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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

I. Schillevoort · A. de Boer · R.M.C. Herings
R.A.C. Roos · P.A.F. Jansen · H.G.M. Leufkens

Antipsychotic-induced extrapyramidal syndromes

Risperidone compared with low- and high-potency conventional antipsychotic drugs

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Abstract *Aim*: To compare the risk of extrapyramidal syndromes (EPS) between patients using risperidone and those using low-potency conventional antipsychotic drugs (APDs) in outpatient clinical practice, as measured by the use of anticholinergic medication. We tried to replicate results from previous clinical trials that compared risperidone with high-potency APDs.
Method: Data was obtained from the PHARMO database containing filled prescriptions of 450,000 community-dwelling people in The Netherlands from 1986 to 1998. From the patients aged 15–54 years who had been newly treated with APDs, we defined mutually exclusive cohorts according to the APD first prescribed to a patient. APD exposure was followed until the first prescription of anticholinergic medication and was censored when APD prescribing was interrupted or switched. We estimated relative risks between risperidone and commonly used low-potency and high-potency APDs using Cox proportional hazards models, adjusting for age, gender, dose and other potential confounders.
Results: In 4094 patients who had been newly prescribed antipsychotic drugs, the overall incidence rate of anticholinergic drug therapy was 556 per 1000 person–years, which was dose dependent. Prescribed doses of all antipsychotics were low. While, in accordance with previous trials, risperidone showed a lower risk of EPS than the high potency APDs such as haloperidol (RR 0.26; 95% CI 0.10–0.64), we did not observe a lower EPS rate than low-potency APDs (risperidone vs thioridazine RR 1.73, 95% CI 0.49–6.13; risperidone vs pipamperone RR 2.50, 95% CI 0.78–8.04).
Conclusion: The reduced EPS rates observed when comparing risperidone with high-potency antipsychotics such as haloperidol may not apply to comparisons with low-potency drugs.

Keywords Risperidone · Antipsychotic agents · Extrapyramidal syndromes · Parkinsonism

I. Schillevoort (✉) · A. de Boer · R.M.C. Herings
H.G.M. Leufkens
Department of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht University, POB 80082, Utrecht,
The Netherlands
E-mail: i.e.r.m.schillevoort@pharm.uu.nl
Tel.: +31-30-2536719
Fax: +31-30-2539166

R.A.C. Roos
Department of Neurology,
Leiden University Medical Centre, Leiden,
The Netherlands

P.A.F. Jansen
Department of Geriatrics, University Medical Centre,
Utrecht, The Netherlands

Introduction

Extrapyramidal syndromes (EPS, i.e. parkinsonism, dystonia, akathisia and dyskinesia) belong to a group of movement disorders often seen as side effects of antipsychotic drugs (APDs). EPS can adversely affect a patient's well-being, compliance to treatment and, as a result, treatment outcome [1]. Atypical antipsychotics are a new generation of APDs known to have a lower tendency to cause EPS than the older generation. One of the most widely studied atypical antipsychotics is risperidone. Many clinical trials showed that patients treated with risperidone have a reduced frequency of EPS and anticholinergic drug use compared with those using high-potency conventional APDs [2]. However, in non-elderly patients, risperidone has not yet been compared with low-potency antipsychotics, known to have a lower EPS liability than high-potency drugs [3]. Most widely prescribed low-potency APDs in The Netherlands include thioridazine and pipamperone (available in a limited number of European countries), where they accounted for nearly 30% of all APD prescriptions in outpatient practices in 1998 [4]. Thus, it is relevant to

know how risperidone relates to this group of APDs in terms of EPS.

We conducted a study the aim of which was to compare the risk of EPS between patients prescribed risperidone and those receiving low-potency conventional APDs in outpatient clinical practice, using anticholinergic medication as a marker for the occurrence of EPS. To assess the validity of the study method, we also tried to replicate the findings from previous clinical trials comparing risperidone with high-potency APDs.

Methods

Setting

Data were obtained from the PHARMO system, a database that includes information of drug-dispensing records for all 450,000 residents of 11 Dutch cities. The computerised drug-dispensing records were obtained from outpatient pharmacy files. Since virtually all patients in The Netherlands designate a single pharmacy to fill prescriptions from GPs or medical specialists, the PHARMO system provides a complete record of the prescription history of outpatients. In The Netherlands, prescription records are a reliable source of drug exposure measurement [5]. For every dispensed prescription drug, the database contains information on the gender and date of birth of the patient, the dispensed drug, prescriber, dispensing date, amount dispensed and the prescribed dose regimen. All patients and prescribers in the database are anonymous. The duration of use of each dispensed drug is estimated by dividing the number of dispensed tablets by the prescribed number of tablets to be used per day. Thus, for each patient in the system, drug exposure can be ascertained on a day-to-day basis [6]. The PHARMO database has previously been used to study various types of drug-induced morbidity [7, 8]. For this study, we used all available data from 1 January 1986 to 30 June 1998.

Patients

We defined a cohort of patients aged 15–54 years who were prescribed an oral APD for the first time since their enrolment in the PHARMO system. Excluded were: (1) patients enrolled in the PHARMO system for less than 1 year prior to the initial APD prescription, (2) patients already using anticholinergic drugs before the day of cohort entry, (3) patients receiving more than one APD at cohort entry, and (4) patients who used APDs for fewer than 15 days. Follow-up was censored when a patient's exposure to APDs was interrupted for more than 30 days, when a patient switched to other antipsychotic treatment or after 90 days of follow-up, whichever of these came first. The selection procedure resulted in mutually exclusive cohorts of newly treated patients for each individual APD. In this study, we focussed on patients who were initiated on risperidone, the low-potency drugs thioridazine, pipamperone or chlorpromazine, or one of the high-potency APDs previously studied in clinical trials, namely haloperidol, zuclopenthixol and perphenazine.

Previous trials comparing risperidone with haloperidol found a relative risk (RR) of 0.54 for starting with anticholinergic medication [2]. Sample size calculation showed that we needed to include at least 70 patients using risperidone and the same number of patients using a conventional APD to detect such a RR in our study with 80% power, given a type-I error probability of 0.05.

Outcome definition

The outcome of the study was first use of any drug indicated for treatment of drug-induced EPS, which was taken as a measure of the occurrence of EPS. These included the anticholinergic drugs benzatropine, biperiden, dexetimide, orphenadrine, procyclidine and trihexyphenidyl. The risk of developing EPS was considered to be instantaneous, meaning that new use of anticholinergic medication was assessed from day 1 after initiation of antipsychotic treatment until the end of follow-up. Patients who started the antipsychotic and anticholinergic drugs on the same day were excluded because such prescribing practice represents prophylactic use.

Statistical analysis

For each antipsychotic used in the study, we calculated the incidence rate of anticholinergic medication by dividing the total number of events by the total number of exposed person–time. We evaluated the effect of dose for all antipsychotics taken together by calculating the incidence rate in separate dose strata. For each patient, the mean prescribed daily dose during follow-up was expressed as chlorpromazine equivalents. This was done by multiplying the ratio of the mean prescribed daily dose and the defined daily dose (DDD) of the prescribed drug by the defined daily dose of chlorpromazine. One DDD, a technical unit for measurement and comparison of drug use defined by the World Health Organization, also equals the recommended adult daily dose of APDs in The Netherlands [9, 10].

We calculated crude and adjusted RRs and 95% confidence intervals (95% CI) of starting with anticholinergic medication for risperidone compared with the different conventional APDs using a Cox proportional hazards model. All multivariate Cox models included age at cohort entry, gender, calendar year of cohort entry and prescriber (general practitioner, psychiatrist or other) as covariates, as well as terms for the use of benzodiazepines, lithium, tricyclic antidepressants and selective serotonin re-uptake inhibitors in the 30 days prior to cohort entry or during follow-up. Furthermore, to control for possible differences in dosing among APDs, we adjusted for mean prescribed daily dose during follow-up, expressed as chlorpromazine equivalents.

Results

We identified 4094 patients who met all the inclusion criteria of our study. Sixty-six percent started with one of the seven APDs under study. Characteristics of the treatment groups are presented in Table 1. Patients treated with risperidone were younger and more often treated by a psychiatrist than patients receiving other APDs. Prescribed doses of all antipsychotics were considerably lower than their DDD. Median prescribed dose of risperidone was 99 chlorpromazine equivalents (2.0 mg), which was higher than that of other APDs we studied (Table 1). Nevertheless, since the cohorts of conventional APDs were relatively large, for all conventional drugs but chlorpromazine there were at least as many patients prescribed more than 100 chlorpromazine-equivalents per day as in the risperidone group.

We observed 284 patients who received anticholinergic medication during follow-up, which yielded an overall incidence rate of 556 per 1000 person–years. The incidence rate was highest in the age group 20–24 years (1287 per 1000 person–years) and steadily decreased thereafter, until 328 per 1000 person–years in the age group 50–54 years. Women had a lower risk of receiving anticholinergic medication than men (adjusted RR 0.74; 95% CI 0.58–0.93). The incidence rate showed a steady increase

Table 1 Characteristics of antipsychotic drugs (APDs) and their users. *H* high potency, *L* low potency, *A* atypical, *CPZ eq* chlorpromazine equivalents

Exposure	Market share (%)[a]	Class	Patients (*n*)	Mean age	Men (%)	Treated by psychiatrist (%)	Daily dose, median[b]	
							mg/day	CPZ eq/day
Any APD	100	–	4094	36	45.9	29.3	–	75
Risperidone	7.6	A	77	31	48.1	58.4	2.0	99
Haloperidol	14.1	H	744	37*	44.6	10.3*	2.2	84*
Zuclopenthixol	10.8	H	353	37*	41.6	42.5*	6.0	60*
Perphenazine	4.1	H	343	38*	43.1	35.5*	5.3	66*
Thioridazine	9.2	L	625	36*	40.0	29.6*	48.0	48*
Pipamperone	17.2	L	498	35*	53.6	45.0*	40.0	60*
Chlorpromazine	0.4	L	61	41*	68.9*	1.6*	63.0	63*
Other APDs	36.6	–	1393	36*	47.2	28.5*	–	99

[a]Market share, as estimated from prescriptions filled in outpatient pharmacies in 1998 in the catchment area of the PHARMO system, standardised to the Dutch population in 1998 on age and gender [4]
[b]Prescribed daily dose during follow-up. Mann-Whitney *U* test for dose

*$P < 0.05$ compared with risperidone (Student's *t*-test for continuous data, Chi-square test for categorical data)

with increasing dose (Fig. 1), which was also observed for individual antipsychotics (data not shown). We observed no difference in the risk of anticholinergic medication between patients treated by psychiatrists and those treated by GPs (adjusted RR 1.20; 95% CI 0.89–1.62).

The Cox proportional hazards model showed that there was no difference in the risk of receiving anticholinergic medication between patients using risperidone and those using the low-potency antipsychotics thioridazine or pipamperone (Table 2). The number of patients using chlorpromazine was too small to estimate a RR. With respect to the high-potency APDs, we observed that risperidone gave lower EPS rates than haloperidol and zuclopenthixol, though the latter was not statistically significant. Risperidone had a similar EPS rate to perphenazine. All these RR estimates were similar when we restricted the analysis to patients treated by psychiatrists (data not shown).

In stead of adding an anticholinergic drug, in practice the occurrence of EPS may also be followed by changing the APD. Switching of antipsychotic medication during follow-up occurred in 7.8% of the patients in the total cohort. RRs did not substantially change when both switching of APD and the addition of anticholinergic medication was considered a marker for EPS.

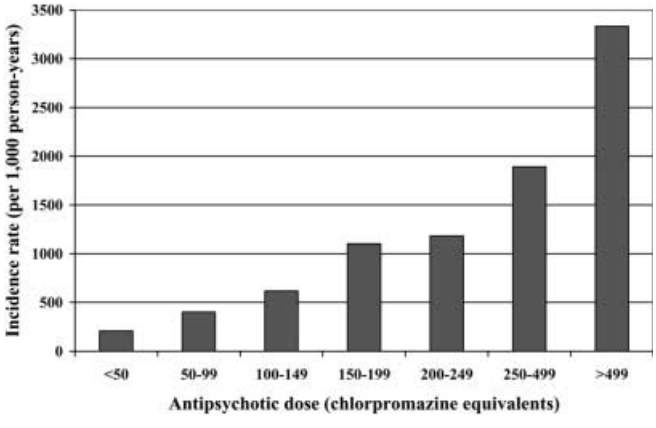

Fig. 1 Association between antipsychotic dose (expressed as chlorpromazine equivalents) and the incidence rate of anticholinergic medication in all 4094 outpatient first-time antipsychotic users

Discussion

We found no difference in anticholinergic drug use between patients prescribed risperidone and patients using the low-potency APDs thioridazine and pipamperone. In contrast, we and others observed a reduced need for anticholinergic medication with risperidone relative to the high-potency APDs haloperidol and zuclopenthixol. The number of patients prescribed chlorpromazine was too small to draw any conclusions.

Antipsychotic-induced anticholinergic medication was lower among older people and women, which was also found in previous observational studies [11, 12]. Since age and gender were adjusted for in the multivariate model, these factors could not explain any of the observed RRs of risperidone versus other APDs. Unfortunately, we had no information on psychiatric diagnosis or the disease severity of our study population. However, previous studies have found that, in patients with mild impairment, severity of psychopathology as such is not associated with the risk of EPS [13, 14]. Although disease severity may affect antipsychotic dosing and thus indirectly influence EPS rates, dosing was adjusted for in the analysis. Despite the dosing differences between conventional APDs and risperidone, there was still a sufficient number of patients prescribed conventional drugs in the higher dose range to allow for these dose adjustments. Thus, any differences in severity of psychopathology between patients using different APDs are unlikely to have biased the results of our study.

The study outcome was a first prescription of anticholinergic medication, which was used to classify absence or presence of EPS. Although anticholinergic

Table 2 Incidence rates and relative risk estimates of anticholinergic medication for risperidone compared with conventional antipsychotic drugs. Relative risks were calculated using a Cox proportional hazards model. *CI* confidence interval, *py* person years

Exposure	Person–time (years)	Events[a] (*n*)	Incidence/1000 py	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)[b]
Risperidone	10.1	6	593.5	–	–
Vs haloperidol	68.7	107	1,557.3	0.44 (0.20, 1.01)	0.26 (0.10, 0.64)
Vs zuclopenthixol	40.0	51	1,275.0	0.49 (0.21, 1.13)	0.43 (0.17, 1.09)
Vs perphenazine	48.1	14	291.3	1.92 (0.74, 5.01)	0.91 (0.21, 3.93)
Vs thioridazine	81.8	15	183.4	3.12 (1.21, 8.04)	1.73 (0.49, 6.13)
Vs pipamperone	76.3	10	131.0	4.25 (1.54, 11.72)	2.50 (0.78, 8.04)
Vs chlorpromazine	4.4	1	225.7	2.97 (0.35, 24.97)	–

[a]Event of extrapyramidal syndromes, as defined by the first prescribing of anticholinergic medication

[b]Adjusted for age, gender, year of cohort entry, prescriber (general practitioner, psychiatrist or other), use of benzodiazepines, lithium, tricyclic antidepressants and selective serotonin re-uptake inhibitors in the 30 days prior to cohort entry or during follow-up and mean presribed dose during follow-up, expressed as chlorpromazine equivalents

drugs are unlikely to be prescribed for other reasons than EPS in a non-elderly population using APDs, this marker will not have identified all patients with EPS. First, symptoms of EPS may have gone unnoticed by the treating physician. Second, if correctly diagnosed, EPS may also have been treated by reducing the dosage of the APD or by switching to another APD. RR estimates may have been biased when this underestimation of EPS occurrence differs among different antipsychotics. Difference in assessment, diagnosis or treatment of EPS may result particularly from the observed difference in type of prescriber between risperidone and other APDs. However, our data showed similar degrees of anticholinergic drug prescribing between psychiatrists and GPs. Furthermore, the main results of our study did not change when switching of antipsychotic medication was taken as a marker for EPS. While these observations argue against such a bias, it cannot be completely ruled out.

Our results may also have been influenced by treatment non-compliance, which is known to be substantial with antipsychotic medication [15]. Apart from EPS, other side effects of APD treatment such as sedation, weight gain or sexual dysfunction may also contribute to non-compliance. As a result, the frequency of EPS in our study would most likely have been higher if all APD medication had been taken as prescribed. However, since we have no information on the relative frequency of side effects of risperidone versus low-potency APDs, it is difficult to speculate on their effect on our study results and we cannot exclude any differences in non-compliance.

How generalizable are our findings to other treatment settings? Our study population is characterised by outpatient treatment with low doses of APDs, suggesting that patients had only mild psychopathology. In many other settings, however, dosing is likely to be higher, especially when patients are more severely ill. Based on its pharmacological properties, Kapur and Remington argued that risperidone's superiority in terms of EPS diminishes as dosing increases [16]. Consistent with the higher doses of APDs, clinical trials comparing risperidone with haloperidol showed less favourable RRs of EPS than our study (RR 0.54, 95% CI 0.42–0.70 [2]). However, trials of risperidone versus zuclopenthixol and perphenazine gave results comparable to our findings (RR 0.52, 95% CI 0.30–0.89 [17] and 0.83, 95% CI 0.47–1.49 [18], respectively). We are aware of only one study that compared risperidone with low-potency APDs. In line with the presumed association between dosing and relative EPS liability, low-dose risperidone (1 mg/day) showed a trend towards a lower EPS rate than thioridazine in a retrospective study among demented elderly patients [19]. Taken together, in settings where dosing is higher than in our study, RR estimates for risperidone are likely to be similar or less favourable than those we observed, compared with both low- and high-potency APDs.

Concern about EPS is an important aspect in choosing among different APDs, considering the possible impact on compliance and treatment outcome. Recent guidelines for treatment of schizophrenia recommend atypical antipsychotics when avoidance of EPS is an important treatment goal [20]. Our study suggests that low-potency conventional APDs may also be prescribed for this purpose in non-elderly patients. Given the low costs of these drugs, this is a relevant expansion. With regard to future research, our findings indicate that results from studies with high-potency drugs such as haloperidol do not necessarily apply to all conventional APDs. Thus, complete assessment of the added value of new APDs over the existing arsenal of low-cost conventional APDs requires comparative studies with both high- and low-potency APDs.

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