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MOVEMENT DISORDERS - SHORT COMMUNICATION

Transdermal rotigotine for the perioperative management of Parkinson's disease

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Abstract Continuous delivery of antiparkinsonian medication during a perioperative period is desirable to avoid 'off'-symptom complications in surgical patients with concomitant Parkinson's disease (PD). Fourteen PD patients undergoing surgery under general anesthesia were switched from oral dopaminergic medication to transdermally delivered 24-h rotigotine (median dose 12 mg/24 h) for the perioperative period. Rotigotine treatment was considered feasible by patients, their anesthesiologists and neurologists with good control of PD symptoms and easy switching and re-switching of PD medication.

For the NEUPOS Study Group.

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Introduction

Concomitant Parkinson's disease (PD) is a significant factor for perioperative morbidity in surgical patients (Mueller et al. 2009). Among other problems, cessation of oral dopaminergic medication during the perioperative period may result in a variety of 'off'-symptoms and increased peri and postoperative complications (Gálvez-Jiménez and Lang 2004). Sudden withdrawal of dopaminergic medication may also cause parkinsonism–hyperpyrexia syndrome (Frucht 2004). Alternative routes of administration for continuous drug delivery such as nasogastric or intraduodenal levodopa, intravenous amantadine, or subcutaneous apomorphine are invasive and imply additional risks of ECG changes and nausea; intravenous amantadine is not available in the United States. Clinical data to support the safe perioperative use of these compounds are sparse. A retrospective analysis of data from two large multicenter trials suggested rotigotine, a non-ergot dopamine agonist with D3/D2/D1 activity, as a possible perioperative management option for PD patients (Korczyn et al. 2007). Rotigotine has been formulated for transdermal delivery in a 24-h patch, which ensures continuous drug release and stable plasma concentrations over a period of 24 h (Braun et al. 2005). This prospective, open-label, exploratory trial investigated the feasibility of switching PD patients scheduled for surgery under general anesthesia from their usual PD medication to rotigotine transdermal patch for the perioperative period.

Table 1 Feasibility of switching to rotigotine treatment during the perioperative period rated by neurologists, anesthesiologists, and patients (full analysis set; $n = 9$)

	I completely agree 1	2	3	4	5	I do not agree at all 6
Neurologists						
Switch from previous PD medication was easily feasible	8 (88.9%)	0	0	1 (11.1%)[a]	0	0
Re-switch was easily feasible	8 (88.9%)	0	0	0	0	1 (11.1%)
No unexpected PD symptoms perioperatively	7 (77.8%)	2 (22.2%)	0	0	0	0
The patch is a feasible option	8 (88.9%)	1 (11.1%)	0	0	0	0
Anesthesiologists						
No unexpected PD symptoms perioperatively	8 (88.9%)	1 (11.1%)	0	0	0	0
Handling of the patch was simple	7 (77.8%)	2 (22.2%)	0	0	0	0
Handling was not time consuming	8 (88.9%)	1 (11.1%)	0	0	0	0
The patch is a feasible option	6 (66.7%)	2 (22.2%)	0	1 (11.1%)[a]	0	0
Patients						
Perioperative patch treatment was easily feasible	8 (88.9%)	1 (11.1%)	0	0	0	0
The symptoms of my PD were well controlled	7 (77.8%)	2 (22.2%)	0	0	0	0
In the course of surgery, I felt safe with the PD patch	6 (66.7%)	2 (22.2%)	0	1 (11.1%)	0	0

Data are number of patients (%)

PD Parkinson's disease

[a] The same patient was rated '4' by the neurologist and the anesthesiologist

Methods

Patients and study design

Fourteen patients with idiopathic PD from six German trial sites were enrolled in this prospective, open-label, multicenter trial (NCT00594464) approved by the respective local institutional review boards and conducted according to the Declaration of Helsinki and Good Clinical Practice. Only patients who required PD medication, who were scheduled for an operation under general anesthesia, and who had a physical status classification according to the American Society of Anesthesiologists (ASA) (Camporesi et al. 1991) of stage II or III were included in the trial. All patients gave written informed consent.

Following a pretreatment visit (eligibility assessment) and baseline assessments on the day before surgery, patients received transdermal 24-h rotigotine patches at approximately 7 p.m. on the evening before surgery, replacing their regular PD medication(s) (defined as PD medication taken within 2 days prior to switching). The last administration of previous PD medication was at noon of the preoperative day for most PD medications, i.e., cabergoline was stopped upon baseline assessment and the last levodopa-containing preparations were administered in the evening of the pre-operative day. Rotigotine dose determination was at the discretion of the neurologist; general guidance regarding target doses was given according to published literature (LeWitt et al. 2007; Giladi et al. 2007; Poewe et al. 2007; Deutsche Gesellschaft für Neurologie website). After surgery, previous PD medication was to be resumed in the evening of the operative day; if required, rotigotine could be applied for up to 2 weeks following surgery. The trial was completed by a safety follow-up 2 weeks after discharge from the hospital.

Clinical assessments

Feasibility of switching to rotigotine treatment for the perioperative period was assessed by anesthesiologists on the day of surgery, and by neurologists and patients at safety follow-up using feasibility questionnaires (Table 1). Rating scales ranged from 1 (I completely agree) to 6 (I do not agree at all).

Safety [adverse events (AEs), vital signs, 12-lead ECG, clinical laboratory parameters] was monitored in all patients throughout the study. Additionally, blood samples for the determination of rotigotine plasma concentrations were obtained prior to the removal of the first 24-h patches and analyzed by liquid chromatography with tandem mass spectrometry. The apparent rotigotine dose is an estimate of the amount of rotigotine delivered to the skin within 24 h and is calculated as the difference of the initial drug content in the unused patch and the residual drug amount in the used patch. Rotigotine was quantified in the used first 24-h patches by a validated method.

The study design did not include collection of Unified Parkinson's Disease Rating Scale (UPDRS) data because it

Table 2 Baseline characteristics of the study population ($n = 14$)

Patient	Age (years)	Gender	BMI (kg/m^2)	Hoehn & Yahr stage	PD duration (years)	Substituted PD medication (mg levodopa equivalent dose)	Rotigotine dose (mg/24 h)
10101	56	Female	25.8	2	3.1	905	16
10102	70	Female	25.7	3	7.0	500	16
10201	76	Male	23.0	2	6.7	370	8
10202	71	Male	27.3	2	2.7	400	8
10203	63	Female	29.1	1	11.9	1,400	14
10204	80	Male	30.9	3	9.3	800	6
10601	68	Female	25.0	3	14.7	775	8
10602	65	Female	27.3	1	2.7	670	12
10603	71	Female	30.5	3	20.7	100	2
10604	67	Male	28.7	4	12.8	1,295	16
10605	65	Male	24.9	4	8.0	700	16
10901	72	Male	24.0	3	0.6	150	6
11101	72	Female	24.1	1	10.2	650	12
11201	66	Male	22.0	3	3.4	600	12

BMI body mass index, *PD* Parkinson's disease

was felt that owing to the effect of surgery during the short study period, no clinically relevant statement about motor responses upon a change of PD medication was possible. An estimate is, however, provided by the answers of neurologists and patients to the feasibility questions ("unexpected symptoms of PD"). Owing to the exploratory character of the study, no formal sample size calculation was undertaken. Descriptive statistical analysis was performed with the SAS program (SAS Institute, Cary, NC, USA, version 9.1) using a full analysis set (FAS) patient population who had valid data for all three feasibility assessments. For a direct comparison of the substituted PD medications at doses of equivalent efficacy, all the dosages were converted to levodopa dosage equivalents according to the following formula (modified from Hobson et al. 2002):

Total levodopa equivalents = regular levodopa dose × 1 + levodopa continuous release dose × 0.75 + ([regular levodopa dose + continuous release levodopa dose × 0.75)] × 0.25 if taking tolcapone or entacapone) + pramipexole dose × 67 + ropinirole dose × 16.67 + pergolide dose × 100 + bromocriptine dose × 10 + cabergoline dose × 50 + amantadine dose × 0.5 + selegiline dose × 10 + rasagiline dose × 100.

Adverse events were encoded using the Medical Dictionary for Regulatory Activities version 9.1.

Results

Fourteen patients (7 female/7 male, mean age 68.7 ± 5.9 years, mean Hoehn & Yahr stage 2.5, mean PD duration 8.1 ± 5.6 years) received rotigotine treatment. Table 2 lists the baseline characteristics for each patient. Surgery was postponed in two patients; 12 (85.7%) patients underwent surgery as per protocol, one of them withdrew his consent postoperatively.

Orthopedic surgery was the most common surgical procedure (7 patients); others included midfacial tumor extirpation, bladder extirpation, plastic surgery, pars plana vitrectomy and cerebral shunt implantation. Most patients (71.4%) were on more than one PD medication within 2 days prior to switching. Substituted PD medication included levodopa (13), dopamine agonists (3 pramipexole, 3 ropinirole, 1 cabergoline), amantadine (4), catechol-*O*-methyltransferase inhibitors (4), rasagiline (1) and biperiden (1). The mean levodopa equivalent dose for the substituted PD medication was 665 ± 359 mg (Table 2). The majority of patients (64.3%) received rotigotine for 24 h; three patients (21.4%) were exposed for 2 days and two patients (14.3%) for 5 days. The median rotigotine dose was 12 mg/24 h (range 2–16 mg/24 h). Rotigotine doses for each patient are provided in Table 2.

Assessment outcomes

All three feasibility assessments were available for nine patients (64.3%) who were included in the FAS patient population. Table 1 lists the questionnaire ratings. The majority of neurologists (88.9%), anesthesiologists (88.9%) and all patients (100%) completely agreed (rating of 1) or agreed (rating of 2) with the statement that rotigotine transdermal patch presents a feasible option for the perioperative management of PD patients. All patients stated that their PD symptoms were well controlled (rating of 1 or 2) which corresponded to the specialists' opinion that most

patients did not show unexpected perioperative PD symptoms. Handling of the patch, switching and re-switching of PD medication were also rated easily feasible. In case of further surgery, the majority of the patients (88.9%) would again choose rotigotine transdermal patch.

Ten patients (71.4%) reported a total of 46 adverse events (AEs), mostly mild to moderate in intensity. At the end of the trial, 93% of AEs were listed as recovered; two AEs were recovered with sequelae (joint dislocation, dysesthesia) and one AE (iron deficiency) was ongoing. Five serious adverse events (SAEs) occurred; one was considered highly probably related to rotigotine treatment (hallucinations as described below), one may have been related (ventricular asystole as described below) and three were considered not drug related (mild post-procedural hematoma, moderate wound healing disturbance, and severe joint dislocation). A 72-year-old male on 6 mg/24 h rotigotine presented with moderate visual hallucinations (SAE) and severe nausea after surgery. The rotigotine dose remained unchanged and he recovered from the hallucinations on the same day and from nausea the day after. A 56-year-old female on 16 mg/24 h rotigotine had a ventricular asystole (SAE) after surgery which resolved spontaneously after 12 s without any therapeutic intervention. Rotigotine was withdrawn. The patient had experienced marked blood loss during surgery, requiring pharmacological intervention with catecholamines. Clinical chemistry assessed in the hours before the AE revealed low potassium and hemoglobin values; additionally, a low central venous pressure was reported. Concomitant medications at the time of the event were escitalopram oxalate (10 mg) once daily for depression and esomeprazole (40 mg) once daily for reflux oesophagitis. The patient had been on daily doses of 4.2 mg pramipexole, 400 mg of a levodopa/carbidopa/entacapone formulation and 100 mg levodopa/carbidopa extended release l/c which had been stopped the evening before surgery and resumed the day after surgery. Given the patient's clinical status during surgery and before the event, an association to rotigotine treatment seems unlikely but cannot be excluded.

There were no clinically relevant changes for the other safety parameters. Rotigotine plasma concentrations could be determined in ten patients (71.4%) and ranged between 0.164 and 4.230 ng/mL. Mean plasma concentrations (and apparent rotigotine doses) were in the same range as in previous clinical trials (Schwarz Pharma Ltd 2010; Güldenpfennig et al. 2005).

Discussion

Switching PD patients from oral dopaminergic medication to rotigotine transdermal patch for the perioperative period was considered feasible by a majority of neurologists, anesthesiologists, and their patients in this exploratory study. Handling of the patch was deemed simple, and switching and re-switching of PD medication easily feasible. Patient acceptance was high and, in case of further surgery, the majority would again choose rotigotine transdermal patch. Most patients had been on a regimen comprising at least two antiparkinsonian medications; apparently, previous polypharmacy did not influence the feasibility of switching to the patch.

Rotigotine absorption was not influenced by surgical procedures; apparent doses and plasma concentrations were within the published range (Schwarz Pharma Ltd 2010; Güldenpfennig et al. 2005).

Rotigotine-related adverse events were limited to two dopaminergic side effects in one patient (severe nausea and moderate hallucinations) and one ventricular asystole; and both were classified as serious. Both the patients recovered fully. While hallucinations and nausea are dopaminergic side effects, an association of the cardiac disorder to rotigotine seems unlikely. A recent thorough QT/QTc study in patients with advanced PD demonstrated that rotigotine application up to doses of 24 mg/24 h did not induce any QTc interval changes or other ECG abnormalities, indicating that the drug does not affect cardiac repolarization (Malik et al. 2008).

Considering the likely complications arising from discontinuation of oral dopaminergic PD medication with shorter half-lives during the perioperative period (Gálvez-Jiménez and Lang 2004; Frucht 2004) and the practical problems associated with current alternative parenteral administration routes, rotigotine transdermal patch may offer a feasible alternative for perioperative PD management.

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