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CASE REPORT

Parenteral ziprasidone: a new atypical neuroleptic for emergency treatment of psychosis in Parkinson's disease?

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This is a report on a case series of five patiens with psychosis in Parkinson's disease who were treated successfully with an intramuscular injection of ziprasidone (10–20 mg) for acute agitation. No deterioration of motor function or other clinically relevant side effects were seen. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — Parkinson's disease; psychosis; treatment; neuroleptic; ziprasidone

INTRODUCTION

Psychosis is a common problem in advanced Parkinson's disease (PD) (Poewe, 2003; Fernandez *et al.*, 2003). States of acute agitation with hallucinations, paranoidal delusions and confusion often require parenteral treatment with antipsychotic drugs. In PD patients typical neuroleptics such as haloperidol involve the risk of akinetic crisis and neuroleptic malignant syndrome. The only atypical neuroleptic available so far for parenteral application is olanzapine which can cause deterioration of motor function in PD patients and a drop of blood pressure as well (Fernandez *et al.*, 2003; Goetz *et al.*, 2000). The atypical neuroleptics clozapine and quetiapine seem to contain the lowest risk of deleterious effects on parkinsonian symptoms but are only available for enteral treatment (Fernandez *et al.*, 2003; Matheson and Lamb, 2000; Parkinson Study Group, 1999; The French Clozapine Study Group, 1999).

PATIENTS AND METHODS

Ziprasidone, a new atypical neuroleptic for parenteral intramuscular emergency treatment of acute psychosis, was used in five patients with Parkinson's disease. The mean age was 71 years (Table 1). No patient fulfilled the clinical criteria for dementia with lewy bodies. All patients had suffered from PD for several years and were admitted to our specialized centre for movement disorders and PD because of an acute state of self-endangering agitation with hallucinations, delusions, anxiety and confusion during treatment with dopaminergic, anticholinergic or antiglutamatergic therapy. Antiparkinsonian treatment was reduced or stopped as far as possible in all patients before emergency treatment with ziprasidone. Two of the patients had been treated with atypical neuroleptics before (clozapine, quetiapine). ECG-recordings with 10 leads were done 12 to 72 h before and—assuming a half-time of ziprasidone of about 6 h—2 to 8 hours after the injection. The QT and RR intervals were measured manually and the QTc interval was calculated according to the formula of Bazett $QTc = QT\ (ms)/\sqrt{RR\ (s)}$ (Bazett, 1920). Blood pressure and body temperature were measured before and 1–4 h after the injection. An intramuscular injection was done in the gluteal muscle using 10 mg (three patients) or 20 mg (two patients) of ziprasidone. The psychopathological findings were rated on the brief psychiatric rating scale (BPRS) immediately before the injection and 2 h after injection. Motor function (bradykinesia, muscle rigidity, tremor) was monitored clinically before treatment and several

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Table 1. Clinical data

Patient	Age	Sex	Antiparkinsonian medication	Injected dose of ziprasidone
1	69	M	Levodopa, entacapone, pergolide	20 mg
2	59	F	Levodopa, clozapine	10 mg
3	81	M	Levodopa, quetiapine	10 mg
4	74	M	Levodopa, pergolide, amantadine	20 mg
5	71	F	Levodopa	10 mg

times during the first 24 h after the injection by the same examiner.

RESULTS

All patients showed moderate to good effects on agitation and excitement 30–60 min after injection of ziprasidone. The BPRS sum scores showed a reduction in all patients 2 h after injection (mean BPRS sum score from 72.2 to 47.6; $p = 0.006$; Table 2). 20 mg of ziprasidone seemed to be more effective and both patients receiving this dose had the best effects. Most of the patients showed moderate sedation, fell asleep for a few hours or were compliant enough to take their oral medication after one intramuscular injection. Only one patient receiving an injection of 10 mg required reinjection (again 10 mg). The main effects of the emergency treatment were moderate sedation and a reduction of confusion and anxiety. The clinical effects lasted for several hours in all patients. Oral neuroleptic maintenance treatment with clozapine or quetiapine could be started or continued in all patients after some hours. Clinical examinations during the first 24 h after injection showed no increase in bradykinesia, muscle rigidity or tremor. The QTc intervals before treatment were between 385 and 425 ms. Two to eight hours after injection the QTc intervals were calculated between 387 and 430 ms. Two patients showed a slight prolongation of 2 and 6 ms after treatment, whereas two patients showed a reduction of the QTc interval of 4 and 8 ms. No patient showed a clinically relevant drop of blood pressure or bradycardia.

Table 2. BPRS sum scores before and 2 h after injection of ziprasidone

Patient	Before treatment	After treatment
1	66	36
2	80	71
3	78	51
4	74	38
5	63	42
Mean scores ($p = 0.006$)	72.2	47.6

DISCUSSION

This is the first report on a case series of parenteral treatment of psychosis in PD patients with ziprasidone. Ziprasidone is a new atypical neuroleptic drug with predominant 5HT2a- antagonism, 5HT1a- agonism and low dopamine D2- and alpha1-antagonistic effects (Sallee *et al.*, 2003). Extrapyramidal side effects in the treatment of patients with schizophrenia are rare. Ziprasidone is available for parenteral intramuscular injection and enteral application (Altamura *et al.*, 2003). In Germany it is licensed for the treatment of schizophrenia in a dose range from 20 to 160 mg/d.

Five patients are reported with acute psychosis in PD who showed moderate to good effects on agitation and confusion in the emergency situation and a significant reduction of the BPRS sum scores 2 h after an injection of 10–20 mg of ziprasidone. Until now only two case reports and one anecdotal abstract (Lopez Del Val and Santos, 2004) have been published on enteral treatment with ziprasidone in PD patients. A patient with resistant psychosis responded to the treatment with a maximum dose of 80 mg/d of ziprasidone without worsening of motor function (Connemann and Schondeldt-Lecuona, 2004). Another PD patient was treated with 40 mg of ziprasidone and developed elevation of creatinine kinase and body temperature so that neuroleptic malignant syndrome was discussed in this patient and ziprasidone was stopped (Gray, 2004). More data concerning the treatment of psychosis in PD with ziprasidone are lacking. Due to this limited experience in PD patients, ziprasidone was not given as a maintenance treatment to our patients after the emergency injection.

No relevant worsening of bradykinesia, muscle rigidity and tremor or a drop of blood pressure occurred in our patients during the first 24 h after the injection. No formal rating of motor function was done because patients were mainly incompliant and sedation being one of the treatment effects interacts with motor parameters such as bradykinesia so that it is difficult to differentiate these in the confused patient. The absence of deterioration of motor function in our patients may be due to the rather low doses of 10–20 mg of ziprasidone used and the single application. The frequency of extrapyramidal side effects of ziprasidone in patients with schizophrenia has been estimated to equate to that of olanzapine (Tarsy *et al.*, 2002) which seems to have a higher risk

of worsening motor function in PD compared with clozapine (Fernandez *et al.*, 2003; Goetz *et al.*, 2000). There are no reports in the literature on the parenteral treatment of psychosis in PD with olanzapine. Compared with this substance the lower anticholinergic effects of ziprasidone may be a possible benefit in the treatment of confused patients.

No consistent changes in the QTc intervals were seen in our patients during treatment with ziprasidone. Asymptomatic prolongation of the QTc interval was described in patients with schizophrenia during treatment with ziprasidone, as reported for other typical and atypical neuroleptics. In lower dose, placebo controlled, studies a dose dependent effect was postulated: ziprasidone given in doses of < 80 mg/d caused a mean prolongation of the QTc interval of 0.6 ms, at 80 mg/d of 5.9 ms and at higher doses a maximum prolongation of 9.7 ms. No case of torsades de points has been described so far (Weiden *et al.*, 2002). Due to the lack of data in older patients and in patients with cardiovascular comorbidity, treatment of patients with risk factors for QTc prolongation or a combination with substances causing QTc prolongation is not recommended.

It is concluded that intramuscular injection of 10–20 mg of ziprasidone seems to be an effective and safe emergency treatment for acute psychotic agitation in Parkinson's disease. Due to the limited experience with this substance in PD and in older patients the control of motor function, body temperature, QTc interval and blood pressure is strongly recommended. Further studies are necessary to estimate the effects of maintenance treatment of PD patients with ziprasidone.

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