

A Prospective, Multicenter, 2-Year Echocardiographic Study on Valvular Heart Disease in Parkinson's Disease Patients Taking Rotigotine and Other non-Ergot Dopamine Agonists

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Abstract

Objectives: We explored the possible risk of valvular heart disease (VHD) in Parkinson's disease (PD) patients taking rotigotine compared to other non-ergot dopamine agonists (DA) as requested by the EMA (European Medicines Agency) in terms of assessing the longterm safety associated with the cumulative dose of rotigotine.

Methods: We performed a prospective, multicenter, open-label, 2-year echocardiographic study in PD patients taking rotigotine or other non-ergot DA (piribedil, pramipexole, ropinirole). Valvular pathology was assessed by transthoracic echocardiographic examinations according to American Society of Echocardiography recommendations and a scoring system for restrictive VHD at 1-month, 12-months and 24-months follow-up examination. Routine neurological and physical examinations with special attention toward clinical symptoms of heart failure were performed after 1, 6, 12, 18 and 24 months.

Results: 102 out of 107 screened patients were enrolled into the study. Due to drop-outs along the 2-year follow-up, 66 patients (28 rotigotine, 38 other non-ergot DAs [3 piribedil, 20 pramipexole, 15 ropinirole]) completed the 12-months visit and 53 patients (23 rotigotine, 30 other non-ergot DAs [3 piribedil, 16 pramipexole, 11 ropinirole]) completed the 24-months visit. No patient showed clinical symptoms of heart failure or echocardiographic evidence of restrictive VHD during the 2-year period. Analyses of valve regurgitation (VR) revealed no case of severe or moderate VR in the rotigotine group. Only one patient taking pramipexole showed moderate VR at 1-month and 12-months follow-up visit decreasing to mild degree at 24-months follow-up.

Conclusions: This is the first prospective study assessing the possible risk of VHD in patients taking rotigotine. We did not find valvular pathology suggestive for restrictive VHD or increased risk of cardiac VR in PD patients receiving rotigotine or other non-ergot DAs. Future studies are needed to explore the clinical relevance and the relationship between non-ergot DAs and heart failure including effects of cumulative dose or comedication with other antiparkinsonian drugs.

Keywords: Parkinson's disease; Rotigotine; Non-ergot dopamine agonists; Adverse drug reactions; Valvular heart disease; Valvular regurgitation; Fibrotic reactions; Echocardiography

Introduction

Treatment of Parkinson's disease (PD) is still a challenge and focuses on the symptomatic control of motor and non-motor symptoms without inducing intolerable side effects. Levodopa remains the gold standard of therapy, but the emergence of motor complications may compromise the long-term therapeutic response [1]. Therefore, dopamine agonists (DA) are frequently used and have been shown to be efficacious for delaying levodopa-induced motor complications [2]. However, their use is restricted by the risk of adverse drug reactions including central and peripheral nervous effects [3].

Variable pharmacodynamical properties of DAs exhibit differences in their adverse drug reactions profile. Besides their specific affinities for dopamine receptors, most ergot DAs demonstrate higher affinities to serotonergic receptors (5-HT₁ and 5HT₂) than non-ergot DAs [4]. The

activation of 5-HT_{2B} receptors by ergot DAs such as bromocriptine, pergolide and cabergoline has been suggested to mediate valvular heart disease [5]. 5-HT_{2B} receptors are expressed in heart valves and might induce mitogenesis as well as proliferation of fibroblasts [6]. The fibrotic

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changes cause stiffening and retraction of valves leading to insufficient leaflet coaptation and clinically significant regurgitation that required surgical valve replacement in some patients.

Several echocardiographic prevalence studies reported increased risk of valvular heart disease (VHD) in patients taking ergot DAs (cabergoline, pergolide) compared to non-ergot DAs (pramipexole, ropinirole) [7-9] and an association between cumulative dose and severity of valve regurgitation [9]. A systematic review confirmed these findings assessing an increased risk of cardiac valve regurgitation associated with the use of ergot DAs and not of non-ergot DAs [10]. However, published studies of pergolide did not reveal valvulopathy in about two-thirds of patients despite several years of exposure [11]. Therefore, the role of individual vulnerability and susceptibility as well as the reversibility of fibrotic reactions still have to be clarified [12,13].

The non-ergot DA rotigotine has been developed as an effective antiparkinsonian drug acting as a full agonist on D3, D2 and D1 dopamine receptors through a novel transdermal delivery system [14]. It exerts low affinity to α -adrenergic receptors and no relevant affinity to the 5-HT2B receptor. A recent study assessed the impact of rotigotine on cardiovascular autonomic function in 20 de novo PD patients [15]. Rotigotine did not modify cardiovascular parameters, including orthostatic blood pressure response and cardiac responses to the valsalva maneuver or to deep breathing.

Rotigotine was approved and admitted to the European market in 2006. Systematic data on the long term safety associated with the cumulative dose of the compound after several years of exposure were missing. On request by the EMA (European Medicines Agency) we initiated in 2011 the first prospective trial to assess the possible risk of VHD in PD patients receiving rotigotine compared to other non-ergot DA agonists over a 2-year period.

Patients and Methods

From March 2011 (first patient in) to April 2014 (last patient out), we conducted a prospective, multicenter, open-label, 2-year echocardiographic study in PD patients taking rotigotine or other non-ergot DA (piribedil, pramipexole, ropinirole). The study protocol was approved by the ethics committee of the Philipps University of Marburg in agreement with the ethical principles of the Declaration of Helsinki. Patients were recruited from an outpatient setting at 11 centres of office-based neurologists in Germany. All patients' gave their written informed consent to participate.

Eligible patients were Caucasian men and women aged > 18 years with a diagnosis of PD (UK PD Society Brain Bank Clinical Criteria). Exclusion criteria included: history of carcinoid disease, history of post inflammatory or degenerative (calcifying) cardiac valvular disease, history of significant coronary heart disease, previous treatment with another DA for more than 3 months and within half a year before enrolment, and prior medication with ergot derivatives. After baseline assessment follow-up visits for routine neurological and physical examinations with special attention toward clinical symptoms of heart failure were performed after 1, 6, 12, 18 and 24 months. Routine transthoracic echocardiographic examinations were done by experienced cardiologists (individually associated to the study sites) at 1-month (T1), 12-months (T2) and 24-months (T3) follow-up visit. The cardiologists were not blinded to treatment status. Severity of valvular regurgitation (grade 0 normal, grade 1 mild, grade 2 moderate, grade 3 severe) was defined following international standard criteria of the American Society of Echocardiography [16]. Mitral or tricuspid valves were termed fibrotic if leaflets showed limited motility and

if the leaflets or the subvalvular apparatus were retracted toward the apex. Aortic valves were regarded as restrictive if the valve opened or closed with doming of leaflets. Restrictive VHD was graded according to van Camp et al. [11]: Score 1 proven restrictive VHD (pathology and/or regression after discontinuation of therapy), score 2: serious VHD (insufficiency jet $\geq 2/4$) suggestive for restrictive VHD or fibrotic alteration of the tricuspid valve even if less than 2/4, score 3: mild to moderate VHD (insufficiency jet $< 2/4$) suggestive for restrictive VHD, score 4 no restrictive VHD.

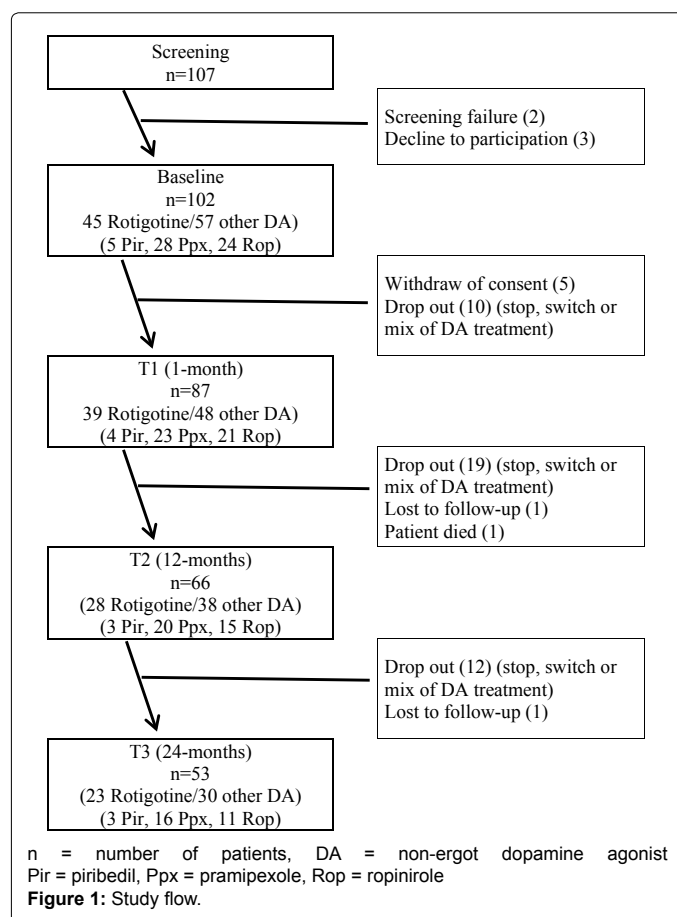
Statistical Analysis

Statistical analyses were performed with SPSS 17.0 for Windows. Data are presented as mean \pm standard deviation (SD) and range. Patients with echocardiographic finding of VR were presented descriptively.

Results

102 out of 107 screened patients were enrolled in the study. Due to drop-outs along the 2-year follow-up, 66 patients (28 rotigotine, 38 other non-ergot DAs [3 piribedil, 20 pramipexole, 15 ropinirole]) completed the 12-months visit and 53 patients (23 rotigotine, 30 other non-ergot DAs [3 piribedil, 16 pramipexole, 11 ropinirole]) completed the 24-months visit. Figure 1 shows the study flow and the number of patients taking rotigotine or other non-ergot DA over the 24-months period. Table 1 presents sample characteristics of the patients.

During the 24-months study follow-up no patient showed clinical symptoms of heart failure. No echocardiographic evidence of restrictive



	Rotigotine	Piribedil	Pramipexole	Ropinirole	Pooled other non-ergot DAs Pir/Ppx/Rop
No. of patients	23	3	16	11	30
Female, n (%)	9 (39%)	1 (33%)	10 (63%)	4 (36%)	15 (50%)
Age, years: mean \pm SD (range)	70,9 \pm 8,9 (51-88)	67,7 \pm 7,5 (59-72)	70,6 \pm 6,5 (58-85)	71,2 \pm 3,8 (63-76)	70,5 \pm 5,7 (58-85)
PD duration, years: mean \pm SD (range)	4,2 \pm 3,9 (0-16)	1,7 \pm 0,6 (1-2)	4,9 \pm 2,9 (0-13)	6,6 \pm 4,8 (1-18)	5,2 \pm 3,8 (0-18)
Hoehn&Yahr stage, mean \pm SD	2,0 \pm 0,8	1,0 \pm 0,0	1,8 \pm 0,7	2,0 \pm 0,4	1,8 \pm 0,6
I - I,5, n (%)	8 (35%)	3 (100%)	5 (31%)	1 (9%)	9 (30%)
II-II,5, n (%)	8 (35%)	-	9 (56%)	9 (82%)	18 (60%)
III, n (%)	7 (30%)	-	2 (13%)	1 (9%)	3 (10%)
Duration of treatment (months), mean \pm SD (range)	44,6 \pm 22,7 (24-88)	38,4 \pm 13,4 (29-54)	47,5 \pm 26,0 (24-99)	46,9 \pm 25,1 (26-118)	46,4 \pm 24,3 (24-118)
Cumulative dosage (mg), mean \pm SD (range)	9.367 \pm 5.569 (1.460-19.754)	160.900 \pm 79.617 (86.400-244.800)	2.696 \pm 2.391 (721-9.280)	13.395 \pm 4.893 (7.212-21.072)	-
Average dosage (mg/day), mean \pm SD (range)	6,9 \pm 2,9 (2-16)	133,2 \pm 29,1 (100-150)	1,7 \pm 0,7 (0,5 - 3,2)	11,0 \pm 5,5 (2,0-24,00)	-

n = number of patients, SD = standard deviation
Pir = piribedil, Ppx = pramipexole, Rop = ropinirole

Table 1: Demographic and clinical data of patients.

VHD was found and all patients showed a VHD score of 4 (no restrictive valve dysfunction) at 1-month, 12-months and 24-months follow-up examination. Analyses of valve regurgitation revealed no case of severe valve regurgitation (grade 3). Only one patient taking pramipexole showed moderate VR (grade 2) at 1-month and 12-months follow-up visit with a subsequent decrease to mild degree (grade 1) at 24-months follow-up. This was a 77 years old female patient suffering from PD for 6 years before study enrolment. According to the exclusion criteria of the study history of postinflammatory or degenerative (calcifying) cardiac valvular disease was not existent, cardiovascular risk factors were not documented. She had been treated with slow-release pramipexole 0,52 mg/d for 1,5 years and with L-Dopa 300mg/d half a year before enrolment. The dose of both drugs remained fixed throughout the complete study duration. As at 24-months follow-up examination the VR resolved in mild degree a causal relationship to the cumulative dose of pramipexole cannot be assumed. Mild VR was found in 3 patients of the rotigotine group (each one at 1-, 12- and 24-months follow-up visit), in one patient taking piribedil (at 12- and 24-months follow-up visit), in 3 patients taking pramipexole (each one at 12- and 24-months follow-up visit) and in 2 patients taking ropinirole (each one at 1-, 12- and 24-months follow-up visit) without any clinical symptoms of heart failure. One patient of the rotigotine group, two patients taking pramipexole and one patient taking ropinirole started with DA treatment at baseline visit and were suffering from hypertension. All other patients with mild VR were already taking the respective DA at the time of study enrolment. Preexisting VR of these patients with mild or moderate VR could not be evaluated due to missing transthoracic echocardiographic examinations before enrolment in the study.

Due to the single case of moderate VR, the considerable inhomogeneity of treatment group sizes and duration of drug intake, missing data on possibly pre-existing VR and the high prevalence of mild VR in the general population a reliable statistical analysis of the incidence of VR with the use of different DA agonists could not be performed.

Discussion

Pharmacovigilance data on the adverse drug reaction profile associated with the cumulative dose of a compound are essential for

assessing long term safety and demanded by the authorities, respectively the EMA. This was the first prospective trial to assess the possible risk of VHD over a 2-year period in PD patients receiving rotigotine compared to other non-ergot DAs (piribedil, pramipexole, ropinirole). Our findings are in line with the results of previous non-prospective studies reporting no increased risk of cardiac VR or valve pathology suggestive for restrictive VHD in patients taking the non-ergot DAs pramipexole and ropinirole¹⁰. During our 24-months follow-up no patient showed clinical symptoms of heart failure, echocardiographic evidence of restrictive VHD or severe VR.

DAs provide symptomatic relief of motor symptoms in both early and advanced PD, but their use is restricted by the risk of side effects [2]. DAs exhibit important differences in pharmacodynamic properties leading to variable adverse drug reaction profiles. These can be classified as central (e.g. behavioural syndromes, sedative effects) or peripheral, some of which affect the cardiovascular system [2]. Cardiovascular effects of DAs are thought to be related to the activation of dopaminergic and non-dopaminergic receptors [17,18]. D1-like and D2-like dopamine receptors located at various sites within the vascular, cardiac and renal regions have been shown to mediate cardiovascular and renal effects [19]. The different subtypes of α 2-receptors regulate the norepinephrine and noradrenaline release in sympathetic neurons [20,21]. Besides specific and variable affinities for dopamine receptors among different DAs, ergolinic derivatives exert high to moderate affinity to α 1- and α 2-adrenergic as well as serotonergic (5-HT1 and 5-HT2) receptors. Non-ergot DAs in general lack appreciable effects on 5-HT or α 1-receptors but retain activity on α 2-adrenergic receptors [4]. While the incidence of restrictive VHD is attributed to the activation of 5-HT2B receptors by ergot DAs such as bromocriptine, pergolide and cabergoline [5], the association between exposure to DAs and occurrence of heart failure is still a matter of debate. Limited data of 2 studies suggest that cabergoline and pramipexole may increase the risk of heart failure [22,23]. As to cabergoline the occurrence of valve fibrosis may account for heart failure, the increased risk for peripheral edema of pramipexole could have led to a false diagnosis of heart failure in patients taking pramipexole. Nevertheless, Renoux et al. did not reveal an association between increased risk of heart failure with pramipexole and history of previous cardiovascular or

peripheral edema [23]. Interestingly in our study only one patient taking pramipexole showed moderate VR (grade 2) at 1-month and 12-months follow-up without clinical symptoms of heart failure. At 24-months follow-up VR decreased to mild degree (grade 1) while the patient continued taking slow-release pramipexole on a fixed dose of 0,35mg/d. Whereas pramipexole and its cumulative dose may not be accounted for VR in this patient, the etiology of moderate VR and the resolving in mild degree VR at the end of the study remains unclear. Furthermore, preexisting VR could not be excluded, as transthoracic echocardiographic examinations before enrolment in the study had not been performed. Further 9 patients (3 rotigotine, 1 piribedil, 3 pramipexole, 2 ropinirole) showed mild VR. With regard to the high prevalence of mild VR in the general population and the known positive correlation between higher age and the severity of VR [24], the overall prevalence of mild VR of 16.98% in our geriatric study population may be considered to be rather low.

Further long term studies are needed to investigate the relationship between non-ergot DAs and heart failure. Recently, a pooled analysis of all randomized, placebo-controlled, phase II and III clinical trials of pramipexole was performed by the US FDA (Food and Drug Administration). The frequency of newly diagnosed heart failure was non-significantly higher with pramipexole (0,29%) as compared to placebo (0,14%) [25]. To our knowledge, no data are available on the association between exposure to rotigotine and the occurrence of heart failure. A recent study investigated the impact of rotigotine on cardiovascular autonomic function in 20 early PD patients. Rotigotine did not modify cardiovascular parameters, including orthostatic blood response, cardiac responses to the valsalva maneuver, or to deep breathing. These findings may be due to its low affinity for α 2-adrenergic receptors and negligible affinity to D1 dopamine receptors being 100-fold weaker than to D3-like binding sites [26].

Our study had several limitations. The "strict" inclusion/exclusion criteria resulted in a small number of eligible patients for enrolment in the study. The prospective design of the study over a 24-months period and the necessity to stay on the same DA for 2 years led to many drop-outs and further diminished the population for final analysis. This resulted in uneven numbers and heterogeneity between the treatment groups and impeded sound statistical analyses assessing differences in the incidence of VR among the respective DAs. Despite the benefit of the prospective study design, information on possible pre-existing VR before initiation of DA treatment was missing. Furthermore, a control group was missing even though previous studies did not report increased risk of VR for non-ergot DAs compared with controls [10]. It has to be stressed that the echocardiographic examinations had some further limitation. Although the assessments were done by experienced cardiologists following international standard criteria of the American Society of Echocardiography [16] a centralized, independent and treatment-blinded evaluation of the examinations was not provided. Moreover, patients already taking the respective DA before baseline visit as well as patients initiating DA therapy were enrolled into the study leading to considerable differences in DA treatment duration. Eight patients of the rotigotine group and one patient taking pramipexole started with DA treatment at baseline visit, all other patients were already taking the respective DA at the time of study enrolment. In summary, the lack of a control group, the non-blinded status of the cardiologists to DA treatment and the non-homogeneity of duration of drug intake might have significantly affected the reliability and reproducibility of the data.

In conclusion, this first prospective study on VHD in patients taking rotigotine versus other non-ergot DAs revealed no case of valvular pathology suggestive for restrictive VHD or increased risk of cardiac

VR. Future studies are indispensable to investigate the clinical relevance and the relationship between non-ergot DAs and heart failure including effects of cumulative dose or comedication with other antiparkinsonian drugs and the characterisation of an at-risk population.

Conflicts of Interest and Sources of Funding

Karla Eggert and Wolfgang Oertel received consulting honoraria and honoraria for study coordination by UCB Pharma GmbH (Germany). Kerstin Anvari, Stephan Behrens, Michael Dapprich, Reinhard Ehret, Wilfried Lueer, Alexander Nass, Robert Pfister, Sigrud Planz-Kuhlendahl, Gerd Reifschneider, Alexander Simonow, and Michael Schwalbe received study investigator fees by UCB Pharma GmbH (Germany). This study was supported by the Federal Ministry of Education and Research, German Competence Network on Parkinson's disease (01G19901, 01GI0201, 01GI0401) and by UCB Pharma GmbH (Germany). No other funding was received for this work.

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