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

https://doi.org/10.1016/S0924-9338(99)80614-2 Published online by Cambridge University Press

disposition of ziprasidone was characterized in patients for this study. The results were consistent with predictions from the single dose, showing attainment of peak exposure within approximately 30 min, dose-related increases in exposure, and little drug accumulation. The model refinement afforded from the multiple-dose patient data was then used for population modeling and covariate identification for phase III studies of IM ziprasidone. Thus, the approach used here demonstrated that population pharmacokinetic modeling is a useful tool in understanding drug disposition in subject populations where pharmacokinetic sampling is limited. Ziprasidone IM has a linear pharmacokinetic profile. Therapeutic plasma concentrations are attained rapidly.

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RELATIONSHIPS BETWEEN OXCARBAZEPINE METABOLITES LEVELS, PROPHYLACTIC EFFICACY & SIDE EFFECTS

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Oxcarbazepine (OXC) is the keto derivate of carbamazepine with the same pharmacologic properties. 19 patients with affective & schizoaffective psychoses were treated with OXC for no less than 1 year & levels of OXC, its monohydroxy derivative (MHD) & glucuronide conjugate (GLC) were measured in plasma by 15 points during this period. First week with a steady-state within the mean plasma level of OXC was 0.189 ± 0.29 mkg/ml & maintaned stable during long-term treatment. Negative correlation between prophylactic efficacy and the individual OXC biotransformation speed was found. So the prophylactic effect was better in patient with high & permanent plasma level of MHD. There was strong linear correlation between early sedative side effects & MHD/GLC (0.9, $p < 0.01$). Obviasly the speed of MHD transformation to GLC is responsible for individual neurotoxic effects of OXC.

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IMPAIRMENT OF AUTONOMIC CARDIAC VAGAL FUNCTION UNDER CLOZAPINE

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Objective: To evaluate peripheral measures of autonomic neurocardial function in schizophrenics treated with clozapine.

Methods: Twenty clozapine treated schizophrenics (DSM-III-R) underwent standardised cardiovascular autonomic function tests (1). Moreover, serial computerized investigations of heart rate variability (HRV, 2) were performed in seven untreated schizophrenics before and under 100 mg clozapine. Exclusion criteria were cardiac, pulmonary or neurological disease, thyroid disease, diabetes mellitus, alcoholism and drug dependence.

Results: According to established criteria (1) in clozapine treated schizophrenics the percentages of pathological tests were 70% for the 30:15 ratio, 60% for the deep-breathing-test and 30% for the Valsalva-test. Compared to healthy controls (n = 79) untreated schizophrenics showed a significantly higher mean resting heart rate and more low-frequency power (spectral analysis VLF-LF, 0.003–0.15 ms^2) suggesting a higher level of arousal in these patients. Clozapine treatment was followed by a decrease of the VLF- and LF-power. In addition there was a substantial decrease in all HRV-parameters known to reflect parasympathetic activity (e.g. mean coefficient of variance, root mean square of successive differences, high frequency power).

Conclusion: Taken together our data indicate a substantial impairment of cardiac vagal function in most clozapine treated patients, which may in part be due to clozapine's striking anticholinergic and -alpha-2-adrenergic properties. Survival studies in patients with diabetes, chronic alcoholism or myocardial infarction indicate a higher mortality rate due to cardiovascular causes in patients with cardiac vagal dysfunction compared to those patients without autonomic abnormalities. On the basis of these findings long-term survival studies of patients with and without neuroleptic-induced autonomic neurocardial dysfunction seem warranted.

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CLOZAPINE TREATMENT IN THERAPY-REFRACTORY SCHIZOPHRENIA: AN ECONOMIC ANALYSIS

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A recent study carried out at the Psychiatric Department of Magenta Hospital is based on data collected on the 15 schizophrenic patients who started clozapine therapy between 1993 and 1996. Patients included in the study were resistant to at least two conventional antipsychotic treatments. This was a mirror-image designed study with data covering the year prior to commencing clozapine and the year following the stablishment of the clozapine therapy. Three of the 15 patients who received clozapine dropped out before the twelfth month of treatment. Considering the 12 patients on clozapine treatment for at least one year, average score in item 1 of CGI changed from 6.3 ± 0.8 (SD) to 4.8 ± 0.9 after one year of treatment. Over the same period GAF improved from 20.9 ± 7.4 to 43 ± 13.4 ($p < 0.05$). The 12 patients had 32 admissions for 1,294 hospital days in the "pre clozapine" period and 16 admissions totalling 706 hospital days in the "post clozapine" period. In the "post-clozapine" period patients had a higher utilisation rate of days spent in residential rehabilitation centres (+33.9%) and of community services, expecially in the rehabilitation area. The total annual cost per patient of antipsychotic therapy "pre-clozapine" was 534.085 It L. and after commencement of clozapine was 3.441.439 It L. Cost of community services was higher after commencement of clozapine (4.680.083 It L. per patient, compared with 1.770.458 It L. in the pre clozapine period). However, higher cost for drug therapy and community services in the post-clozapine period were more than offset by lower cost of acute hospital care (43.672.500 It L. vs. 23.827.500 It L.). Consequentely, the total cost per patient of clozapine regimen (55.521.464 It L.) was 13% lower than traditional treatment (63.406.584 It L.).

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CLOZAPINE VERSUS TYPICAL ANTIPSYCHOTICS IN SCHIZOPHRENIA: EPS RETROSPECTIVELY (1–20 YEARS) AND PROSPECTIVELY (5 YEARS)

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Schizophrenic patients in long-term monotherapy with clozapine (n = 100) and perphenazine, flupenthixol or zuclopenthixol (controls

https://doi.org/10.1016/S0924-9338(99)80614-2 Published online by Cambridge University Press