Psychoses:
– treatment

CISORDINOL (ZUCLOPENTHIXOL) IN THE TREATMENT OF SCHIZOPHRENIA. RELATION BETWEEN DOSE, PLASMA CONCENTRATION AND EFFECT

F Haffner [1], O Lingjærde [2], E Mæhlum [3], et al
1.Psychiatric Institute, Frederiksborg General Hospital, Copenhagen, Denmark; 2. University Unit , Gaustad Hospital, Oslo, Norway; 3. H. Lundbeck A/S, Norway

Objectives . To investigate the relation between dose, plasma concentrations and efficacy of peroral Cisordinol in schizophrenic patients, in order to establish a reference plasma concentration range for optimal treatment. Materials 50 patients with schizophrenia (DSM-III-R),with no concomitant serious medical condition, were included. There were 26 women and 24 men. Age ranged from 18 to 87 years, mean 51 years.10 patients dropped out during the study, 2 due to adverse effects, 6 due to clinical deterioration, or lack of improvement, and 2 of the patients withdraw their consent. Methods After at least 4 days washout, patients were randomly assigned to a high or a low dose for 16 weeks. The dose could be doubled at week 6 and 12. Oxazepam was allowed for sedation when required, but no concomitant antipsychotics were allowed. The patients condition was followed with the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions (CGI). Results 40 patients were evaluable. Pasma concentration correlated significantly with daily dose , whereas no simple relation berween plasma concentration and improvement was found.However among the patients experiencing a reduction in total BPRS score of 50% or more, 59 % had plasma concentrations between 7 and 35 nmol/l. Conclusions A definite consentration range within which all schizophrenic patients would receive optimal Cisordinol treatment was not found. However, a majority of responding patients fell within the rather wide range of 7 to 35 nmol/l. With some reservation, therefire, this can be suggested as a reference range for schizophrenic patients treated with Cisordinol.

AMISULPRIDE VS FLUPENTIXOL IN PRODUCTIVE SCHIZOPHRENIA: A CONTROLLED DOUBLE-BLIND STUDY

A Hillert[1], M Philipp[1], WF Gattaz[2], H Sauer[3], H Wetzel[1], O Benkert[1], and the Amisulpride Study Group
[1] Department of Psychiatry, University of Mainz, Germany,
[2] Central Institute of Mental Health, Mannheim, Germany,
[3] Department of Psychiatry, University of Heidelberg, Germany

Amisulpride (AMI), a novel substituted benzamide with selective affinity for dopamine D_2 and D_3 receptors, preferentially active in limbic areas and devoid of cataleptogenic potential even at high doses in animal studies, was tested against flupentixol (FLU) as reference drug in a double-blind multicenter study including predominantly productive patients with a DSM III-R diagnosis of schizophrenia, paranoid or undifferentiated type with acute exacerbation.
132 patients were included in the study, 70 received AMI (1000 mg/d), 62 FLU (25 mg/d) for a treatment period of 6 weeks.
Efficacy and safety were assessed using BPRS (score 1 to 7), SAPS, SANS, CGI, GAS, Simpson-Angus Scale, Barnes Akathisia Scale, and AIMS.
Both drugs significantly improved the acute psychotic symptomatology (BPRS total score: AMI D0 56.1±10.8, Dend 32.4±15.4 vs FLU D0 49.8±9.3, Dend 33.3±15.6) A similar decrease was found in SAPS scores: AMI D0 59.2±23.4, Dend 14.7±23.4, FLU 52.8±18.4, Dend 20.1±31.1.
SANS scores also decreased in both groups: AMI D0 41.7±15.9, Dend 22.8±19.4, FLU D0 32.0±14.3, Dend 22.3±22.0.
Discontinuation rate was not different between the 2 groups, 72.9% of AMI and 59.7% of FLU patients completed the treatment period.
Discontinuation due to adverse events was significantly higher in the FLU group (17.7% vs 5.7%, $p<0.05$).
Extrapyramidal symptoms, akathisia and dyskinesia scores were significantly higher in the FLU group at the end of treatment, confirming the better neurological tolerability of AMI.
Biological safety data did not show any clinically relevant modification under treatment in both groups.
With respect to efficacy and safety, the results of this study indicate a benefit risk ratio in favour of AMI in acute schizophrenic patients mainly due to better extrapyramidal tolerability.

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RANDOMIZED, DOUBLE-BLIND, CONTROLLED TRIAL OF RISPERIDONE VERSUS CLOZAPINE IN PATIENTS WITH ACUTE EXACERBATIONS OF SCHIZOPHRENIA

E. Klieser, *F. Rappard
Psychiatric Department, Heinrich-Heine-University, Bergische Landstrasse 2, D-4000 Dusseldorf 12, Germany. *Janssen GmbH, Raiffeisentraße 8, 4040 Neuss 21 (Rosellen), Germany.

Conventional neuroleptics often leave a substantial proportion of schizophrenic patients with considerable residual symptoms, particularly negative symptoms, and troublesome side effects including extrapyramidal symptoms (EPS). Although clozapine is effective against both positive and negative symptoms of schizophrenia and is rarely associated with significant EPS, a number of other side effects have been reported including a 1-2% incidence of potentially lethal agranulocytosis. The serotonin-dopamine antagonist (SDA) risperidone is effective against positive, negative and affective symptoms of schizophrenia, with a low incidence of EPS. This study compared the efficacy and tolerability of risperidone and clozapine. Patients with acute exacerbations of chronic schizophrenia were randomized to double-blind treatment with risperidone 4 mg (n=20), risperidone 8 mg (n=19) or clozapine 400 mg (n=20) daily for 28 days. Treatment efficacy was assessed using the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI); tolerability was measured by the Simpson & Angus scale for EPS, the Association for Methodology and Documentation in Psychiatry (AMDP) scale for somatic side effects and by spontaneous reports of adverse events. There was a reduction in psychotic symptoms and global improvement in all three treatment groups with no significant differences in side effects between the groups except for salivation which was more pronounced in clozapine-treated patients ($p<0.01$ vs risperidone). Risperidone had no effect on vital signs, whereas clozapine-treated patients had a mean reduction in heart rate of 10 bpm. It is concluded that risperidone 4 or 8 mg daily is at least as effective as clozapine 400 mg daily, and is better tolerated. Risperidone appears to be a therapeutic alternative to clozapine.

PROPHYLACTIC LITHIUM IN WOMEN AT HIGH RISK FOR POSTPARTUM PSYCHOSES.

JL Klompenhouwer, AM van Hulst, RC van der Mast, FK Lotgering
Vincent van Gogh Institute for Psychiatry, Dept. Biological Psychiatry, P.O. Box 5, 5800 AA Venray, The Netherlands

The development of an adequate strategy in preventing the recurrence of puerperal psychosis in patients at high risk for such a recurrence was the aim of this study.
The figures in the literature on the subject of recurrence risks of postpartum psychoses vary between 20 and 50% depending on the risk factor studied. A personal history of (bipolar) mental illness, a family history of psychiatric illness (especially affective disorder) and a previous episode of postpartum psychosis are such risk factors. The recurrence rate of 41% we recently reported in a follow-up study of patients treated in Rotterdam because of postpartum psychosis illustrates this risk. In this study we present the case vignettes of the first (six) patients and the results in sixteen patients given prophylactic lithium after eighteen pregnancies. The prophylactic lithiumcarbonate treatment was well tolerated and in general patients expressed great satisfaction with the program, for it was the first time most of them could happily enjoy the puerperium. We report a recurrence rate of 11% (2 recurrences in 18 cases) in patients prophylactically treated with lithiumcarbonate in Rotterdam, and a recurrence rate of 13% if the results of an international "three centers study" to which we contributed are taken into account. This recurrence risk falls well below the risk of recurrence if only a single risk factor existed. The results of this study strengthen the evidence that lithiumcarbonate given immediately after delivery is effective in reducing the risk of recurrence of postpartum psychoses and bipolar disorder in the puerperium.

EFFECT OF CLOZAPINE ON COGNITIVE FUNCTIONS IN CHRONIC SCHIZOPHRENIC PATIENTS

HS Lee, JH Kim, MJ Jeong, JY Jeon, CH Kim, DH Song, KJ Yoo
Department of Psychiatry, Yonsei University, College of Medicine, Youngdong P.O.Box 1217, Seoul, Korea.

Prior reviews have indicated that antipsychotic drugs may impair planning ability and memory but otherwise may even improve attention and reaction time performance. This study was performed to evaluate the effect of clozapine on cognitive functions and psychopathology in chronic schizophrenic patients. Neuropsychological tests such as Wisconsin Card Sorting test, Digit Span test and Judgement of Line Orientation test were applied to 21 chronic schizophrenic patients and 21 normal controls. The schizophrenic patients were retested with the same instruments after 3 months of treatment period with clozapine. Psychopathology was assessed in the same patients before initiation of clozapine and at 12 weeks using BPRS. Cognitive impairment was found in each measure of executive function, attention, short-term memory and visual perception ability as compared with normal controls. After 12 weeks of clozapine treatment, significant improvement occured in the attention, short- term memory and visual perception ability as well as psychotic symptoms including both positive and negative symptoms, but had little effect on executive functions. Short-term treatment with clozapine may possibly improve parts of cognitive functions of chronic schizophrenics, and these effects can contribute to increase capacity for work and social function.

AMISULPRIDE VERSUS PLACEBO IN THE LONG-TERM TREATMENT OF NEGATIVE SCHIZOPHRENIA

H Loo[1], MF Poirier-Littré[1], O Fleurot[2], M Théron[2], W Rein[2]
[1] SHU, Hôpital Ste. Anne, F 75014 Paris,France
[2] Synthélabo Recherche, F 92225 Bagneux, France

Amisulpride is a substituted benzamide with high selectivity for dopamine D_2 and D_3 receptors, preferentially binding to presynaptic receptors in low doses. Animal pharmacology studies predict antinegative activity at low doses with a low risk of extrapyramidal effects even at high doses. Low doses (100 - 300 mg/d) significantly improved negative schizophrenic patients compared to placebo in a short-term (6 weeks) study. A long-term study of six months duration was undertaken in predominantly negative schizophrenic patients to confirm data on short term efficacy over a longer period of time.
141 patients fulfilling DSM III-R criteria of schizophrenia, disorganised or residual type were included in the study. To select predominantly negative patients, SANS total score at inclusion had to be ≥60, SAPS total score < 50. 69 patients received amisulpride (AMI) 100 mg/d, 72 patients placebo (PLA). Baseline mean SANS scores were almost identical 81.5±13.7 (PLA), 81.9±13.4 (AMI). At endpoint 29 patients (AMI) and 11 (PLA) had a SANS improvement score ≥ 50%, the mean SANS scores were significantly lower in the amisulpride group (AMI 48.4±27, PLA 64.8±26.1, $p<0.0005$). Similar significant differences in favour of amisulpride were found for global improvement (CGI, $p<0.004$), global assessment of functioning (GAF, $p<0.03$) and thymasthenia (SET, $p<0.003$). Productive symptoms (SAPS scores) were low at baseline and did not increase over the treatment period (PLA D0 19.4, Dend 19.3, AMI D0 22.4, Dend 20.8). The response pattern remained stable over the treatment period: responders (CGI) after 3 months remained responders up to the endpoint. 38 patients (AMI) and 23 (PLA) completed the study, the dropout rate was significantly higher in the placebo compared to the amisulpride group (PLA 68%, AMI 45%, $p<0.007$), mainly for insufficient treatment response. Clinical safety was satisfactory, there was no difference in EPS (Webster scale) and in dyskinesia (AIMS) scores between AMI and PLA. 46% of patients in PLA group had at least one emergent adverse event during treatment vs 59% of AMI patients. Weight gain and endocrine symptoms were slightly higher in the AMI group compared to PLA.
Amisulpride showed stable and consistent therapeutic effects and a satisfactory safety profile in negative schizophrenia over a six month treatment period.

MEDICATION MANAGEMENT FOR TRAINING SCHIZOPHRENIC PATIENTS

J. Meder, M. Sawicka
Institute of Psychiatry and Neurology, Sobierkiego Str. 1-9, 02-957 Warszawa, Poland

The main cause of therapeutic failure consists in patient noncompliance with treatment regimens. In schizophrenia indices on noncompliance with medication regimen are higher tan in other mental disorders. For 3 years Polish-American research entitled"Medication Management In Schizophrenia" has been provided at the department. Medication module designed in the ACLU Clinical Research Center for Schizophrenia and Psychiatric Rehabilitation is the highly structured behavioral method for improving patients conscious participation in their pharmaco therapy. Subjects in the hour research program were 97 chronic schizophrenic patients referred to the rehabilitation day-center. The results were as following: Medication management training has a positive effect on patients social skills and mental status, as well as on their acquirement of mediation knowledge and compliance.

RESISTANT DEFICIENT SCHIZOPHRENIA AND CLOZAPINE BRING HOPE TO CHRONIC DEFICIENT PSYCHOSIS

P. PRINCET
CHS FAINS-VEEL 55000 BAR-LE-DUC FRANCE

METHODOLOGY

8 Patients:
3 Deficient Schizophrenia appeared after about the age of 18;
5 Infantile Psychosis evolving into a deficient schizophrenia;
Rating with BPRS (Brief Psychiatric Rating Scale) before starting the treatment :
13 Ratings
8 Positive; 5 Negative
Starting:
From 25 mg up to 600 mg in 4 weeks;
A blood formula controlled every week ;
A clinical observation day by day through more than 18 weeks;

RESULTS

7 observations upon 8 show interesting results;
Clinical behaviour:
Regression of affective recess;
Patients more sociable and smiling;
Regression of agressivity and agitation;
Evolution of BPRS: Better on negative ratings (hostility, emotional recess, motive slowing down, lack of cooperation, affectively dull) than positive ratings (agressivity, delirium)
Dose: Between 300 mg and 600 mg
Benefits: Amelioration of their way of life;
Possibility of making projects;
Slowing down of the evolution to dementia;
Objections: Work with nurses staff;
Problem of agranulosis needing blood taking.

SCHIZOPHRENIA IN REMISSION - HOW MUCH DOES SOCIAL DEVELPOMENT AT ONSET AND THE PATIENT'S ATTITUDE TOWARDS THE ILLNESS INFLUENCE SOCIAL REHABILITATION

B Nowotny, H Häfner
Central Institute of Mental Health, P.O. Box 12 21 20, D-68072, Mannheim, Germany

One of the focuses of the Mannheim ABC (Age, Beginning and Course) Schizophrenia Study deals with social aspects of onset and course of Schizophrenia, including antecedants, prodromal, prepsychotic phase, first admission and early course of the disease. In previous studies we could show that the extent of social development together with gender and age at onset of psychotic symptoms predicted social disability at 2-year follow-up. In addition we studied the influence of patient's attitude towards the illness.

Onset and early course was investigated by means of a first episode sample (n=232) of a defined catchment area (1,5 Mio. inhabitants). A representative part of the sample (n=133) has been followed up 1/2 year, 1 year and 2 years since first hospitalization. By means of the Instrument for Retrospective Assessment of Onset of Schizophrenia (IRAOS) we gained information on signs and symptoms of the beginning disease and, as well as aspects of social development such as education, vocational training, employment, income, living conditions and close relationships. The prospective investigation included social disability (DAS) and the patient's attitude towards the illness.

We began by reconstructing the symptom development. Then steps of social ascent and decline during the early course were looked at. Finally we examined the patient's attitude towards the illness at index admission and at follow-up as well it's impact on social disability at 2 year follow-up.

PHASE I CLINICAL TRIALS OF DOPAMINE D1 RECEPTOR ANTAGONISTS.

BK Skrumsager, JV Christensen, L Ynddal, M Sloth-Nielsen
Pharmaceuticals Division, Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark.

New selective D1 dopamine antagonists have been developed with similar effects in animal models for antipsychotic action as that of D2 antagonists. The potential antipsychotic effect of selective D1 antagonists is under evaluation in man. NNC 01-0687, NNC 01-0756 and NNC 22-0010, new benzazepines derivatives with high affinity to the D1 receptor, are studied in placebo controlled phase I studies. NNC 01-0687 was administered as single oral doses between 1-25 mg to healthy male volunteers. The maximum tolerated single dose was 25 mg. After multiple doses, 5-15 mg t.i.d. for 10 days, the most frequently reported adverse events were tiredness and dizziness. After a single oral dose NNC 01-0687 was quickly absorbed with the highest plasma concentrations (C_{max}) observed ½ or 1 hour after dosing. Mean C_{max} was 358 ng/ml after a dose of 25 mg. The mean elimination half-life ($t_{\frac{1}{2}}$) was estimated to 3.6 hours and the AUC indicated linear pharmacokinetics.
In the single dose studies NNC 01-0756 was administered intravenously by short term infusion over 30 minutes (range: 0.2-2.4 mg) and orally by capsules (range: 4-100 mg). I.v. administrated NNC 01-0756 was assessed as safe. The frequency and intensity of CNS-related adverse events at the 1.2 mg, and more pronounced at the 2.4 mg dose level, indicate that a dose range was attained which revealed distinct effect on the CNS, such as tiredness, dizziness, restlessness, and sweating. Similar pharmacodynamic effects, but less pronounced, were seen after an oral dose of 100 mg NNC 01-0756. Linear regression on AUC(0-2h) vs. doses indicated linear kinetics within the dose range. C_{max} increased fairly proportional with the doses administered.
NNC 01-0687 and NNC 01-0756, were in general well tolerated by the healthy volunteers in doses expected to be therapeutic relevant, as PET-studies show that the doses used in the phase I studies induce a considerable occupancy of D1 receptors in the human brain. Phase I studies of NNC 22-0010 are ongoing.

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TREATMENT WITH CLOZAPINE

MB Tomé de la Granja, P Jones, RM Murray
Institute of Psychiatry, University of London, De Crespigny Park, London SE5 8AF, United Kingdom

The dibenzodiazepine clozapine has been in relatively common use in the treatment of intractable schizophrenia in Britain and the United States since the drug's re-introduction in 1990. A retrospective case control study of 115 schizophrenic patients who have received clozapine at a British psychiatric hospital is presented. The modal maintenance dose of 600 mg per day is higher than that in most European practice, but in keeping with that of the United States.

Neuroimaging was evaluated as a predictor of the response of treatment-resistant schizophrenia to clozapine in 65 patients. Cerebral atrophy was measured with respect to ventricular volumes, ventricle to brain ratio (VBR) and sulcal widening. The estimations were made in ignorance of whether the scan concerned was of a patient who had or had not responded to clozapine. Similar measurements were made on scans of schizophrenics who had responded to conventional anti-psychotic medication. Odds ratio analysis was performed in order to look for linear trends in the association between the extent of cerebral atrophy and clinical response to clozapine.

Clinical resistance to clozapine was not associated with enlargement of the lateral ventricles or lateral cortical atrophy, as indicated by the width of the Sylvian fissure. Resistance to clozapine was more likely where radiological evidence of disease of the small cerebral blood vessels was present.

ELTOPRAZINE IN SELF-INJURIOUS BEHAVIOUR

WMA Verhoeven, S Tuinier and YWMM van den Berg
Vincent van Gogh Institute for Psychiatry, Dept. Biological Psychiatry, P.O. Box 5, 5800 AA Venray, The Netherlands

Since the last decade three biochemical hypotheses have been proposed as pathogenetically relevant for SIB: the endorphin hypothesis resulting in studies with opiate antagonists, the dopamine hypothesis leading to some studies using D_1-DA-receptor blockers and the serotonin hypothesis prompting trials with various serotonin modulating compounds. The latter is based on preclinical data about the involvement of serotonin in certain forms of animal agonistic behaviour and on those from human research on aggressive and suicidal behavior, suggesting a role of central serotonin function in aggressive disorders irrespective the clinical diagnosis.
The results from animal research prompted clinical studies with the serotonin agonistic compound Eltoprazine (DU 28853) in patients with aggression regulation disorders. The present study involved a baseline controlled trial comparing Eltoprazine 0-60 mg with placebo including 10 mentally retarded subjects with manifest self-injurious behavioral acts. During the first 4 weeks of active treatment the daily dose was gradually increased to 40 mg, after which the dosage was optimalized individually regarding adverse reactions and therapeutic response. For the evaluation of the effect different instruments were used of which the most important were: frequency of SIB measured by the MOAS automutilation subscale, intensity measured by the VAS and applied restraints assessed by item 3 of the SIBQ. Analyses of the data revealed a clinically relevant improvement of SIB in 5 out of 9 patients, that was accompanied by other behavioural phenomena like increased alertness and activity, enhanced sociability and elevation of mood. In all but 1 patient a gradual behavioural tolerance emerged after 8 weeks of treatment resulting in complete loss of effect in week 12. It is concluded that serotonin modulating agents, like Eltoprazine, might have therapeutic properties in SIB-associated disorders.

A EUROPEAN PLACEBO CONTROLLED, DOSE-FINDING STUDY IN SCHIZOPHRENIC PATIENTS WITH A POTENTIALLY ANTIPSYCHOTIC DRUG (ORG 5222)

FINNISH-NORWEGIAN Org 5222 dose-finding study group
MC Vrijmoed de Vries: Organon Int'l bv, PO Box 20, Oss, NL.

The efficacy of Org 5222, a combined dopaminergic and serotonergic receptor antagonist, was investigated in a placebo controlled, dose-finding study in 3 Finnish and 5 Norwegian hospitals. After an initial placebo washout period of 3-7 days, 130 patients meeting DSM-IIIR criteria for schizophrenia were randomized into 5 double-blind groups with fixed oral doses of Org 5222 (0.2, 0.5, 1 and 2 mg twice daily) and placebo for six weeks. Efficacy of treatment was determined by Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI) and the number of dropouts due to lack of efficacy. Safety was assessed by use of Simpson and Angus extrapyramidal side effect scale, laboratory data including prolactin, vital signs including ECG, physical examinations and open reporting of adverse experiences.

RESULTS	Org 5222 (mg/day)				
Primary efficacy variable	0	0.4	1	2	4
PANSS change from baseline					
Total score	-4.7	0.7	-0.0	-9.7	-7.8
Positive subscore*	-0.4	0.1	0.2	-3.8	-3.7
Negative subscore	-1.5	0.1	-1.0	-1.3	-1.1
CGI change item endpoint	4.0	4.5	4.0	3.8	3.6
Number (%) of dropouts for lack of efficacy **	10 (38%)	11 (42%)	11 (44%)	7 (28%)	4 (14%)
No clinically significant changes of any safety parameters were observed					

*trend test p=0.009; **trend test p=0.031

Conclusion: taking into account the dose-related trends in some of the primary efficacy measures, the minimal effective dose of Org 5222 may be 4 mg per day.

Paroxetin und Neuroleptika in der medikamentösen Therapie der wahnhaften Depression

M. Wolfersdorf, F. König, Th. Barg, R. Straub, M. Löble, M. Leibfarth, I. Grünewald
PLK Weissenau, Abteilung Psychiatrie I der Universität Ulm, D - 88214 Ravensburg, FRG

In der Behandlung wahnhaft depressiver Patienten ist die Kombination eines tri- oder tetrazyklischen Antidepressivums (TZA, TeZA) mit einem Neuroleptikum derzeitiger medikamentöser Standard. Erfahrung mit neuen selektiven Serotonin-Wiederaufnahmehemmern (SSRI) liegen kaum vor. In dieser offenen Pilotstudie (Anwendungsbeobachtung) wurden bisher 14 wahnhaft Depressive mit dem SSRI Paroxetin, 20 mg pro die und 150 - 200 mg Zotepin und/oder 5 - 10 mg Haloperidol behandelt. Ergebnisse und Verlauf vor allem bei den wahnhaften Symptomen (Hamilton-Depressionsskala) werden berichtet.

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