Bratisl Lek Listy 2008; 109 (6)
273 – 275

CLINICAL STUDY

Side effects of ropinirole in patients with idiopathic Parkinson's disease

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Abstract: *Objective:* Results achieved in treating the Parkinson's disease (PD) by the dopamine receptor agonist, ropinirole, have been hampered by its side effects. According to the MEDLINE, the most common side effects of ropinirole are extreme sleepiness and/or sudden sleep attacks, nausea, dyspepsia, vertigo, orthostatic hypotension and leg oedema.
Methods: The prospective research included PD patients who were administered non-ergoline dopamine agonist, ropinirole, over this period of time. The control group of patients were treated with levodopa.
Results: The research included 50 patients: 31 women and 19 men, of the mean age of 61.4±4.3 years. One patient reported sleepiness and one of them sudden sleep attacks. Nausea was experienced by three patients, and vertigo by two. Depression, orthostatic hypotension, leg oedema, dyspepsia, dry cough and hypersalivation were registered in particular cases. The control group of PD patients, treated with levodopa, comprised 52 patients, 33 women and 19 men of the mean age of 63.2±4.1 years. In the control group, nausea was registered in two patients.
Conclusions: The non-ergoline dopamine agonist, ropinirole, most commonly causes nausea and sleepiness, less commonly uncontrollable sleep attacks, vertigo, dyspepsia, orthostatic hypotension, leg oedema. Dry cough and hypersalivation are recorded sporadically *(Tab. 1, Ref. 22).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: side effects, ropinirole, Parkinson's disease.

Although dopamine receptor agonists are not simple to use, they are assumed to have an increasing importance in the treatment of early and advanced symptoms of Parkinson's disease (PD). The new agonists, pramipexole and ropinirole are generally adequate without levodopa for early symptoms, and carry the hope for a more acceptable profile of long-term side effects (1, 2). Ropinirole (Requip, GlaxoSmithKline) is a novel non-ergoline dopamine D2 agonist indicated in the treatment of early and advanced Parkinson's disease. When taken as oral tablets, ropinirole is rapidly and almost completely absorbed, and it is extensively distributed from the vascular compartment. The bioavailability is approximately 50 %. Ropinirole shows low plasma-protein binding. The drug is inactivated by metabolism in the liver, and none of the major circulating metabolites have pharmacological activity (3, 4).

In clinical tests, the following side effects have been recorded in patients who were administered with ropinirole therapy for the first time: nausea, sleepiness, leg oedema, gastritis (dyspepsia), vomiting, syncope, vertigo, and hallucinations. Upon termination of the therapy, the side effects disappear. No chronic effects jeopardising the vital functions have been recorded. The scope of this prospective research is to analyze ropinirole side effects in idiopathic PD patients.

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Materials and methods

This prospective study includes patients with idiopathic PD who were administered ropinirole therapy for the first time. Ropinirole is administered as a monotherapy. All patients are followed up for six months following the introduction of therapy. Ropinirole is introduced gradually over a four-week period, and the further dosage is determined depending on their clinical status. The treatment was performed with ropinirole starter-pack, 0.25 mg tablets, and following the introduction of the drug into medication, with 1 mg and 2 mg tablets. The ropinirole titration was started with 0.75 mg/day (0.25 mg three times a day) during the first week, to be followed with 1.5 mg/day (0.50 mg three times a day) in the second week, and 2.25 mg/day (0.75 mg three times a day) in the third week. After four weeks, each PD patient was evaluated, and his/her personal requirements for further ropinirole dosage increase were assessed. Each patient's disability degree was assessed by the Hoehn and Yahre scale before commencing and upon completion of the therapy, i.e. after six month of medication. The control group comprised patients with

idiopathic Parkinson disease, whose therapy did not include the dopamin agonist ropinirole but the well-known levodopa-benzeraside monotherapy (Madopar tbl. 125 mg, Hoffmann La Roche) with an indivudually determined dosage. The control group of patients corresponded with the tested group by their age, sex and duration of the disease. All tentative patients in both groups were excluded in case of depression or dementia. The patients are controlled several times: twice during the dosage titration after the second and the fourth weeks, and also monthly during the therapy for six months. At the follow-up examinations, there are performed blood tests, biochemical tests (blood glucose, urea, creatinines, and liver tests) and the neurological status.

Results

This prospective research is performed at the Department of Neurology, Split Clinical Hospital and General Hospital Slavonski Brod from 1 August, 2003 till 31 May, 2005. The tests included 102 patients with idiopathic PD. The patients were divided into two groups, depending on the therapy applied – ropinirole or levedopa. The research included 50 patients with PD treated with ropinirole: 31 women and 19 men. Their age ranged from 51 to 67 years, the mean age being 61.4±4.3 years. Their PD symptom periods were present for the period ranging from one half to two years. The drug was administered in line with the manufacturer's schedule as a monotherapy.

The average dosage ropinirole was 4 to 6 mg/d. Blood and biochemical tests revealed no significant changes as related to the initial values recorded at the beginning of the therapy.

Side effects at introduction and during the period of the therapy were noticed in eight patients, six of them had their therapy terminated for this reason, whereas in two patients who experienced increased sleepiness the dosage was decreased (Tab. 1).

During the follow-up of 50 PD patients, we recorded increased sleepiness in three of them (6 %), and sudden and uncontrollable sleep attacks in one case (2 %). Nausea was recorded in three patients (6 %), and vertigo and instability in two patients (4 %). Nausea was recorded in one patient, as well as orthostatic hypotension, leg oedema and dyspepsia. Some patients produced multiple side effects. Only one patient developed dry cough and hypersalivation, however upon the termination of the therapy the latter side effects dissapeared. No correlations between particular ropinirole therapy side effects have been noticed.

Tab. 1. Side effects of ropinirole in patients with idiopathic Parkinson's disease.

Case	Gender	Age	Disease duration (years)	Side effects
1	F	50	2	depression, sleepiness
2	F	64	2	sleepiness, orthostatic hypotension
3	F	52	1.5	dyspepsia, leg oedema
4	M	62	1	dry cough, hypersalivation
5	F	60	1.5	vertigo, nausea
6	M	60	0.5	sleepiness, nausea
7	F	65	1	vertigo, nausea
8	M	63	2	sleep attacks

The control group of PD patients treated with levodopa comprised 52 patients, 33 women, and 19 men of the mean age of 63.2±4.1 years. In the control group, there were two cases of nausea registered.

The tested groups of patients treated with ropinirole and levodopa, statistically do not differ in their disability degree as measured by the Hoehn and Yahr scale.

Discussion

According to MEDLINE, the most common side effects induced by ropinirole are extreme sleepiness and/or sudden and uncontrollable sleep attacks, especially in cases where patients are simultaneously administered other potentially sedative drugs. The sudden sleep attacks disappear after the termination of drug therapy, the same happens also with sleepiness (5–8).

In various studies of application of various DAs (bromocriptin, ropinirole), sleep attacks and/or sleepiness as well as sleep disorder incidence differs by 10–30 % (9–11).

Uncontrollable sleep attacks in DA-treated patients occur in range of 3.8–9.2 %. There is no study analysing merely the ropinirole-induced side effects.

In our research, 6 % of the patients reported sleepiness. Uncontrollable sleep attacks incidence in our research occurred in 2 %. The research indicates a significantly lower incidence of sleepiness and uncontrollable sleep attacks in PD patients treated with ropinirole.

A typical side effect induced by dopamine agonists, including ropinirole, is nausea (12–14). Research of 053 Study Group indicates that nausea incidence in PD patients treated with ergoline DA and non-ergoline DA significantly differs. With bromocriptin it occurs in 6.6 % and with ropinirole in 3 % (15). In our research of ropinirole-treated patients, nausea was suffered by 6 % of the tested patients, one patient suffered from dyspepsia.

This study, that may be criticised for its small sample as well as for several subsorts of DA (pergolide, pramipexol and ropinirole) indicates that in the research, only one PD patient experienced orthostatic hypotension due to ropinirole therapy at the beginning of the treatment (3, 16). Based on the latter side effect of ropinirole the therapy had to be terminated. Less commonly recorded are cases of leg oedema occurring during the ropinirole therapy (3, 17), as was the case in our research as well. Ropinirole side effects as hallucinations and sexual delinquency are extremely rarely recorded in literature. In our study no cases of the latter effects (18–20), have been recorded.

None of the non-ergolic DA (pramipexol, ropinirole) proved the risk of developing the retroperitoneal fibrosis (21) or alopecia (22).

The literature available through MEDLINE describes no cases of dry cough and hypersalivation, which we encountered in one

of our patients. In the WHO register of side effects, there are reported eight cases of dry cough and three cases of hypersalivation in ropinirole therapies. Our results indicate that there is no statistically significant difference between the effects of DA ropinirole and levodopa at the beginning of therapy as assessed by the Hoehn and Yahr scale. Levedopa causes fewer side effects in the early stage of the treatment, but also causes early diskinesias, wherefore with younger patients we always prefer the DA treatment (12).

To conclude with, all the above stated ropinirole side effects are of mild character, causing no consequences, disappearing soon after the termination of drug administration.

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Received March 30, 2007.
Accepted April 18, 2008.