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The Safety of Risperidone: a Post-Marketing Study on 7684 Patients

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Risperidone is a relatively new antipsychotic agent licensed for the treatment of schizophrenia and other psychotic conditions in patients aged 15 years or older. This study examines the safety of risperidone used in general practice. Information was collected for 7684 patients included in a non-interventional observational cohort study conducted by means of Prescription-Event Monitoring. Incidence rates were calculated to rank the frequency of reported events. Drowsiness/sedation was the most frequent reason for stopping risperidone and the most frequently reported event. Extrapyramidal symptoms were reported rarely, but were more frequent in the elderly. 98 (1·3 per cent) patients were aged less than 15 years. Eight overdoses of risperidone alone were reported with no serious clinical sequelae. Risperidone appears to be well tolerated. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — risperidone; safety; extrapyramidal symptoms; schizophrenia; psychosis; prescription-event monitoring

INTRODUCTION

Risperidone is one of several new 'atypical' antipsychotic agents licensed for the treatment of schizophrenia and other psychotic conditions in patients aged 15 years and over. Schizophrenia is a chronic, incurable disease and many patients will require maintenance therapy for prolonged periods. Reduction in relapse must be weighed against an increased risk of serious side effects with medical therapy such as extrapyramidal symptoms and tardive dyskinesia. The development of drugs with fewer serious side effects remains important for the management of schizophrenia. This non-interventional observational cohort study quantitatively examines the safety of risperidone in a large population of patients treated in general practice.

METHODS

Patients were identified from prescriptions for risperidone written by general practitioners (GPs) in England in the immediate post-marketing period. Prescription data were supplied in confidence by the Prescription Pricing Authority between July 1993 and April 1996. Questionnaires were then sent to the prescribing GPs at least 6 months after the date of the first prescription for each individual patient. Questionnaires requested information on the age, sex, indication for treatment, dates and duration of treatment, all events that had occurred after risperidone was prescribed and the reasons for stopping therapy. The term 'event' was defined as including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction or any complaint considered of sufficient importance to enter into the patient's notes (Freemantle *et al.*, 1997).

Exposure data comprised the original prescriptions for risperidone and outcome data were the events reported on the questionnaires. All events were coded onto a computer by using a dictionary arranged in a system-organ classification.

Statistical analysis

Incidence rates (IDs) were calculated for all events occurring during treatment with risperidone during each specified time period. The figures are

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expressed as number of reports per 1000 patient-months of treatment (Freemantle *et al.*, 1997). IDs for events occurring in the first month of treatment (ID_1), during the second to sixth months of treatment (ID_2) and for events occurring during the overall treatment period (ID_A) were calculated.

Selected events and pregnancies were followed up by contacting the patient's GP or hospital consultant for further information. Deaths with no specified cause were followed up by obtaining death certificates from the Office for National Statistics.

General consideration

Considerable care has been taken to preserve the confidentiality of data and the study has been conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical Sciences (1993).

RESULTS

14 282 patients were identified from prescription data. 9174 (64 per cent) of the 14 282 questionnaires posted were returned. 1490 (16 per cent) of these were classified as void (patient no longer registered with GP, 913; blank questionnaires, 329; no record of risperidone in the records, 179; risperidone prescribed but not taken, 65; patient's doctor moved, 4). Useful information was therefore available for 7684 patients.

Age and sex

The sex and age distribution of the cohort is shown in Figure 1. The mean age for males was $38{\cdot}8 \pm 16{\cdot}8$ years and the mean age for females was $50{\cdot}5 \pm 20{\cdot}4$ years. The sex was not specified for 60 (0·8 per cent) patients. A difference in the age distributions for males and females was observed. The distribution of males was skewed with a predominance of young males.

Indications

The two major indications for prescribing risperidone were schizophrenia (43·9 per cent) and psychosis (14·6 per cent) as expected. The indications were similar for both sexes.

Duration of therapy

After 6 months, 5155 (76·0 per cent) of the 6779 patients for whom data were available were still receiving prescriptions for risperidone.

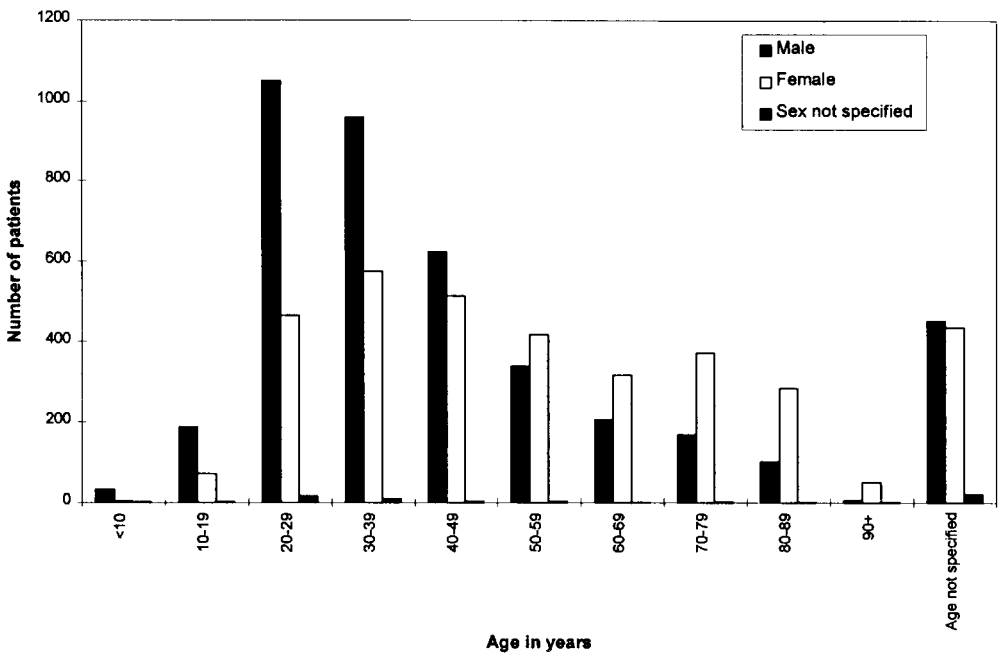

Figure 1. Age and sex of patients prescribed risperidone

Reasons for stopping risperidone

The most frequent reasons for stopping risperidone were drowsiness and sedation as shown in Table 1.

The events

Drowsiness/sedation were the most frequent events reported in the first month of treatment (Table 2) when

N_1 = total number of reports of each event during the first month of treatment,
N_2 = total number of reports of each event during treatment in months 2–6 and
N_A = total number of reports of each event during the total treatment period.

The denominators in patient-months are also displayed, when

D_1 = total number of patient-months during the first month of treatment,
D_2 = total number of patient-months during treatment months 2–6,
D_3 = total number of patient-months during treatment after month 6 and
D_A = total number of patient-months during the whole treatment period.

Selected events

The incidence of reported extrapyramidal symptoms was 5·9 per 1000 patient-months in the first month of treatment and 3·2 per 1000 patient-months during the overall treatment period. Specific reports of involuntary movement were very rare. There were only four reports of dyskinesia and one report of tardive dyskinesia which resulted in risperidone being discontinued. No confirmed reports of neuroleptic malignant syndrome or ventricular arrhythmia were considered related to risperidone.

Children aged less than 15 years

Ninety-eight patients were aged less than 15 years (37 were aged less than ten years). Forty-nine children were prescribed risperidone for attention-deficit hyperactivity disorder. Forty-seven (95·6 per cent) of these included an opinion about the effectiveness of treatment. Risperidone was reported to have been effective in 39 (83·0 per cent). One GP reported that a seven-year-old discontinued risperidone as a result of abnormal liver function test. No other serious events were identified in children.

Table 1. Most frequent reasons for stopping risperidone

Reason for stopping	Number of reports*
Not effective	414
Non-compliance	119
Drowsiness	60
Sedation	48
Hospital admission	45
Depression	37
Lassitude	34
Condition improved	33
Schizophrenia	33
Agitation	32
Effective	29
Dizziness	28
Malaise	27
Unspecified side effects	27
Extrapyramidal symptoms	25
Hallucinations	22
Headache	21
Anxiety	20

*Individual patients could have more than one reason reported.

Patients aged 70 years or over

Nine hundred and eighty five (12·8 per cent) of the patients were aged 70 years or over. The most frequently reported events in this age group were also drowsiness/sedation (Table 3).

Toxicity

The majority of reported overdoses involved mixtures of drugs. Eight involved risperidone alone. The largest dose of risperidone taken was 58 mg. None of the eight patients suffered serious sequelae. One death resulted from an overdose of mixed drugs including risperidone (the other drugs were unknown).

Pregnancies

Nine patients took risperidone during ten pregnancies (one patient had two pregnancies while taking the drug). The outcomes of these pregnancies were seven live births and three early therapeutic terminations of pregnancy. There were no abnormalities reported among the live births.

Table 2. Ranked incidence densities (ID) per 1000 patient-months

Denominators (patient-months of treatment)	D_1	D_2	D_3	D_A
Male	3539	15312	10258	29109
Female	3002	12822	8048	23872
Sex not specified	49	208	152	409
Total	6590	28342	18458	53390

Event	N_1	N_2	ID_1	ID_2	ID_1–ID_2	99% CI* min	99% CI* max	N_A	ID_A
Drowsiness, sedation	87	110	13·2	3·9	9·3	5·5	13·1	243	4·6
Non-surgical admissions	56	212	8·5	7·5	1·0	−2·2	4·2	388	7·3
Dose increased	54	71	8·2	2·5	5·7	2·7	8·7	160	3·0
Malaise, lassitude	45	92	6·8	3·2	3·6	0·8	6·4	176	3·3
Respiratory tract infection	44	192	6·7	6·8	−0·1	−3·0	2·8	325	6·1
Nausea, vomiting	41	67	6·2	2·4	3·9	1·2	6·5	139	2·6
Extrapyramidal symptoms	39	88	5·9	3·1	2·8	0·2	5·4	170	3·2
Agitation	37	68	5·6	2·4	3·2	0·7	5·7	131	2·5
Headache, migraine	35	43	5·3	1·5	3·8	1·4	6·2	90	1·7
Depression	31	125	4·7	4·4	0·3	−2·1	2·7	197	3·7
Dizziness	30	36	4·6	1·3	3·3	1·1	5·5	88	1·6
Hallucination	30	81	4·6	2·9	1·7	−0·6	4·0	150	2·8
Menstrual disorder	11	41	3·7	3·2	0·5	−2·7	3·6	79	3·3
Anxiety	24	34	3·6	1·2	2·4	0·5	4·4	77	1·4
Insomnia	24	55	3·6	1·9	1·7	−0·3	3·7	102	1·9
Condition improved	22	31	3·3	1·1	2·2	0·3	4·1	72	1·3
Non-compliance	21	66	3·2	2·3	0·9	−1·1	2·8	120	2·2
Tremor	21	39	3·2	1·4	1·8	−0·1	3·7	75	1·4
Impotence, ejaculation failure	11	27	3·1	1·8	1·3	−1·2	3·9	49	1·7
Constipation	20	42	3·0	1·5	1·6	−0·3	3·4	89	1·7
Schizophrenia	19	64	2·9	2·3	0·6	−1·2	2·5	118	2·2
Pain abdomen	17	44	2·6	1·6	1·0	−0·7	2·8	84	1·6
Micturition disorder	16	54	2·4	1·9	0·5	−1·2	2·2	87	1·6
Suicide attempt, drug overdose	16	60	2·4	2·1	0·3	−1·4	2·0	110	2·1
Dose reduced	15	52	2·3	1·8	0·4	−1·2	2·1	88	1·6
Fall	14	32	2·1	1·1	1·0	−0·6	2·5	59	1·1
Oedema	14	43	2·1	1·5	0·6	−1·0	2·2	81	1·5
Weight gain	14	32	2·1	1·1	1·0	−0·6	2·5	75	1·4
Galactorrhoea	6	17	2·0	1·3	0·7	−1·6	2·9	31	1·3
Aggression	13	37	2·0	1·3	0·7	−0·8	2·2	65	1·2

*99% confidence interval.

Deaths

There were 221 verified deaths. Causes of death were ascertained for 192 of these. With the exception of the overdose of mixed drugs (see above), no death was attributed to risperidone.

DISCUSSION

There was no interference with the decision of doctors to prescribe risperidone and the study is therefore free of this potential selection bias. GPs were asked to report all events during and after treatment with risperidone and the study was therefore capable of identifying signals which none of the GPs suspected to have been due to an adverse drug reaction.

64 per cent of the questionnaires were returned. Data were thus available for 64 per cent of the first 15 000 patients in England to be dispensed the drug. This is a satisfactory response rate compared with GP postal surveys in general (McAvoy

Table 3. Ranked incidence densities (ID) per 1000 patient-months for patients aged 70 years and over

Denominators (patient-months of treatment)	D_1	D_2	D_3	D_A
Male	223	865	451	1539
Female	599	2536	1455	4590
Sex not specified	4	21	3	28
Total	826	3422	1908	6156

Event	N_1	N_2	ID_1	ID_2	ID_1–ID_2	99% CI* min	99% CI* max	N_A	ID_A
Drowsiness, sedation	21	23	25·4	6·7	18·7	3·9	33·5	53	8·6
Respiratory tract infection	10	50	12·1	14·6	−2·5	−13·7	8·7	73	11·9
Extrapyramidal symptoms	10	29	12·1	8·5	3·6	−7·0	14·3	48	7·8
Non-surgical admissions	9	28	10·9	8·2	2·7	−7·5	12·9	50	8·1
Oedema	9	13	10·9	3·8	7·1	−2·7	16·9	37	6·0
Constipation	8	12	9·7	3·5	6·2	−3·0	15·4	27	4·4
Agitation	8	11	9·7	3·2	6·5	−2·7	15·7	23	3·7
Confusion	7	16	8·5	4·7	3·8	−5·0	12·6	29	4·7
Fall	7	15	8·5	4·4	4·1	−4·7	12·9	29	4·7
Dose reduced	7	14	8·5	4·1	4·4	−4·3	13·1	22	3·6
Tremor	7	8	8·5	2·3	6·1	−2·4	14·7	17	2·8
Hallucination	7	1	8·5	0·3	8·2	−0·1	16·5	11	1·8

*99% confidence interval.

and Kaner, 1996). There is no reason why non-responding GPs should have a greater proportion of patients experiencing events than responding doctors. We therefore consider it unlikely that the response rate in this study will affect our results.

A high proportion (16 per cent) of questionnaires were classified as void. The majority of voids were as a result of patients no longer being registered with the GP. Migrant patients and temporary residents often have incomplete medical data. Such patients are usually excluded from general practice studies as part of the original study criteria. The methodology of PEM can result in an artificially low response rate.

Risperidone appeared to be well tolerated with 76 per cent of patients still being prescribed the drug after 6 months. It is not possible to estimate the degree of compliance with prescribed medication in this study and non-compliance has been reported in 33–54 per cent of outpatients taking oral antipsychotic medication (Hale, 1993).

The most frequent reasons for discontinuing treatment were drowsiness and sedation. The most frequent reasons for stopping treatment were also the most frequently reported events in the first month of treatment. The incidence of reported events in this study are lower than those reported in published trials. Sedation has been reported in about 25 per cent of patients taking risperidone, headache in 20 per cent and nausea in 9 per cent (Anon, 1993). The difference may be due to a combination of factors. Clinical trial subjects are often followed up intensely, whereas patients may not routinely report minor complaints to their GPs. When patients are monitored by psychiatrists or community psychiatric nurses, events might not be recorded in the GP records. Finally, GPs may fail to report all events on the questionnaires.

Extrapyramidal symptoms are a recognised problem with established antipsychotic drugs and may be a predisposing factor for tardive dyskinesia (Kane *et al.*, 1986). The incidence of reported extrapyramidal symptoms and movement disorders in this study is low. The onset of tardive dyskinesia can be insidious and the 6 month observation period used in this study may have resulted in an underestimate of the overall incidence. However, there has also been evidence that severe disabling tardive dyskinesia is likely to develop within the first 6 months of treatment (Caligiuri *et al.*, 1997). Drowsiness/sedation, extrapyramidal symptoms and tremor were reported more frequently among the elderly.

No reports of dystonia, dyskinesia or extrapyramidal symptoms were considered to be caused by risperidone in children. This study therefore

provides valuable data on the safety of risperidone in a group younger than that in which the use of the drug is advised with the current prescribing recommendations. The authors wish to emphasise that the use of risperidone in children is unlicensed at the time of submission of this paper. The safety of risperidone for use during pregnancy has not been established. Although risperidone has not shown direct reproductive toxicity in animal studies, some indirect, prolactin- and CNS-mediated effects have been reported (Association of the British Pharmaceutical Industry, 1998). There were no foetal abnormalities reported in the seven live babies exposed to risperidone in utero in this study.

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