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Clinical Topics

Tardive dyskinesia associated with metoclopramide

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Abstract

Eleven cases of tardive dyskinesia associated with metoclopramide have been reported to the Swedish Adverse Drug Reactions Advisory Committee from 1977 to 1981, 10 of which developed during the past three years. All patients were women, with a mean age of 76 years. Median duration of treatment before the onset of symptoms was 14 months. Calculated from total drug sales and prescription statistics the incidence of tardive dyskinesia during treatment with metoclopramide was estimated to be one in 2000-2800 treatment years. Extrapolation of data on long term treatment (more than six months) of patients aged 70 years or more, from a survey based on individual prescriptions yielded an incidence of more than one in a 1000 patients.

Long term treatment with metoclopramide is accompanied by a substantial risk of developing tardive dyskinesia especially among elderly people.

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Introduction

Metoclopramide stimulates peristalsis of the oesophagus and the intestine and accelerates gastric emptying.¹ It also has the ability to block central dopaminergic receptors.¹ Because of these properties metoclopramide has been used in gastroenterology and as an antiemetic. Neurological side effects such as acute dystonia may occur at the start of treatment,¹ and reversible Parkinsonism later. The first report of a more serious long term complication, tardive dyskinesia, was published in 1978 in this journal,² and was soon followed by more cases.³ An analysis of reports to the Swedish Adverse Drug Reactions Advisory Committee in relation to data on sales and prescriptions during the past years indicate that this serious complication of treatment with metoclopramide may well be more frequent than hitherto recognised.

Methods and materials

Voluntary reporting of suspected adverse drug reactions to the Swedish Adverse Drug Reactions Advisory Committee started in 1965, and since 1975 the reporting of fatal, otherwise serious, and new reactions are compulsory. The reports are scrutinised by a medical officer and discussed by a working party, and the probability of a causal relation is finally settled by the full committee, which has representatives from many clinical specialties. Since 1972 total drug sales, expressed as value, volume, or so called defined daily doses⁴—have been provided by the National Corporation of Swedish Pharmacies. Since 1974 this corporation has also run a continuous prescription survey where the patient's age and sex, and the name, amount, and dosage of the drug are recorded from a random one in 288 sample of all prescriptions dispensed from the pharmacies.⁵ Individual drug purchases are provided from the county of Jämtland, where all purchases have been recorded for a random one seventh of the population since 1970.⁶

Results

ADVERSE REACTIONS

During the period 1977 to 1981 the Swedish Adverse Drug Reactions Advisory Committee received 37 reports of neurological complications arising during treatment with metoclopramide, and 11 of these were compatible with the syndrome tardive dyskinesia. Most commonly the symptoms consisted of orofacial involuntary movements (buccolingual masticatory syndrome). All 11 patients were women, with a mean age of 76.5 years. The prescribed daily doses ranged from 10 to 60 mg and were often variable but all patients had taken at least 30 mg a day during parts of their treatment. Median duration of treatment before the onset of symptoms was 14 months (range four to 44), but in four cases tardive dyskinesia developed within six months. In three cases it appeared after withdrawal of metoclopramide and in eight cases during treatment. Table I shows the data on the patients. The relation between the adverse symptoms and metoclopramide was often not recognised immediately, so median duration of metoclopramide treatment was 24 months (four to 50). In two cases the symptoms improved after treatment, with thioridazine in one case and metoclopramide in the other, but in the other cases the symptoms remained during the follow up period (one to 17 months, median seven months).

ESTIMATES OF INCIDENCE OF TARDIVE DYSKINESIA 1977-81

Based on total sales figures the overall incidence of reported tardive dyskinesia was 11 in 11 million prescribed daily doses, which equals one in 2760 patient years. When related to outpatient prescriptions of metoclopramide tablets the incidence was one in 17 800 prescriptions. With an average treatment time of 42 days this estimate can be expressed as one in 2050 patient years.

Extrapolation from Jämtland to the whole of Sweden of the number of people aged 70 years or more who were taking the drug for at least six months yields a "population at risk" of less than 10 000, and the incidence would then be higher than one in 1000 as 10 of the cases belong to this age group.

Discussion

The first two cases of tardive dyskinesia occurring during treatment with metoclopramide and reported in Sweden were published in February 1981,⁷ and a warning based on an additional three cases was sent out by the Swedish Adverse Drug Reactions Advisory Committee in June the same year.⁸ During the next six months five more cases were reported and, on retro-

TABLE I—Details of patients developing tardive dyskinesia after treatment with metoclopramide

Case No	Sex	Age (yr)	Dose (mg/day)	Duration of treatment (months)	Time until onset of symptoms (months)	Symptoms and comments	Duration of follow up (months)
1	F	74	30-40	24	6	Buccolingual masticatory syndrome; hyperkinesia of neck and trunk; accentuation of symptoms after drug withdrawal	1
2	F	71	30-60	30	20	Buccolingual masticatory syndrome; hyperkinesia of head and shoulders	10
3	F	84	30	21	6	Buccolingual masticatory syndrome	9
4	F	71	40	4	4	Buccolingual masticatory syndrome; follow up 17 months	17
5	F	77	10-30	22	12	Buccolingual masticatory syndrome	3
6	F	86	30	44	44	Parkinsonism discovered during treatment; drug withdrawn and she immediately developed buccolingual masticatory syndrome and hyperkinesia of head, trunk, and extremities	1
7	F	72	30	15	16	Parkinsonism developed during treatment; metoclopramide withdrawn and one month later developed buccolingual masticatory syndrome but Parkinsonism improved	7
8	F	78	20-60	3.5	4	Few years ago cerebrovascular lesion with hemiplegia of left side as sequelae; two weeks after withdrawal of drug developed involuntary movements of right eyelid and buccolingual masticatory syndrome	2
9	F	69	20-30	34	14	Buccolingual masticatory syndrome and akathisia; metoclopramide withdrawn and thioridazine given instead; two months later improvement of symptoms	2
10	F	86	30	28	24	Buccolingual masticatory syndrome	8
11	F	73	60	~50	36	Buccolingual masticatory syndrome; metoclopramide temporarily withdrawn but she improved only at resumption of treatment; after withdrawal no development of tardive dyskinesia	3

Follow up = time from withdrawal of metoclopramide to date of report.

TABLE II—Sales and prescriptions of metoclopramide in Sweden 1977-1981

	1977	1978	1979	1980	1981	Mean
Total sales in PDD × 10 ⁶ (PDD = 30 mg)	1.79	2.01	2.46	2.51	2.20	2.19
No of prescriptions × 10 ³ (10 mg tablet)	30.0	33.4	42.4	53.9	36.0	39.1
Treatment time (days) per prescription (30 mg/day)	38	42	43	42	45	42

PDD = Prescribed daily doses.

SALES AND PRESCRIPTIONS

Table II shows data on sales and prescriptions of metoclopramide in Sweden 1977-81. During this period an average of 39 000 prescriptions were dispensed each year, the average daily dose prescribed was 30 mg, and the average duration of treatment was 42 days for each prescription. Thirty per cent of the prescriptions were issued to patients aged 70 years or more, and 63% were issued to women.

In Jämtland total sales of metoclopramide were about the same (85%) as in Sweden as a whole. The age and sex distributions of the patients were also representative. From the sample data it could be calculated that 1400 patients had purchased metoclopramide during these five years. Single purchases dominated (71%) and only 11% had made four or more purchases. In the sample there were 20 patients who had purchased metoclopramide four times or more and 18 of these had been prescribed amounts large enough for treatment for at least six months (mean 10, SD four months) during this five year period. Twelve of these 18 were aged 70 years or more (mean 74, SD 12 years) and 11 were women. From this we calculated that 0.3% of the male and 0.8% of the female population aged 70 years or more in Jämtland could have taken metoclopramide for at least six months.

spective analysis, another case of tardive dyskinesia, already reported in 1977 as "extrapyramidal disturbance," was found. This illustrates the natural course of spontaneous reporting of new serious adverse drug reactions and the importance of repeated information. Previous analyses have shown that only 20 to 40% of the classical serious adverse reactions—for example, Stevens-Johnson's syndrome and blood dyscrasias, have been reported to the committee.^{9 11}

The true incidence of tardive dyskinesia during or after long term treatment with metoclopramide is therefore not known, nor are there any exact figures of the population at risk or of critical exposure. The estimate of reported incidence based on total sales figures and the number of outpatient prescriptions are probably too low, as metoclopramide is used mostly for short periods only. Incidence based on extrapolation of data from Jämtland is uncertain because of the small size of the sample. A much larger population must therefore be studied before any firm conclusions on the real incidence can be drawn. These data, however, clearly indicate that tardive dyskinesia

can be a more common complication of long term treatment with metoclopramide than has been recognised hitherto.

Ten out of the 11 women described were over 70 years of age. Age is an important predisposing factor in the development of tardive dyskinesia during treatment with neuroleptics and is associated not only with increased prevalence and severity but also with decreased frequency of improvement.¹² Only 30% of patients who had taken metoclopramide in Sweden were 70 or over, but two thirds of those receiving long term treatment in Jämtland were over 70. Thus it seems as if the elderly, who are especially sensitive to tardive dyskinesia are also given long term treatment more often than are younger patients.

Women seem to have higher overall prevalence of tardive dyskinesia than men.¹³ This sample is too small, however, to draw any firm conclusions. Moreover, tardive dyskinesia has previously been reported also in men in association with metoclopramide.^{2 3 14}

Few of these patients had also taken concomitant drugs known to induce tardive dyskinesia, and neither the doses nor the exposure time were sufficient to consider them responsible for the reactions. Elderly people may develop spontaneous oral dyskinesias resembling tardive dyskinesia without having a history of exposure to neuroleptics¹³ and some of these cases may therefore be coincidental. The incidence of spontaneous dyskinesia in the elderly, however, is about 5% (19 untreated samples totalling 11 000 patients) and compares with about 20% in patients treated with neuroleptics (56 studies including nearly 35 000 subjects).¹³ This indicates that taking neuroleptics is an important risk factor. Moreover, spontaneous dyskinesia was seen almost exclusively in patients with concomitant organic brain dysfunction like epilepsy, senile dementia, etc.

The risk of developing tardive dyskinesia should be considered when long term treatment with metoclopramide is contemplated. Available data on sales and prescriptions also indicate that this risk may well be higher than hitherto recognised. Thus metoclopramide should not be prescribed especially to the elderly for long term treatment of minor illnesses or symptoms.

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MATERIA NON MEDICA

Wot, no doctors?

Crowds are enjoying the splendid new 20th century collection at the National Portrait Gallery. Marina Vaizey complained in the *Sunday Times* of the limited range of subject: "industrial, financial and union power is practically invisible . . . as though we were a society made up of politicians, academics, artists and entertainers." This is unfair: there is a large section on labour and the trade unions, and industry is well represented by such household names as Austin, Bentley, Bowater, Burtin, Ferguson, de Havilland, ICI (Melchett), Marks and Spencer (Sieff), Morris (Nuffield), Rootes, and Selfridge. She may have missed these sections because of the cunning space saving turntables, a system allowing four different displays to rotate in turn to the viewer.

I found only one subject omitted. Naturally there are dozens of painters, whole walls of musicians, and every kind of entertainer, but there is no section on medicine. Yes, as the carousel turned on the science section I caught glimpses of a trio of physiologists (Adrian, A V Hill, Sherrington), and a sprinkling of pathologists (Almroth Wright, Bedson, Chain, Colebrook, Fleming, Florey, Krebs, Spilsbury). There are a couple of "women helpers" (Grantly Dick Read and Marie Stopes), and at a pinch I could include two deserters from medicine, for literature (Somerset Maugham) and painting (Henry Lamb), but there are no doctors at all, not one clinician in our national hall of fame's top 500 of the century.

Perhaps the *BMJ* should run a competition like "My 100 Best Novels" to nominate 20 doctors of the 20th century? Of course the NPG should show Tony Hancock and Max Wall; but why not Thomas Horder and Moynihan?—J H BARON, consultant physician, London.

Beer, bedding, and afterbirths

A horticultural reference in a recent Personal View evoked a clear mental picture of a blossomless and peerless pear tree I acquired long ago on moving house. So, in the autumn, I treated it to two placentas, burying one on its western and the other on its eastern side. The next blossoming led to such a heavy pear crop that only ruthless thinning saved the branches.

One sparked memory leads to another and I remember the National Dried Milk tins, each accommodating one afterbirth, which were deposited on the surgery door step by kindly district midwives who shared my view that it was profligate to waste such protein rich sources; I buried their contents deep in my compost bin. Liberal application of the result enabled the growth of splendid vegetables by the "no digging" gardening method.

Another horticultural tip of less medical flavour—though it was acquired by my uncle, Dr Christopher Clayson, when he was visiting a Newcastle brewery to discuss his ideas on licensing reform—is upon the nurture of leeks. In autumn dig out a trench of sufficient size and in it bury a hair mattress.* In spring plant out your leeklets above it, and to achieve prize winning size each plant should be watered with half a gallon of stale beer weekly. Eventually I had the opportunity to carry out these instructions: firstly, a neighbour threw out a mattress and, secondly, a five gallon bin of home brew went wrong. It was sufficient to treat a short row and they grew to treble the size of their already large peers.

The following spring I watered my only row of leek seedlings with the diluted lees of a batch of home brew, thinking to build up their strength before planting them out. All but three died, which surely indicates some moral.—BEVIL COWAN, Burton-in-Wirral, Cheshire.

* Very best results are obtained from specimens with high nitrogen content (CWC, personal communication).