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A Pilot Study of Intramuscular Ziprasidone in the Short-term Treatment of Patients with Acute Exacerbation of Schizophrenia

SHLOMO BROOK*
Sterkfontein Hospital, P Bag X 2010, Krugersdorp, 1740, South Africa

Ziprasidone is a novel antipsychotic which, in oral formulation, has been shown to be effective and well tolerated in the treatment of acute psychosis. This pilot study examined the efficacy and tolerability of the intramuscular (IM) formulation and the transition from IM to oral ziprasidone in patients with acute schizophrenia. The study design was an open, prospective, 5-day treatment trial of IM ziprasidone followed by oral dosing in 12 patients with acute exacerbation of schizophrenia. Various doses (2·5, 5, 10, or 20 mg) up to 60 mg/day total were administered over 3 days, followed by transition to oral ziprasidone on Days 4–5. All patients completed the study. Mean improvements between baseline and Day 3 were observed in Brief Psychiatric Rating Scale (47·8 to 28·9) and Clinical Global Impression of Severity (6·1 to 5·3), and improvements were maintained on Days 4 and 5. No extrapyramidal syndrome, acute dystonia, or serious adverse events were reported. In these patients, IM ziprasidone 20–60 mg/day reduced psychomotor agitation and other symptoms of psychosis. The transition from IM to oral ziprasidone was well tolerated. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — ziprasidone; efficacy; tolerability; intramuscular formulation; acute schizophrenia

INTRODUCTION

Often the intensity and severity of symptoms experienced by acutely agitated psychotic patients preclude oral administration of medication. Currently, the range of intramuscular (IM) medication for the treatment of such patients generally is restricted to conventional neuroleptic agents and/or sedatives. While effective in reducing symptoms (Foster *et al*., 1997), these agents often have undesirable adverse effects, and switching to oral treatment may be problematic. Conventional neuroleptics are associated with extrapyramidal symptoms, such as akathisia and dystonia, and with orthostatic hypotension (Foster *et al*., 1997; Dubin *et al*., 1986), while the use of benzodiazepines runs the risk of excess sedation (Salzman, 1988).

Ziprasidone is a novel antipsychotic with a unique pharmacological profile (Seeger *et al*., 1995). It has a very high affinity for $5HT_{2A}$ receptors and a high affinity for D_2 receptors, predicting efficacy in the positive and negative symptoms of schizophrenia with a low capacity to induce extrapyramidal side effects. In addition, it has high affinity for $5HT_{1A}$, $5HT_{1D}$ and $5HT_{2C}$ receptors, which predicts efficacy in affective symptoms. It has relatively modest affinity for H_1 and α_1 receptors and negligible affinity for m1 receptors, which predicts a lower propensity for adverse events such as sedation, postural hypotension and cognitive impairment.

In clinical trials, oral ziprasidone 80–160 mg/day has been shown to be rapidly effective and well tolerated in treating patients with an acute episode of schizophrenia or schizoaffective disorder (Tandon *et al*., 1997). It significantly reduced overall psychopathology, positive symptoms and negative symptoms and, at 160 mg/day, associated symptoms of depression.

The evidence from trials of the oral formulation, coupled with ziprasidone's unique pharmacology, encouraged the development of an IM formulation of ziprasidone. Investigation of the pharmacokinetics of this formulation revealed that exposure was dose-dependent and that maximum serum

* Correspondence to: S. Brook, Sterkfontein Hospital, P Bag X 2010, Krugersdorp, South Africa 1740.

concentrations were attained within approximately 30 min (Miceli *et al*., 1998). Administration of multiple doses resulted in dose-dependent increases in exposure and little drug accumulation.

This single-center, pilot study examined the efficacy and tolerability of this formulation in a range of dosage regimens and the transition from IM to oral ziprasidone in patients with an acute episode of schizophrenia.

METHOD

Adult patients aged 18–65 years with an acute episode of chronic or subchronic schizophrenia (DSM-III-R [American Psychiatric Association, 1987]) were included. Patients with substance-induced psychotic disorders were excluded. All patients gave written informed consent, and the study received approval from local ethics committees.

Patients received 3 days of treatment with ziprasidone IM (10–60 mg/day), followed by 2 days of oral ziprasidone. No other antipsychotic medication was given. A variety of protocol-defined, fixed dosage schedules were administered (Table 1). The first six patients were assigned to one of four constant dose regimes, and the second six patients were assigned to one of two dose-escalation regimes. Consecutive doses of 20 mg were separated by at least 4 h, and all other doses were separated by at least 2 h. Injections were given in the upper arm or in the gluteal region. On Day 4, patients received oral ziprasidone in a BID schedule with food, with the total dose twice the Day 3 IM dose. On Day 5, patients received a single morning dose of 20–100 mg, based on clinical judgement. Patients were allowed lorazepam, benztropine, and propanolol as needed.

Efficacy was assessed using the Brief Psychiatric Rating Scale (BPRS) (Woerner *et al*., 1988) (rated 1–7, adjusted to 0–6), and the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) (Guy, 1976). To investigate the effect on specific symptoms of acute psychosis, the BPRS agitation cluster (items 2 [anxiety], 6 [tension], 10 [hostility], and 17 [excitement]) was determined. Assessments were made at screening and within 2 h after each morning dose, except on Day 4 when assessment was before the first oral dose.

All observed or volunteered adverse events occurring within 6 days of the last day of treatment were recorded. The Simpson–Angus (Simpson and Angus, 1970) and the Barnes Akathisia scales (Braude *et al*., 1983) were assessed at baseline and on Days 4 and 5. The degree of sedation was assessed 3–4 h after each morning IM dose. Blood pressure and pulse rate were measured immediately before and 30 min after each IM dose, and at study completion. An ECG was obtained at screening, on Day 4 before the first morning dose, and at study completion.

Since this was a pilot study, with the primary aim of establishing tolerability, no formal statistical analyses were conducted. The mean and standard deviation (SD) were calculated for each efficacy variable at each assessment. Simpson–Angus and Barnes Akathisia scales scores were summarized as the percentage of patients with an increase, decrease or no change from baseline and as the mean change and SD at each assessment.

RESULTS

All 12 patients completed the 5-day study period; none withdrew due to adverse events. All patients were diagnosed as suffering an acute exacerbation of schizophrenia, classified as disorganized (n=9),

Table 1. Summary of IM ziprasidone dosing regimes used in the study

Number of patients	Day 1	Day 2	Day 3
2	10 mg bid	10 mg bid	10 mg bid∗
1	10 mg tds	10 mg tds	10 mg tds
1	10 mg bid	10 mg tds	10 mg tds
2	20 mg bid†	20 mg bid	20 mg tds
3	2·5 mg qid	5 mg qid	10 mg qid
3	5 mg qid	10 mg qid	20 mg tds

∗One patient received 5 mg as the last dose instead of 10 mg.
†One patient received 20 mg as the first dose and 10 mg as the second dose.

paranoid ($n=2$) or undifferentiated ($n=1$). The patients were all men, 10 black and two white. Their mean age (range) was 26 years (19–39 years), and their mean weight (range) was 57·5 kg (47–73 kg). One patient had mild akathisia on entry. Four patients required lorazepam during the night while on ziprasidone IM. No patient required benztropine or propanolol.

Mean BPRS total scores showed numerical improvements on Day 1. This improvement continued over the 3-day IM treatment period, and was maintained during the 2-day oral treatment period (Table 2). There were similar improvements in the BPRS agitation cluster items. Total improvements were also reflected in the changes in CGI-S and CGI-I (Table 2).

No serious adverse events occurred. Four patients experienced an adverse event on ziprasidone IM and two on oral ziprasidone, most were of mild or moderate severity. One patient had mild nausea on Day 4 with an oral dose of 120 mg/day. One patient on 10 mg IM BID experienced vomiting on Day 2 and recurring penile erection on Days 1, 2, and 3. The erection did not meet the clinical criteria for priapism since it was transient, was not painful, and did not require treatment. The patient had no previous history of this problem, and it did not recur.

No extrapyramidal syndrome (EPS), dystonia, tachycardia, or postural hypotension were reported. One patient, with mild akathisia on entry, had moderate akathisia on Day 3. There were no clinically meaningful changes in cardiovascular function and no ECG abnormalities.

Most (10/12) patients had an improvement or no change in their Simpson–Angus scores on Day 5. Mean (SD) Simpson–Angus scores at baseline and mean (SD) changes from baseline on Days 4 and 5 were 3·9 (7·0), −0·6 (5·8), and −1·3 (6·1), respectively. Most (9/12) patients on Day 5 experienced an improvement or no change in their Barnes Akathisia score. Mean (SD) Barnes Akathisia scores at baseline and mean (SD) changes from baseline to Days 4 and 5 were 0·4 (1·0), 0·0 (1·1), and 0·3 (1·2), respectively.

Ziprasidone IM had a tranquilizing effect that, with doses of 20 mg, was apparent within 30 min.

DISCUSSION

This study was the first Phase II trial of an IM formulation of a novel antipsychotic. The results indicate that ziprasidone IM 2·5 mg QID–20 mg TID is well tolerated and reduces psychomotor agitation and symptoms of psychosis in patients with an acute exacerbation of schizophrenia. The 12 men who took part in this study had moderate levels of overall psychopathology including anxiety, tension, excitement, and hostility. Prospectively defined fixed-dose and dose-escalation regimens were employed to investigate the tolerability of a range of doses.

Changes in mean scores on efficacy rating scales for this series of patients indicated that ziprasidone IM had an effect within 2 h of the first dose. This improvement continued during the IM treatment phase, and resulted in a substantial improvement on the third and final day of IM treatment. There was a marked reduction in symptoms of psychomotor agitation, as shown by the improvement in mean BPRS agitation cluster items. The diversity of dosage regimens used precludes definite state-

Table 2. Mean scores on measures of psychopathology in patients ($n=12$) with an acute exacerbation of schizophrenia or schizoaffective disorder treated with IM ziprasidone for 3 days followed by treatment with oral ziprasidone

			IM treatment						Oral treatment phase			
	Baseline		Day 1		Day 2		Day 3		Day 4		Day 5	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BPRS total	47·8	10·5	43·3	12·0	32·2	17·7	26·3	17·4	28·2	16·1	28·9	16·8
BPRS anxiety	3·3	0·6	2·9	0·9	2·2	1·0	1·7	1·3	2·2	1·5	1·7	1·4
BPRS tension	3·1	0·8	2·8	1·4	1·9	1·4	1·3	1·3	1·6	1·5	1·4	1·3
BPRS hostility	2·3	1·0	2·1	1·0	1·0	1·0	0·3	0·7	0·4	0·9	0·4	0·7
BPRS excitement	3·2	1·3	2·6	1·7	2·2	2·2	1·3	1·6	1·2	1·4	1·4	1·8
CGI-S	6·1	0·3	6·0	0·0	5·4	1·2	5·3	1·4	5·0	1·3	5·3	1·4
CGI-I	N/A	N/A	3·8	0·4	3·3	1·2	3·0	1·3	2·9	1·3	3·3	1·4

ments regarding the effect of dose on efficacy, however clinical observation suggested that the benefits were prominent at doses >10 mg/day, with a tranquilizing effect observed within 30 min of doses of 20 mg. The effect of ziprasidone IM was maintained after transition to oral ziprasidone.

Four patients required nighttime lorazepam while on ziprasidone IM, and this may potentially have influenced psychopathological status. In addition, this was a noncomparative study, and therefore the effect of non-specific factors, such as admission to hospital, cannot be excluded from an effect on psychopathology.

Ziprasidone was well tolerated, and no clinically meaningful changes in cardiovascular function were observed. Side-effects associated with conventional IM neuroleptics, such as excessive sedation, dystonia, akathisia, and hypotension (Dubin *et al*., 1986), which often add to the distress associated with acute agitation and increase the need for medical monitoring, were not apparent in this pilot study.

Patients were not profoundly sedated but generally remained calm, conversant, and ate and drank normally. While short-term sedation is desirable to calm very agitated patients, the mental confusion and profound sedation often associated with neuroleptics and sedatives are not always beneficial (Salzman, 1988). In addition, no patient experienced dysphoria, another unpleasant side-effect associated with some antipsychotics.

This open, pilot study recruited only a small sample of patients and did not include a placebo arm or an active comparator. However, based on the results, further evaluation of the efficacy and tolerability of rapid-acting ziprasidone IM in acutely psychotic patients in larger, comparative studies, as well as the transition to the oral formulation, is warranted.

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