J Neural Transm (2007) 114: 219–221
DOI 10.1007/s00702-006-0606-3
Printed in The Netherlands

Journal of Neural Transmission

Rotigotine transdermal system for perioperative administration

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Received: May 3, 2006 / Accepted: November 6, 2006 / Published online: December 21, 2006

Summary We present a series of patients participating in clinical trials with the rotigotine transdermal system. All patients were scheduled for surgery with general anaesthesia unrelated to the trial procedure or to rotigotine. Perioperative administration of rotigotine appeared to be feasible and efficacious. No safety issues emerged from these observations.

Keywords: Rotigotine, surgery, anaesthesia

Introduction

Parkinson's disease (PD) is a common disease in the western society. The incidence of PD increases with advancing age and is thus affecting approximately 3% of population over 66 years (Moghal et al., 1994). Since surgery is increasingly performed in the elderly population, PD is an important cause of perioperative morbidity with an estimated number of approximately 10.000 PD-patients/year undergoing inpatient surgery in Germany (Statistisches Bundesamt; Weitkunat et al., 2000). Falls in PD patients may contribute significantly to these figures: according to Wielinski et al. (2005), 36% of PD patients sustained an injury during a two-year period, requiring surgery in 13% and health care services in 76% of these patients.

Perioperative management of PD remained grossly unchanged for years. Current recommendations suggest administering the last dose of oral medication just before surgery and to continue as early as possible after surgery. However, this treatment is limited in several aspects: most of the currently available oral dopaminergic medications are characterized by a relatively short half life. This leads to PD-related complications such as upper and lower airway impairment, gastrointestinal, autonomic and psychiatric dysfunction, especially in extended operations or prolonged postoperative controlled ventilation periods. Re-initiation or adjustment of PD-therapy after such episodes is often prolonged. Alternative therapeutic strategies are invasive, complicated, and expensive. They include the administration of levodopa either via nasogastral tube or intraduodenally, amantadine intravenously, or the administration of apomorphine subcutaneously.

Thus, the current situation is characterized by a need for a perioperative drug regimen which would be able to provide long-lasting, dopaminergic stimulation, associated with easy handling and a simple switch procedure for preoperative initiation.

Rotigotine is a non-ergot DA with a D3/D2/D1 receptor profile. It is designed as a transdermal patch, to release the active substance over 24 hours following application to the intact skin.

In the course of clinical trials on rotigotine, several patients underwent surgery under general anaesthesia for reasons unrelated to trial medication and without interruption of the rotigotine transdermal treatment. In this paper, we describe our experience with these procedures.

Clinical setting

Several clinical trials using rotigotine in early PD patients (defined as taking an agonist as monotherapy) have been performed. For the purpose of this analysis, we included

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data from two prospective, double-blind, placebo-controlled, multicenter trials in the United States, Israel and Europe. Several subjects underwent surgery under general anaesthesia for reasons unrelated to the trial medication and without interruption of the rotigotine transdermal treatment. According to the trial protocols, the rotigotine patches were applied once daily. Concomitant PD medication with the exception of levodopa and dopamine agonists were permitted.

Results

In the course of the period under investigation, 837 trial participants with a mean age of 61.7 years (range 30–68 years) were screened. Forty-five patients were identified undergoing 47 surgical episodes with implied general anaesthesia. Twenty-eight patients thereof were treated with rotigotine and underwent 30 surgical episodes. Rotigotine was kept unchanged in 25 of these patients (26 surgical episodes; 85%). The decision for the perioperative management of the trial medication was left to the discretion of the investigator. Postoperatively, deep vein thrombosis, infection and pain were each reported in one patient respectively. No perioperative worsening of the symptoms of PD were reported. UPDRS Part III scores were measured regularly in the course of the trials in intervals of up to 12 weeks. The comparison of pre- and postoperative sum-scores revealed a difference of 0.4 points (Standard deviation 3.08). Table 1 shows a summary for these patients.

Table 1

Patient no.	Sex/age	Surgical procedure	Rotigotine dose at the time of the procedure (mg/day)
1	M/53	bilateral inguinal hernia repair	13.5
2	F/69	total knee replacement	18.0
3	F/72	coronary bypass surgery	18.0
4	M/67	bursectomy	9.0
5	F/63	skin tumor excision	18.0
6	M/74	inguinal hernia repair	18.0
7	M/71	laminectomy	18.0
8	F/60	total hip replacement	13.5
9	F/75	total hip replacement	13.5
10	F/78	hysterectomy	13.5
11	F/69	correction of foot malformation	13.5
12	M/56	laminectomy	13.5
13	F/63	laminectomy	13.5
14	M/83	transurethral prostate resection	13.5
15	M/87	defibrillator implantation	13.5
16	F/52	anterior colporraphy	18.0
17	F/73	cholecystectomy	13.5
18	M/46	appendectomy	18.0
19	F/63	total hip replacement	18.0
20	F/75	ovariectomy	13.5
21	F/73	cholecystectomy	13.5
22	F/79	cataract surgery	18.0
23	M/69	tooth extraction	13.5
24	M/67	prostatectomy	22.5
25	M/77	inguinal hernia surgery transurethral prostate resection	18.0

Discussion

Advances in surgical and anaesthetic techniques have enabled surgery in patients of advanced age and in those with relevant comorbidity, including those with PD.

Given the forecasted demographic changes in industrialized nations in the future and the increasing prevalence of PD with age, perioperative management of these patients will gain additional importance in the future. It has been shown that patients with PD have a significantly longer acute hospital stay and higher mortality than non-PD patients (Pepper and Goldstein, 1999). One of the major problems during the perioperative phase is the discontinuation of the oral dopaminergic therapy required for treatment of the disease (Kraft et al., 2004). An abrupt discontinuation can lead to akinetic crisis or parkinsonian-hyperpyrexia syndrome, which is clinically indistinguishable from the potentially lethal neuroleptic malignant syndrome (Thomas et al., 2003; Frucht, 2004; Granner and Wooten, 1991). Additionally, the expected worsening of parkinsonian rigidity and bradykinesia leading to immobility coupled with swallowing difficulties and inability to clear oral and pulmonary secretions may predispose these patients to perioperative complications such as pneumonia. In the postoperative period, insufficient therapy may lead to increased rigidity and immobility, which in turn, hampers nursing care and increases the risk of deep vein thrombosis and pulmonary emboli. The post-operative period may also be complicated by nausea and vomiting, which could limit the application of oral medicines. Although different parenteral routes to deliver antiparkinsonian medications (e.g., intravenous levodopa (Rosin et al., 1979), amantadine sulphate (Kornhuber et al., 1993), and subcutaneous and intravenous apomorphine and lisuride (Broussolle et al., 1992; Galvez-Jimenez and Lang, 1996, 2004) are available in the various countries, practical problems such as dosing and dose adjustments, complications, and side effects make these alternatives cumbersome, and their use has not gained broad acceptance.

Perioperative complications pose a significant problem in the PD population with a clear need for a new application route of dopaminergic therapy. The rotigotine transdermal delivery system may offer an alternative for PD patients through the perioperative period.

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