Extrapyramidal reactions with metoclopramide

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Abstract

The epidemiology of extrapyramidal reactions to metoclopramide was studied by examining reports in the Adverse Reactions Register of the Committee on the Safety of Medicines and comparing these with prescribing figures by general practitioners in the United Kingdom for metoclopramide (Maxolon). In the period 1967-82 there were an estimated 15·9 million prescriptions and 479 reports of extrapyramidal reactions (455 of dystonia-dyskinesia, 20 of parkinsonism, and four of tardive dyskinesia). When corrected for prescribing rates the relative risk of dystonia and dyskinesia was 1·8 in female compared with male patients (95% confidence interval 1·4-2·2). The overall reporting rate for dystonia and dyskinesia was 28·6/million prescriptions but was significantly more common in young adults ($p < 0·0001$) and especially girls and women aged 12-19 (190·7 reports/million prescriptions). By contrast parkinsonian reactions were significantly more common in the elderly ($p < 0·0001$).

Introduction

Extrapyramidal reactions are well recognised adverse effects of drugs with dopamine receptor antagonist properties. With phenothiazine neuroleptic drugs the frequency of extrapyramidal reactions seems to correlate with their antipsychotic potency, and dystonic and dyskinetic symptoms occur most often in patients aged under 45 years.[1] Since the introduction of metoclopramide (a selective D_2 dopamine antagonist) as an antiemetic drug in 1967 numerous reports have been published about an association between its administration and the occurrence of various extrapyramidal reactions,[2-6] but little attempt has been made to study their epidemiology. We have therefore examined reports of extrapyramidal adverse reactions associated with metoclopramide contained in the Adverse Reactions Register of the Committee on the Safety of Medicines together with prescribing data by general practitioners in the United Kingdom provided by Intercontinental Medical Statistics Limited.

Patients and methods

All reports (yellow cards) of extrapyramidal reactions contained in the Adverse Reactions Register of the Committee on the Safety of Medicines for the years 1964-82, when metoclopramide was the suspected drug, were examined: patients' age and sex were recorded together with details of the reaction, prescribed dose and route, indication, time of onset of the reaction, outcome, and concomitant treatment with drugs. The reaction interval was determined from the date and time of prescription or administration to the date and time of onset of the reaction. As dystonias (including oculogyric crisis and opisthotonos) and acute dyskinesias (including orofacial dyskinesias) often occurred simultaneously and had a similar reaction interval and distribution of age and sex we have categorised these together as dystonic-dyskinetic reactions.

Prescribing data by general practitioners for metoclopramide were generously provided by Intercontinental Medical Statistics Limited. As 95% of prescriptions in general practice for metoclopramide are for Maxolon only prescriptions for this preparation have been used. Analysis of prescriptions by sex and age (in groups 0-4, 5-11, 12-19, 20-39, 40-54, 55-64, and 65 years or more) was available to us. Reporting rates of adverse reactions are expressed per million prescriptions. We have assumed that these are proportional to the population incidences and that repeat prescriptions are unlikely to be represented more commonly in one particular age and sex group.

Reporting rates of adverse reactions were compared for different ages and sexes by taking the logit of the proportion of reported reactions in each age and sex group and fitting a series of generalised linear models with a binomial error.[7] Thus effects of age and sex (and any interaction between age and sex) could be tested for significance using an analysis of deviance, in which differences between deviances from successive models are compared with a χ^2 distribution.

Results

The Adverse Reactions Register of the Committee on the Safety of Medicines contained 479 reports of extrapyramidal reactions for the period under study, when metoclopramide was the suspected drug: 455 were of dystonic-dyskinetic reactions, 20 of parkinsonism, and four of tardive dyskinesia. The number of reports increased from one during 1967 to a maximum of 79 reports in 1977 and then declined (table I). During the period 1967-77 the number of prescriptions increased from 46 000 to 1·6 million, and the increase in prescriptions seems to have paralleled the increase in reports of adverse reactions during this time. An estimated 15·9 million prescriptions were made for metoclopramide (Maxolon) from 1967 to 1982, of which 60·4% were for female patients.

ACUTE DYSTONIC-DYSKINETIC REACTIONS

Of the 455 reports of acute dystonic-dyskinetic reactions, 318 (70%) occurred in female patients. Patients' ages were recorded in 436 reports and most of these adverse effects developed in those aged 10-29 years (table II). Dystonic-dyskinetic reactions often developed within 24 hours of starting treatment, and 406 (94%) occurred within 72 hours—that is, 257 reports were made within a day, 121 within two, 28 within three, seven within four, nine within five, one each within seven and eight, three within 14, and five after 14 days. All patients recovered, with or without specific treatment, except for one male patient who died on the way to hospital while suffering a dystonic reaction. In 116 reports other drugs were recorded as being prescribed at the same time as metoclopramide (table III).

Table IV shows the reporting rates per million prescriptions. No significant difference in reporting rates existed in groups over the age of 40 years, and these have been pooled for each sex. A highly significant difference in reporting rates existed for the age groups 0-4, 5-11, 12-19, 20-39, and over 40 years after allowing for sex ($\chi^2_4 = 597$; $p < 0·0001$) and also for sex when allowing for age ($\chi^2_1 = 31·16$; $p < 0·0001$). The overall relative risk of a reported reaction for female *v* male patients was 1·8 (95% confidence interval 1·4 to 2·2). Those in the age group 12-19 years had the highest risk, with reporting rates of 109·1 per million prescriptions for male and 190·7 per million for female patients, while the lowest rates were 3·5 per million and 4·2 per million, respectively, in patients aged 65 years and over.

A substantial proportion of patients were receiving doses of metoclopramide in excess of those recommended by the manufacturers (table V). The proportion of patients receiving a relative overdosage fell significantly with age (for linear trend with age $\chi^2_1 = 49·23$; $p < 0·0001$) and did not parallel the age and sex pattern of adverse reporting rates as there was no significant effect of sex on the prescribed

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TABLE I—*Annual reporting rates of extrapyramidal adverse reactions to metoclopramide and annual prescribing figures*

Year:	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982
Reports	1	2	3	4	3	19	22	28	40	52	79	76	59	32	28	25
Prescriptions (thousands)	46	93	160	251	336	631	783	1122	1256	1543	1646	1579	1635	1645	1600	1611

dose in patients with acute dystonia-dyskinesia ($\chi^2_1 = 2{\cdot}51$; NS). Twenty one patients (14 female) received metoclopramide parenterally, but only one received "high dose" metoclopramide to prevent nausea and vomiting associated with treatment with cytotoxic drugs.

The reasons for treatment with metoclopramide were recorded in 333 reports (104 male). The principal indications were nausea and vomiting (263 cases), specific gastrointestinal disorders (54), migraine (nine), and cytotoxic treatment (six).

TABLE II—*Reports of dystonia-dyskinesia (1967-82) by age and sex*

Age band (years)	Male patients	Female patients
0-9	17	20
10-19	62	139
20-29	20	87
30-39	15	29
40-49	3	10
50-59	5	10
60-69	2	7
70 and over	3	6

TABLE III—*Other drugs prescribed to 116 patients suffering from dystonic-dyskinetic reactions and to nine patients suffering from parkinsonism*

	Dystonia-dyskinesia	Parkinsonism
Antibacterials	36	
Antacids	24	
Opioid analgesics	17	3
Non-steroidal anti-inflammatory drugs + paracetamol	11*	
Oral contraceptive steroids	11	
Benzodiazepines	9	
Cytotoxics	7	2
Major tranquillisers	7	1
Diphenoxylate and atropine	5	
Purgatives	5	
β Adrenoceptor antagonists	3	
Salbutamol	3	
Antidiarrhoeals	3	
Lithium	2	
Cimetidine		2
Tricyclics	1	1
Others	6†	

*Four combination tablets: two Paramax, two Migravess.
†One each of hydralazine, digoxin, betahistine, insulin, and Migril and after general anaesthesia.

TABLE IV—*Reports per million prescriptions of dystonic and dyskinetic reactions to metoclopramide by age and sex*

Age band (years)	Male patients	Female patients
0-4	15·3	22·9
5-11	43·5	41·0
12-19	109·1	190·7
20-39	20·5	48·2
40-54	5·1	8·8
55-64	3·5	5·2
65 and over	3·5	4·2

TABLE V—*Proportion of patients prescribed metoclopramide in doses in excess of manufacturers' current recommendations**

Age (years)	No of male patients	%	No of female patients	%
0-11	18/23	78	22/29	76
12-19	29/48	60	49/121	40
20-39	5/33	15	16/112	15
40 and over	3/12	25	3/33	9

*Maximum recommended dosages: under 1 year, 1 mg twice daily; 1-3 years, 1 mg three times daily; 3-5 years, 2 mg three times daily; 5-14 years, 5 mg three times daily; 15-20 years, 5-10 mg three times daily (starting at lower dose); and adult 10 mg three times daily.

PARKINSONISM

Twenty patients (15 female) were reported as developing parkinsonism in association with metoclopramide, and 15 were aged over 55 years. Only seven of the reactions developed within three days of starting treatment with metoclopramide, and seven occurred after more than 28 days of treatment (two of these after five years). All patients recovered after withdrawal of the drug, although in some cases this took several months. Nine patients were receiving other drugs (table III), and the median dose was 30 (range 20-40) mg/24 hours.

The reporting rates per million prescriptions were 0·58 (male) and 0·56 (female) in patients under 65 years and 1·7 (male) and 4·2 (female) for those aged 65 and over. The difference in rates between the sexes was not significant ($\chi^2_1 = 0{\cdot}80$) but there was a significantly higher rate in the elderly ($\chi^2_1 = 13{\cdot}8$; $p < 0{\cdot}0001$).

Discussion

The occurrence of extrapyramidal reactions with metoclopramide is well recognised and most previously published case reports of acute dystonias or dyskinesias have been in female patients under 25 years of age.[3 7] The incidence of acute dystonia-dyskinesia observed by the Boston Collaborative Drug Surveillance Program was one in 758 hospital inpatients of unrecorded age.[8] In a survey from Sardinia all patients presenting at hospital with acute dystonia over nine months were aged 8-42, and in 36 of the 94 patients metoclopramide was the implicated drug.[4]

This study shows that the yellow card reporting of adverse reactions to metoclopramide depends on both age and sex: acute dystonic-dyskinetic reactions are reported predominantly in younger female patients, and with many fewer reports of parkinsonian reactions predominantly for older patients. These differences in age and sex between reporting rates could come from bias due to a relative failure to report acute dystonic-dyskinetic reactions in adults over the age of 40. This seems unlikely: firstly, reports of adverse reactions to drugs to the Committee on the Safety of Medicines generally tend to increase with age and, secondly, reports of parkinsonism associated with metoclopramide occur predominantly in older patients. The differences in age and sex cannot be attributed to differences in prescribing. The figures for prescriptions provided by Intercontinental Medical Statistics Limited are estimates (to the nearest thousand) based on a sample of general practitioners in the United Kingdom; they are the best estimates available. Although they exclude prescribing in hospitals, these comprise only 10% of all prescriptions for metoclopramide (Beecham Pharmaceuticals, personal communication). In performing the analysis of proportions of reported reactions we have treated these figures as if they were exact rather than approximate; unless there are gross errors in the magnitude of these estimates or differential errors for the various age or sex groups this should not affect our conclusions.

In the absence of any clear evidence of bias in reporting we conclude that there are real differences in age and sex in the incidence of acute dystonic-dyskinetic reactions with metoclopramide, and that girls and women aged 12-19 are at special risk.

In this group of female patients the reporting rate of acute extrapyramidal reactions is roughly 1 in 5000: this figure is, however, likely to be a substantial underestimate of the true incidence in view of the known under-reporting (90-99%) of adverse reactions to drugs[9] and the fact that the prescribing data, although excluding prescribing in hospitals, do not take account of repeated prescriptions. The mechanism for this apparent

susceptibility is uncertain. Although many of the children were prescribed doses of metoclopramide above those recommended by manufacturers, relative overdosage, as discussed earlier, does not account for the differences in age and sex. Therapeutic overdosage in the 12-19 year age group may contribute to the high reporting rate, but exclusion of those patients who were prescribed a relative overdose from the analysis means that the sex difference in reporting becomes more pronounced in this age group (table V). As we do not have details of prescribing dosages to the community as a whole assessment of the dose response relation in terms of adverse reactions is impossible. Plasma concentrations and clearances of metoclopramide, however, were similar in children suffering from acute extrapyramidal reactions to those not suffering.[10] Furthermore, prescribing a relative overdose does not account for the age related pattern of reports in the age groups over 20 years, and we therefore favour a pharmacodynamic explanation. This would be supported by the observation that the prolactin response to intravenous metoclopramide, which is due to the dopamine antagonist action of the drug, was substantially greater in 17-20 year old women than men.[11] Moreover, an age related decline in density of D_2 receptors has been shown to occur in the striatum of the rat[12] and in the caudate nucleus, putamen, and frontal cerebral cortex of man.[13]

Only a fairly small proportion of patients were apparently receiving other drugs (table III). Generally, therefore, adverse interactions probably do not account for most of the reactions. Major tranquillisers, oral contraceptive steroids, and lithium, however, are known to precipitate acute extrapyramidal reactions in susceptible patients, and their concurrent use may exacerbate any tendency to extrapyramidal reactions with metoclopramide. Several patients were receiving opioid analgesics or dextropropoxyphene (table III). Delitala *et al* recently reported that morphine enhances the prolactin releasing effect of intravenous metoclopramide,[14] and it is possible that opioids enhance the sensitivity of D_2 receptors within the basal ganglia.

Although acute dystonic-dyskinetic reactions to metoclopramide are self limiting and rarely cause permanent damage, their morbidity is high and many patients reported to the Committee on the Safety of Medicines were admitted to hospital. In the light of present evidence it would seem wise to exercise care in the use of this drug in young people, and especially girls and young women.

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Egg and cows' milk hypersensitivity in exclusively breast fed infants with eczema, and detection of egg protein in breast milk

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Abstract

Forty nine eczematous infants who were still solely and exclusively breast fed and who had never received anything but breast milk were studied for evidence of sensitisation to foods. Thirty four similar infants without eczema formed a control group. The eczematous infants were divided into three groups according to clinical criteria: (1) definite atopic eczema; (2) possible atopic eczema; (3) atopic eczema unlikely. Twenty three infants showed cutaneous hypersensitivity to foods, usually egg and cows' milk. Seven of 14 infants in group 1 and nine of 20 in group 2 were sensitised compared with four of 15 in group 3 and three of 34 controls ($p < 0.01$). Ovalbumin was detected in breast milk from 14 of 19 mothers tested after ingestion of egg, the concentrations being the same for mothers feeding eczematous and normal infants.

Breast fed babies developing eczema may be sensitised by foods eaten by their mothers.

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Introduction

Despite continuing controversy[1 2] it is widely believed that breast feeding partially protects against the development of allergic disease, including atopic eczema.[3 4] This protective effect is not complete, however, as breast fed children sometimes