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

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= 100) were evaluated for extrapyramidal side effects (EPS) (blind) as well as other side effects and mental condition (non-blind).

Methods: Chronic schizophrenic patients were evaluated from the charts from the beginning of the present treatment (1–20 years) and prospectively for 5 years. The following rating scales were used: The Sct. Hans Rating Scale for EPS (SHRS) which includes videotape recording, Brief Psychiatric Rating Scale (BPRS), the UKU side effect scale and the Clinical Global Impression scale (CGI).

Results: There was a significantly lower prevalence of tardive dyskinesia (TD) in clozapine treated patients than control patients, although prior to this treatment there were more TD in the clozapine group ($p < 0.05$). This lower level of TD in the clozapine group was related to a lower induction of new cases ($p < 0.001$) and a tendency towards greater disappearance of TD in the clozapine group than in the control group. Clozapine treated patients without TD had started clozapine and ceased traditional neuroleptics at an earlier age than those with TD. Parkinsonian signs were seen in 33% of the clozapine treated patients versus 61% of the control patients. Psychic akathisia was found in 14% versus 40% and motor akathisia in 7% versus 29% of the patients, all differences significantly in favour of clozapine. The 5-year evaluation is going on and will be reported. Preliminary data suggest that the lower induction of new cases of TD and the tendency towards greater disappearance of TD in the clozapine treated group continues resulting in an additional decrease of TD among the clozapine treated patients.

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LONG-TERM EFFICACY, SAFETY, AND TOLERABILITY OF RISPERIDONE IN ELDERLY PSYCHOTIC PATIENTS

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A 12-month, open-label, multicenter trial of risperidone in elderly psychotic patients is being conducted. Results from 106 patients treated for 3 months (endpoint) are reported. The mean daily dose of risperidone (oral solution) at endpoint was 3.7 mg. Statistically significant improvements in psychopathology (score reductions on the Positive and Negative Syndrome Scale and the Clinical Global Impression scale) were shown by the patients at endpoint; 57% were rated as clinically improved (≥20% reduction in PANSS scores). Severity of extrapyramidal symptoms (scores on the Extrapyramidal Symptom Rating Scale) was low at baseline and was significantly reduced during treatment. Thirty-two patients withdrew from the trial, the most common reasons being adverse events (in 14) and insufficient treatment response (in 8). It is concluded that risperidone is effective, well tolerated, and safe in elderly psychotic patients.

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WIE WIRD RISPERIDON IN DER TÄGLICHEN ANWENDUNG DOSIERT: ZWISCHENERGEBNISSE EINER DEUTSCHEN PHASE IV PRÜFUNG

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Zur Zeit wird in Deutschland eine Phase IV Prüfung durchgeführt mit dem Ziel, die Langzeitanwendung von Risperidon bei der Behandlung der chronischen Schizophrenie unter Alltagsbedingungen zu untersuchen. Die Patienten werden über einen Zeitraum von 2 Jahren beobachtet, in regelmäßigen Abständen werden das Vorhandensein psychotischer Symptome, das psychosoziale Funktionsniveau, die Dosierung und Verträglichkeit evaluiert. Diese Zwischen-auswertung zeigt die Ergebnisse der ersten 886 Patienten, die im ersten Jahr der Studie eingeschlossen wurden über einen Zeitraum von 6 Monaten. Im Mittel waren die Patienten 12 Jahre krank. Die Minussymptomatik war stärker ausgeprägt als die Plussymptomatik. Unter der Behandlung mit Risperidon nahmen sowohl psychotische Symptome als auch vorbestehende extrapyramidalmotorische Symptome sowie die Häufigkeit des Gebrauchs von anticholinerger Medikation ab. Die mittlere Risperidon-Dosis bei Monat 6 war 4.8 ± 1.9 mg pro Tag. Patienten, die mit Neuroleptika vorbehandelt waren, erhielten höhere Risperidon-Dosen als Patienten ohne vorherige neuroleptische Medikation. Im Lauf der Behandlung reduzierte sich die Ko-Medikation mit hochpotenten Neuroleptika, während der Gebrauch von niedrig- und mittelpotenten Neuroleptika als Ko-Medikation im wesentlichen unverändert blieb.

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OVERDOSES WITH 650 MG. OF OLANZAPINE IN A SCHIZOPHRENIC PATIENT

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Olanzapine is an antipsychotic drug that belongs to the tienobenzodiacepine (group) with afinity for the dopaminergic, serotoninergic, adrenergic, histaminergic and muscarinic receptors and a half-life of elimination 30'5 hours. In the present work it's related an intoxication with 650 mg. of Olanzapine (without any other drugs association) in a woman 34 years old, caucasic race, diagnosticated of schizophrenia paranoid with 12 years evolution, she was admitted approximately 8 hours after the ingestion of the drug. Before the arrival of the patient to the Hospital, as related by her relatives, she suffered from a confusional syndrome with language disturbance, ataxia, disorientation, excitement with aggresive behaviour and visual hallucinations. The patient was admitted in the I.U.C. with a coma grade IV/V, intermedium pupils with minimal reaction, hyperreflexia, Babinsky (+), temperature 37'8°C; tachycardia 180 p.p.m. that required treatment with amiodarone; hypotension (80/50) that needed continuous perfusion with norepinephrine during the first six hours of her admission; E.C.G. was normal at all moments, having a sinusal rythnm, without prolongation of the QT; electrolytic balance which didn't need appropiate diuretic support. In 12 hours time she presented a metabolic acidosis that required bicarbonate perfusion; the agitation episodes decreased with clorazepate 130 mg/day i.v.. After 24 hours she was hemodinamically stable, leaving I.U.C. after 48 hours. During her stay at the Acute Care Unit of Psychiatry neither hematologic and biochemical alterated parameters were present, nor persistent somatic (evaluated by U.K.U.) or cognoscitive (Benton visual retention test and Weschler Adult Intelligence Scale) damages related to the intoxication with Olanzapine.

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TREATMENT OF THE SYMPTOMS OF SCHIZOPHRENIA: A META-ANALYSIS COMPARING RISPERIDONE WITH OTHER ANTIPSYCHOTICS

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Combined data on efficacy were available from 12 double-blind short-term comparative trials of risperidone and other antipsy-

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