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.

## Wed-P56

RELATIONSHIPS BETWEEN OXCARBAZEPINE METABOLITES LEVELS, PROPHYLACTIC EFFICACY & SIDE EFFECTS

M. Kouzavkova*, A. Singin, E. Kostiukova, S. Mosolov. *Moscow Research Institute of Psychiatry, Moscow, Russia*

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.

## Wed-P57

IMPAIRMENT OF AUTONOMIC CARDIAC VAGAL FUNCTION UNDER CLOZAPINE

M.W. Agelink[1]*, R. Malessa[2], S. Meinecke[1], T. Zeit[1], W. Lemmer[1]. [1]*Dept. of Psychiatry, EvK Gelsenkirchen, University of Bochum;* [2]*Dept. of Neurology, University of Jena, Germany*

**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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## Wed-P58

CLOZAPINE TREATMENT IN THERAPY-REFRACTORY SCHIZOPHRENIA: AN ECONOMIC ANALYSIS

M. Percudani[1]*, G. Fattore[2], J. Galletta[1], A. Contini[1], A.C. Altamura[3]. [1]*Dipartimento di Psichiatria, Ospedale "G. Fornaroli", Magenta (Mi);* [2]*CeRGAS, Università "L. Bocconi", Milano;* [3]*Istituto Scienze Biomediche, Università di Milano, Ospedale "L. Sacco", Italy*

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.).

## Wed-P59

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

M. Brandt-Christensen*, L. Peacock, J. Gerlach. *Sct. Hans Hospital, DK-4000 Roskilde, Denmark*

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

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