in the 20 mg group compared with the 2 mg group ($P < 0.001$). The percentage of patients classified as responders (prospectively defined as a ≥ 2 point reduction in the BARS at 90 min) was significantly greater in the 20 mg group (65%) compared with the 2 mg group (26%) ($P = 0.001$). The improvement in CGI-severity and PANSS agitation items at 4 h was significantly greater in the 20 mg group compared with the 2 mg group ($P < 0.05$), as was the CGI-improvement score at 4 h. Mild/moderate somnolence and nausea were the most frequently reported adverse events. Mean Simpson-Angus, Barnes Akathisia and AIMS scores improved slightly between baseline and the last observation in both groups; no dose-response relationship was apparent. There were no cases of dystonia reported. The results of this study indicate that patients with psychosis and acute agitation treated with IM ziprasidone 20 mg experienced a rapid and substantial reduction in agitation for at least 4 h after administration. This appears to have been achieved without causing extreme sedation. Ziprasidone IM 20 mg was very well tolerated, particularly with regard to movement disorders.

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INTRAMUSCULAR ZIPRASIDONE 10 MG AND 20 MG IN PATIENTS WITH PSYCHOSIS AND ACUTE AGITATION

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While intramuscular (IM) sedatives and/or conventional neuroleptics are often used in the treatment of psychotic patients with acute agitation, such treatments are associated with excessive sedation and extrapyramidal symptoms. Two 24-h, randomized, double-blind, fixed-dose clinical trials of the rapid-acting IM formulation of the novel antipsychotic, ziprasidone, were conducted in hospitalized patients with psychosis and acute agitation. Patients received an initial IM ziprasidone dose and, if needed, up to three subsequent doses of either 2 mg ($n = 54$) or 10 mg ($n = 63$) (up to q2h) in one study and 2 mg ($n = 38$) or 20 mg ($n = 41$) (up to q4h) in the other. Efficacy was assessed using the CGI, PANSS and the seven-point Behavioural Activity Rating Scale (BARS), a novel measure of agitated behaviour ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). A significant reduction in BARS was observed by 1 h in the 10 mg group ($P < 0.05$) and by 30 min in the 20 mg group ($P < 0.001$). The percentage of patients classified as responders (≥ 2 point reduction in the BARS at 90 min) was significantly greater in the 10 and 20 mg groups compared with the 2 mg groups ($P < 0.05$). After the first injection, the mean AUC for BARS at 2 h and at 4 h was significantly lower in the 10 and 20 mg groups compared with their respective 2 mg groups ($P < 0.001$). In patients initially treated during the day, the improvement in CGI-severity was significantly greater in the 10 and 20 mg groups compared with their respective 2 mg groups ($P < 0.05$). A comparison of treatment effects confirmed a dose-response relationship for the 10 and 20 mg doses. Mild/moderate somnolence and nausea were the most frequently reported adverse events associated with the 10 and 20 mg doses. Mean Simpson-Angus, Barnes Akathisia and AIMS scores improved slightly between baseline and the last observation in all treatment groups. There were no cases of dystonia reported. These results indicate that IM ziprasidone 10 mg and 20 mg are rapidly effective in ameliorating the symptoms of acute agitation associated with psychosis, without causing extreme sedation. Both doses were very well tolerated, particularly in assessments of movement disorders.

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A COMPARISON OF INTRAMUSCULAR (IM) ZIPRASIDONE WITH IM HALOPERIDOL

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This randomized, open-label study in patients with psychotic disorder compared the tolerability and safety of three fixed doses of IM ziprasidone with flexible-dose, IM haloperidol. Patients received either IM ziprasidone 20 mg/day ($n = 69$), 40 mg/day ($n = 71$) or 80 mg/day ($n = 66$), all given qid, or IM haloperidol 10–40 mg/day ($n = 100$), given bid-qid (mostly bid), for 3 days. After IM treatment, patients received 4 days' oral treatment with randomized therapy (ziprasidone 40–200 mg/day, haloperidol initial dose equal to last IM dose). Discontinuation due to adverse events was rare. Almost all adverse events were of mild or moderate severity. Tachycardia and postural hypotension were very infrequently associated with ziprasidone. Notable was the lower incidence of EPS, dystonia and akathisia associated with IM ziprasidone compared with IM haloperidol. The proportion of patients taking benztropine during the study was lower than baseline in the ziprasidone groups but higher in the haloperidol group. Benztropine use was at least two-fold greater with haloperidol than with any ziprasidone dose, both during the IM period and at any time during the study. Ziprasidone IM was most frequently associated with headache, nausea and insomnia. Patients had modest levels of overall psychopathology, as shown by the mean baseline BPRS total and core items scores and the CGI-severity score. In all treatment groups there was a moderate reduction in mean BPRS total score in the IM treatment period which was maintained during the oral treatment period. In the three ziprasidone treatment groups, there was a reduction in mean scores on the Behavioral Activity Rating Scale (BARS), a novel measure of agitated behaviour. This reduction was more rapid than that observed with haloperidol, and was maintained in most patients for at least 2 h post-dose with ziprasidone 5 and 10 mg, and at least 4 h post-dose with ziprasidone 20 mg. Ziprasidone shows promise as a novel IM treatment for acutely agitated patients and may have tolerability advantages over conventional rapid-acting, IM antipsychotics, particlularly with regard to movement disorders.

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CHARACTERIZATION OF THE INTRAMUSCULAR PHARMACOKINETICS OF ZIPRASIDONE IN SCHIZOPHRENIC PATIENTS

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Intensive pharmacokinetic sampling in patients with schizophrenia carries the potential for disease exacerbation and subject withdrawal. An additional problem is that drug intolerance often occurs when multiple dose pharmacokinetic studies are conducted in healthy subjects using therapeutic antipsychotic doses. To obviate this problem, a population pharmacokinetic approach was employed in the Phase I development of rapid-acting intramuscular (IM) ziprasidone to characterize its pharmacokinetics and safety in patients. In this study, patients with schizophrenia received IM ziprasidone doses of 5 mg ($n = 6$), 10 mg ($n = 6$), or 20 mg ($n = 6$) four times daily for 3 days. Pharmacokinetic sampling was limited to 12 samples on Day 1 and 14 on Day 3. Building upon a population pharmacokinetic model established from data-rich, single-dose studies performed in healthy subjects, the multiple-dose

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