-79)	58.6 (21-83)	NS
<i>Movements</i>			
Bucco-linguo-facial	8/9	29/33	NS
Limb Chorea/Stereotypy	4/9	22/33	NS
Dystonia*	2/9	12/33	NS
Pelvic Thrusting	6/9	4/33	p < 0.001#
Respiratory Dyskinesia	5/9	6/33	p < 0.01 #
Akathisia	3/9	6/33	NS
Other Trunk/Abdominal	1/9	4/33	NS

**Statistics using Student's t-test and chi square analysis where appropriate. NS = not significant.

*Dystonia as a minor clinical feature (i.e. excludes cases where dystonia predominated — tardive dystonia)

#Of the 20 patients classified as having Tardive Dystonia (all due to antipsychotics) 2 had respiratory dyskinesias and none had pelvic thrusting. If these cases are included and the comparison is made between all tardive syndromes due to metoclopramide (n = 9) and all cases due to neuroleptics (n = 53) the differences listed in the table (#) remain unchanged.

ments resulted in repetitive forward thrusting of the pelvis. Occasionally, the movements were more prolonged or sustained in a dystonic fashion. There were additional diaphragmatic movements and platysma contractions at approximately the same frequency as the pelvic movements.

Withdrawal of metoclopramide initially resulted in a worsening of the pelvic rocking, but then a slow improvement. Friends commented on an improvement in her voice and speed of voluntary movement. Assessment three months after the first visit revealed a questionable reduction in pelvic rocking (she was quite anxious at the time), mild orofacial dyskinesias not present earlier and pacing movements of the feet while standing. Over the subsequent two years, she continued to improve noting only mild pelvic rocking when anxious or under stress.

PATIENTS, METHODS AND RESULTS

The charts of all patients with a diagnosis of a tardive syndrome seen at the Toronto Western Hospital Movement Disorders Clinic from its opening in mid-1982 until June 1988 were reviewed. All patients had been seen and documented by the author. The dominant movement disorder had been characterized as "classical" (choreatic) tardive dyskinesia or tardive dystonia as defined by Burke et al.²⁵ In all cases, extensive descriptions of the movement disorders were available, outlining the distribution and nature of the abnormal movements seen.

Table 1 outlines the patient data. A total of 42 patients with "classical" tardive dyskinesia had been seen, nine induced by metoclopramide and 33 caused by a variety of antipsychotic drugs. There were no differences in sex or age between these two groups (Table). Twenty patients had tardive dystonia and in all of these cases, the causative agent was an antipsychotic drug. The tardive dystonia group was younger (mean age 36.1 years, range 22-50) and contained more males than females (13:7) (in contrast to the other tardive dyskinesia groups). Because of the differences between the tardive dystonia and tardive dyskinesia populations, the former cases were excluded from further analysis.

The Table outlines a comparison of the clinical features in the two groups with tardive dyskinesia. Pelvic thrusting and respiratory dyskinesias were significantly more common in the metoclopramide group. The frequency of dystonia as a minor component of the movement disorder was no different in the two classical tardive dyskinesia subgroups (i.e. antipsychotics vs metoclopramide). However, in none of the metoclopramide cases did dystonia predominate (i.e. tardive dystonia). There were no other significant differences in the frequencies of various types of abnormal movements accompanying the tardive dyskinesia syndromes.

DISCUSSION

There are a number of reports of tardive dyskinesia due to metoclopramide in the literature.^{1,3,4,24} However, it is extremely difficult to provide an accurate number of the cases reported since some authors have published more than once on the topic and several cases come from country-wide surveys which probably include previously reported patients. Most cases have been poorly described clinically. As expected, and confirmed by the present study, bucco-linguo-masticatory movements predominate. Only rarely are other abnormal movements commonly seen in tardive dyskinesia syndromes mentioned. Interestingly in the second report of tardive dyskinesia due to metoclopramide, one of the three patients demonstrated prominent "repetitive 'copulatory' rocking movements of the pelvis and the lumbar spine" and another patient had involuntary contraction of anal and vaginal muscles.⁴ In a report by Grimes and his colleagues in 1982,⁶ the only one of seven patients who was described in detail had respiratory dyskinesia and grunting in addition to orofacial dyskinesias. Board reported a woman developing transient pelvic rocking movements after several courses of high-dose parenteral metoclopramide.¹⁵ The only case of metoclopramide-induced tardive dyskinesia mentioned in a report by Pall and Williams also suffered from pelvic dyskinesias.²⁰ Finally, the case report of Samie et al²³ demonstrated respiratory and pelvic dyskinesias as part of a severe metoclopramide-induced movement disorder. This limited experience may support the finding of a higher incidence of pelvic and respiratory dyskinesias in this group. The second finding of the current survey was the lack of cases of metoclopramide-induced tardive dystonia. Review of the literature reveals that there have been no examples of well documented tardive dystonia due to metoclopramide reported to date.

The causes for the clinical differences between tardive syndromes induced by metoclopramide and antipsychotic drugs remain to be elucidated. One possible explanation is the difference in the pharmacological profile of metoclopramide compared to classical antipsychotic drugs. For example, although both block central dopamine receptors, in contrast to most neuroleptics, metoclopramide is a pure D2 receptor antagonist with rather weak binding properties as demonstrated by an IC50 for spiperone binding which is 10-100 times greater than that of classical neuroleptics.²⁶ Another explanation might relate to differences in patient populations exposed to the drugs, as has been proposed for antipsychotic-induced tardive dyskinesia.²⁷⁻²⁹ Certain undefined patient characteristics may have predisposed the metoclopramide patients to the greater likelihood of "copulatory" and respiratory dyskinesias while predisposing

those exposed to antipsychotics to dystonia. However, it must be emphasized that the retrospective nature of this survey is a source of several potential confounding variables. Differences in referral patterns, for example between gastroenterologists and psychiatrists, could have been important but unlikely in view of the broad referral base of our clinic and the easy accessibility of health care through government supported health insurance. The predominance of elderly women in the metoclopramide group is of some concern even if there were no significant differences in age and sex between the two tardive dyskinesia populations. The age of the population exposed to the causative drug may also account for the lack of cases with predominant dystonia (i.e. tardive dystonia) in the metoclopramide group. It is still possible that the dominant symptom has as much to do with the age of the patient exposed as it does with the agent. Further assessment of larger numbers of more closely matched patients, ideally in prospective fashion, is required to confirm the findings reported here. The increasing awareness of the potential complications of long-term metoclopramide therapy and the availability of domperidone in Europe and Canada may make the completion of such a study problematic.

REFERENCES

- Bateman DN, Rawlins MD, Simpson JM. Extrapyramidal reactions with metoclopramide. *Br Med J* 1985; 291: 930-932.
- Swett C. Drug-induced dystonia. *Am J Psychiatry* 1975; 132: 532-534.
- Lavy S, Melamed E, Penchos S. Tardive dyskinesia associated with metoclopramide. *Br Med J* 1978; 1: 77-78.
- Kataria M, Traub M, Marsden CD. Extrapyramidal side-effects of metoclopramide. *Lancet* 1978; 2: 1254-1255.
- Stanley M, Ortosen J, Lautin A, et al. Tardive dyskinesia and metoclopramide. *Lancet* 1979; 2: 1190.
- Grimes JD, Hassan MN, Preston DN. Adverse neurologic effects of metoclopramide. *Can Med Assoc J* 1982; 126: 23-25.
- Grimes JD, Hassan MN, Krelina M. Long-term follow-up of tardive dyskinesia due to metoclopramide. *Lancet* 1982; 2: 563.
- Indo T, Ando K. Metoclopramide-induced parkinsonism: Clinical characteristics of 10 cases. *Arch Neurol* 1982; 39: 494-496.
- Wiholm B-E, Mortimer O, Boethius G, Haggstrom JE. Tardive dyskinesia associated with metoclopramide. *Br Med J* 1984; 288: 545-547.
- Orme ML'E, Tallis RC. Metoclopramide and tardive dyskinesia in the elderly. *Br Med J* 1984; 289: 397-398.
- Leopold NA. Prolonged metoclopramide-induced dyskinetic reactions. *Neurology (Cleveland)* 1984; 34: 238-239.
- Shearer RM, Bownes IT, Curran P. Tardive akathisia and agitated depression during metoclopramide therapy. *Acta Psychiatr Scand* 1984; 70: 428-431.
- Jankovic J, Glass JP. Metoclopramide-induced phantom dyskinesias. *Neurology* 1985; 35: 432-435.
- Breitpart W. Tardive dyskinesia associated with high-dose intravenous metoclopramide. *N Engl J Med* 1986; 315: 518.
- Board AW. Tardive dyskinesia associated with high-dose intravenous metoclopramide. *N Engl J Med* 1986; 315: 518-519.
- Patterson JF. Choreiform movement associated with metoclopramide. *South Med J* 1986; 79: 1465.
- Beauchair L, Fontains R. Tardive dyskinesia associated with metoclopramide. *Can Med Assoc J* 1986; 134: 613-614.
- Lazzara RR, Stoudemire A, Manning D, et al. Metoclopramide-induced tardive dyskinesia: A case report. *Gen Hosp Psych* 1986; 8: 107-109.
- Patel M, Louis S. Long-term neurologic complications of metoclopramide. *NY State J Med* 1986; 86: 210.
- Pall HS, Williams AC. Extrapyramidal disturbances caused by inappropriate prescribing. *Br Med J* 1987; 295: 30-31.
- Mahler JC, Brown RP. More on metoclopramide and tardive dyskinesia. *N Engl J Med* 1987; 316: 412.
- Board AW. More on metoclopramide and tardive dyskinesia. *N Engl J Med* 1987; 316: 412-413.
- Samie MR, Dannenhoffer MA, Rozek S. Life-threatening tardive dyskinesia caused by metoclopramide. *Movement Disorders* 1987; 2: 125-129.
- Yamamoto M, Ujike H, Ogawa N. Metoclopramide-induced parkinsonism. *Clin Neuropharmacol* 1987; 10: 287-289.
- Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: Late-onset and persistent dystonia caused by antipsychotic drugs. *Neurology* 1982; 32: 1335-1346.
- Hassan MN, Reches A, Kuhn C, et al. Pharmacologic evaluation of dopaminergic receptor blockade by metoclopramide. *Clin Neuropharmacol* 1986; 9: 71-78.
- Kane JM, Woerner M, Borenstein M, et al. Integrating incidence and prevalence of tardive dyskinesia. *Psychopharmacol Bull* 1986; 22: 254-258.
- Waddington JL, Youssef HA. An unusual cluster of tardive dyskinesia in schizophrenia: Association with cognitive dysfunction and negative symptoms. *Am J Psychiatry* 1986; 143: 1162-1164.
- Chouinard G, Annabele L, Mercier P, et al. A five-year follow-up study of tardive dyskinesia. *Psychopharmacol Bull* 1986; 22: 259-263.