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Original investigations

An open label trial of raclopride in acute schizophrenia. Confirmation of D2-dopamine receptor occupancy by PET

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Abstract. Raclopride, a highly selective D2-dopamine receptor antagonist, was administered in doses up to 4 mg b.i.d. to ten schizophrenic patients in an open label non-comparative study lasting 4 weeks. Safety, tolerability, potential antipsychotic effect, prolactin response and drug effect on plasma homovanillic acid were evaluated. Central D2-dopamine receptor occupancy was determined by positron emission tomography (PET). No major deviations were found in biochemical and physiological safety parameters. Raclopride was well tolerated. The mean BPRS score was reduced by 55% at endpoint. In the global evaluation seven patients were "very much" or "much" improved. Extrapyramidal side effects were recorded in four patients and disappeared after dose reduction or single doses of biperiden. An increase in plasma prolactin of short duration was observed in both sexes. A significant decrease of plasma HVA was obtained after 4 weeks of treatment. In two of the patients the central D2-dopamine receptors occupancy was measured using PET. The receptor occupancy was 68 and 72% which is the same as that found in patients treated with conventional neuroleptics.

Key words: Raclopride – Schizophrenia – Pharmacodynamics – Antipsychotic effect – PET

The demonstration of a linear correlation between drug affinity for central D2-dopamine receptors in animals and their antipsychotic potency in man was the basis for the proposal that the antipsychotic effect of neuroleptic drugs is mediated by blockade of D2-dopamine receptors (Creese et al. 1976; Seeman et al. 1976; Peroutka and Snyder 1980). Sulpiride, a D2-dopamine antagonist (Jenner et al. 1983), is the prototype for the substituted benzamides, the class of neuroleptic drugs most recently developed. In several studies sulpiride has been shown to have antipsychotic properties (Toru et al. 1972; Härnryd et al. 1984a). Raclopride, a new ortho-methoxy substituted benzamide, has a ten-fold higher affinity for D2-dopamine receptors but a several-fold lower affinity for alpha-2 adrenergic receptors compared to sulpiride. Raclopride has negligible affinity for D1-dopamine, serotoninergic, histaminergic or muscarinic receptors (Köhler et al. 1985; Ögren et al. 1986). The development of the significantly more selective D2-antagonist raclopride, has provided an even better tool than sulpiride for the identification of drug effects mediated by a selective D2-dopamine receptor blockade in man. Using raclopride it is accordingly possible to examine if an exclusive blockade of D2-dopamine receptors in man produces an antipsychotic effect.

With the exception of the substituted benzamides, all previously developed antipsychotics have affinity for other central receptor systems besides dopamine. This might cause the great number of side effects described in association with antipsychotic drug treatment. New antipsychotics with a high selectivity for D2-dopamine receptors and a negligible interaction with other receptor systems can be expected to have fewer side effects than hitherto developed drugs. The antipsychotic potential of raclopride has not previously been examined. However, in healthy male volunteers the drug was well tolerated in single oral doses up to 8 mg but not 16 mg because of akathisia (Farde et al. manuscript in preparation).

The development of positron emission tomography (PET) has made it possible to study receptor binding of drugs in the living human brain (Wagner et al. 1983; Sedvall et al. 1986). Raclopride has previously been labelled with the positron emitting isotope ^{11}C and used for the in vivo characterization of binding to central D2-dopamine receptors (Farde et al. 1985, 1986, 1987a). ^{11}C-raclopride passes rapidly through the blood-brain barrier and accumulates in the caudate nucleus and the putamen, regions with high density of D2-dopamine receptors. A quantitative method has been developed for the determination of D2-dopamine receptor density (B_{max}) and affinity (K_d) in the living human brain (Farde et al. 1986). This quantitative method has also been used to estimate the relative degree of D2-dopamine receptor blockade (receptor occupancy) during clinical treatment with antipsychotic doses of several conventional neuroleptics. The degree of receptor occupancy in drug-treated schizophrenic patients as measured with ^{11}C-raclopride was 65–85% (Farde et al. 1986, 1987b).

The first aim of the present open label study of raclopride was to evaluate safety and tolerability in schizophrenic patients and to search for the putative antipsychotic effect of the drug. The second aim was to use PET and ^{11}C-raclopride to determine the degree of D2-dopamine receptor occupancy in raclopride-treated patients.

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Materials and methods

General methods

The design was according to a noncomparative open label trial. Raclopride was administered for 4 weeks. The protocol was approved by the Ethics Committee of the Karolinska Hospital, Stockholm, Sweden.

Selection of patients. Patients with psychosis of acute schizophrenic type recruited at the emergency ward of the Karolinska hospital in Stockholm, were selected for the study. The criteria for a schizophrenic disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, 3rd Ed. 1982) had to be satisfied for inclusion. Minimum total score on the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorman 1962) should be 18 (18 items, each item 0–6; maximal score 108). Patients with an organic mental disorder (DSM-III) or a somatic disease which would interfere with the effects of raclopride or place the patient at risk were excluded, as were patients with alcohol or substance abuse (DSM III). A total number of 11 schizophrenic patients consented to participate after being informed about the aim of the study (Table 1). Six of the patients were men and five were women. Their mean age was 27 years (range 18–40). Six of the patients had their first psychotic episode and seven were admitted to hospital for the first time. One patient received occasional oral doses of thioridazine before admission and had a 1-week washout period before the start of raclopride treatment. The other patients had not been given neuroleptics during the last 6 months before admission. The patients were observed at the ward for 4–8 days prior to the start of raclopride medication.

Dosage of raclopride. Raclopride (oral capsule, 1 mg, 2 mg) was administered twice daily (8 p.m. and 8 a.m.). During the first 4 days, the dose was increased stepwise from 2 mg b.i.d. with a daily increment of 1 mg up to the dose level of 4 mg b.i.d. Dose levels could be reduced at any point during the study if adverse events occurred. The dose level 3 mg b.i.d. was used in the last four patients to obtain indications on an antipsychotic effect also on this dose level (Table 1). The treatment with raclopride continued for 4 weeks.

Concomitant medication. The protocol allowed the administration of oxazepam (Sobril 15 mg or 25 mg, Kabi, Sweden) or diazepam (Valium 2 mg or 5 mg, Roche, Sweden) for sedation. Biperiden (Akineton 2 mg, Meda, Sweden) was allowed to treat extrapyramidal side effects.

Cardiovascular assessments. Blood pressure and pulse rate were recorded on admission to the study, at day 1, 2, 3 and 4 of raclopride treatment and at the end of each week. Recordings were made 60 min after administration of the morning dose. Blood pressure and pulse rate were measured after 5 min in supine and after 1 min in erect position. Electrocardiogram (ECG) was recorded on admission to the study and at the end of each week.

Clinical chemistry and hematology. A battery of clinical laboratory tests of plasma and urine (Härnryd et al. 1984a) was taken on admission to the study and at the end of each week.

Table 1. Patient characteristics

Pat No.	Sex	Age	Type of schizophrenia	Dose level
1	M	26	Paranoid	4 mg b.i.d.
2	F	20	Undifferentiated	4 mg b.i.d.
3	F	40	Disorganized	4 mg b.i.d.
4	M	24	Disorganized	4 mg b.i.d.
5	M	38	Catatonic	2 mg single dose
6	F	22	Undifferentiated	2.5 mg b.i.d.
7	M	24	Paranoid	4 mg b.i.d.
8	M	31	Disorganized	3 mg b.i.d.
9	M	29	Undifferentiated	3 mg b.i.d.
10	F	18	Disorganized	3 mg b.i.d.
11	F	38	Paranoid	3 mg b.i.d.

Type of schizophrenia according to DSM-III. Dose level refers to the initial dose level, before changes due to adverse events or unsatisfactory response

Table 2. The adverse event checklist

A. Specific questioning	B. Extrapyramidal side effects
Drowsiness/somnolence	Akathisia
Tiredness/Fatigue	Hypokinesia/Akinesia
Insomnia	Rigidity
Increased sleep	Tremor
Headache	Acute dystonia
Concentrating difficulty	Dyskinesia
Dizziness on standing up	
Blurred vision	
Dry mouth	
Increased sweating	
Increased thirst	
Increased salivation	
Nausea	
Constipation	
Urinating difficulty	
Breast Swelling	
Milk from nipples	
Sexual dysfunction	
Menstrual disturbance	

Assessments of adverse events. Adverse events were reported by the patients on open as well as after a specific questioning according to the Adverse Event Checklist (Table 2). The following levels of severity were used: 0 = not present, 1 = mild, 2 = moderate, and 3 = severe. The events were recorded and a physical examination was performed on admission to the study, and at the end of each week of raclopride treatment.

The severity of akathisia was rated both according to the Adverse Event Checklist (Table 2) and also according to a scale with defined steps, based on a description by Braude et al. (1984) of mild, moderate and severe akathisia (Table 3). The ratings were performed on admission to the study, at days 1, 2, 3 and 4 of raclopride treatment and at the end of each week.

Ratings of psychopathology. The evaluation of clinical improvement according to The Clinical Global Impression (CGI) (ECDEU 1976) was completed on admission to the study, and at the end of each week of raclopride treatment. Clinical morbidity was rated according to the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorman 1962)

Table 3. Rating scale for the severity of akathisia

0	*No akathisia*
1	*Mild akathisia.* Feeling of unease, inner tension. Present subjectively with no observable signs
2	*Moderate akathisia.* Similar complaints to above. In addition observable motoric signs such as rocking from foot to foot or walking on the spot while standing
3	*Severe akathisia.* Difficulty in maintaining position. For example: Standing up when seated, starting to walk when standing, feeling compelled to leave the couch to take a few steps when lying

and a scale with 12 selected items from the Comprehensive Psychopathological Rating Scale (CPRS) (Montgomery et al. 1978). The ratings were performed by the physician on admission to the study, and at the end of weeks 2, 3 and 4 of raclopride treatment.

Plasma raclopride concentrations. Blood samples for determination of raclopride concentrations in plasma were drawn prior to the start of treatment and after 2 and 4 weeks. Samples were drawn immediately before the morning dose and at 1, 2, 4, 8, 10 and 12 h following the dose. After 4 weeks samples were, in addition, drawn at 24, 26, 28 and 32 h after the last dose.

Plasma prolactin (PRL) and homovanillic acid (HVA) concentrations. Blood samples for determination of PRL and HVA concentrations in plasma were drawn prior to the start of raclopride treatment and after 2 and 4 weeks. Samples were drawn immediately before the morning dose and at 1 and 4 h after the dose. The patients were given an unrestricted diet.

Analytical methods. Raclopride was extracted from plasma as a base into an organic phase. After evaporation of the organic phase the residue was dissolved in buffer and assayed by reversed phase liquid chromatography with fluorescence detection. The limit of determination is 0.5 nmol/l and the within-run precision is 5% at 2.0 nmol/l and 1.5% at 200 nmol/l (Nilsson LB and Briem S, to be published). PRL was analysed by conventional radioimmunoassay (Sereno®, Italy). HVA was determined by coupled column liquid chromatography with dual coulometric/amperometric detection (Edlund 1986). The intra-assay precision was 2–4% and the limit of determination was 6 nmol/l.

Calculations. Since changes in plasma PRL and HVA concentrations not are normally distributed, these values were analysed using Wilcoxon's signed rank test.

PET Examination

Chemistry. ^{11}C-raclopride was prepared by methylation of the desmethyl precursor analoque using ^{11}C-methyliodide (Farde et al. 1985). The specific activity of ^{11}C-raclopride was 300–500 Ci/mmol.

Positron camera system for emission tomography. The four-ring PET system (PC-384) at the Department of Neuroradiology, Karolinska Hospital, Stockholm, was used to follow radioactivity in seven sections covering an axial distance of 10 cm of the brain. The spatial resolution of the reconstructed images is 7.6 mm full-width at half maximum (FWHM). Each study comprised ten sequential scans during a period of 51 min.

Patients selected for PET. Two of the patients who had responded to treatment were selected for PET examination. The first patient, No. 4, was a 26-year-old male treated with 4 mg b.i.d.. A first PET experiment had been performed before raclopride treatment, when this patient was included in a study on D2-dopamine receptor characteristics in drug-naive schizophrenic patients (Farde et al. 1987c). A second PET experiment was performed 6 h after the last intake of raclopride on day 28. The BPRS score had decreased from 42 before treatment to 14 at the PET experiment when receptor occupancy was determined. The second patient, No. 1, was a 40-year-old female treated with raclopride 3 mg b.i.d. A PET experiment was performed on day 31 of raclopride treatment, 6 h after the last dose. The BPRS score had decreased from 41 before treatment to 3 at the PET experiment.

Experimental procedure and calculations. The experimental procedure described by Farde et al. (1986) was followed. ^{11}C-raclopride was injected as a bolus during 10 s. Radioactivity in the brain was then measured according to a preprogrammed sequence for 51–57 min.

Regional radioactivity in the putamen and the cerebellum was measured for each sequential PET scan, corrected for ^{11}C-decay and plotted versus time. Specific binding (B) in the putamen was defined as the difference between radioactivity in the putamen and the cerebellum. The estimate of free radioligand concentration (F) was obtained from the radioactivity in the cerebellum of each patient. The ratio (B/F) of specific binding to free radioligand concentration was calculated. In patient No. 4 D2-dopamine receptor occupancy was expressed as per cent reduction of the ratio B/F when compared to the ratio obtained before treatment. In patient No. 11 the reduction in B/F was calculated by comparison with the mean ratio B/F obtained in 15 drug-naive schizophrenic patients (Farde et al. 1987c).

Results

Dropouts. Patient No. 5 was severely catatonic when entering the study and was excluded after a single dose of raclopride (2 mg), since he had to be given electroconvulsive treatment. No adverse effects were observed after the single dose of raclopride. This patient was not included in the analysis.

Patient No. 6 was excluded from the study after 3 weeks of treatment, because of lack of improvement. This patient was included both in the efficacy and the safety analysis.

Dosage of raclopride and concommitant medication. The dose levels of raclopride most frequently used were 3 mg b.i.d. and 4 mg b.i.d. (Table 1). During a weekend leave, patient No. 3 stopped raclopride medication for 2 days and instead took two doses of perphenazine 4 mg, on her own initiative. Patients 3 and 6 took occasional doses of biperiden because of side effects (cf below). Three patients were occasionally given doses of benzodiazepines. Patient No. 6 was given oxazepam 15 mg t.i.d. during the whole treatment period.

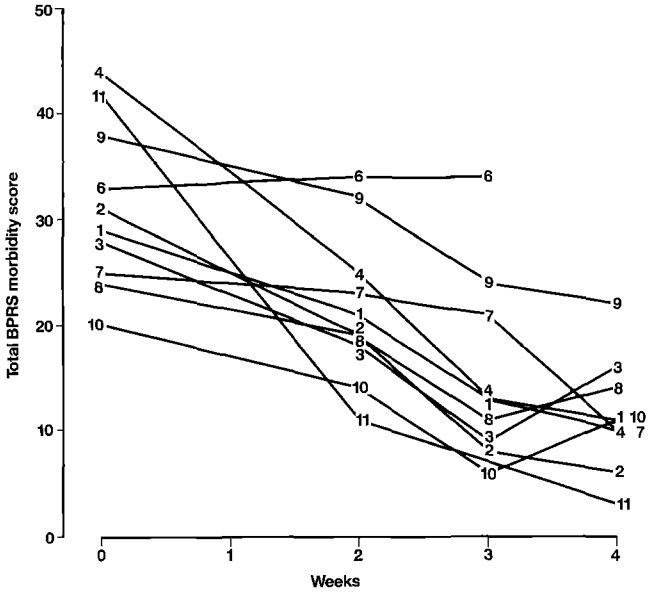
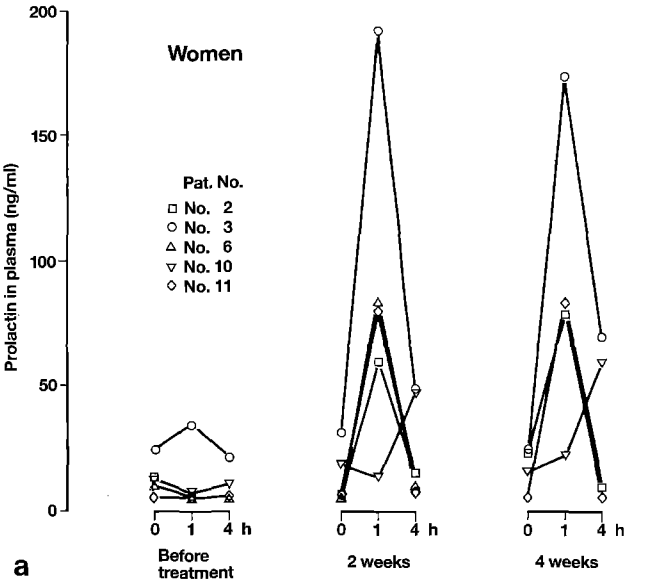


Fig. 1. Total BPRS scores versus time for each patient ($n=10$)



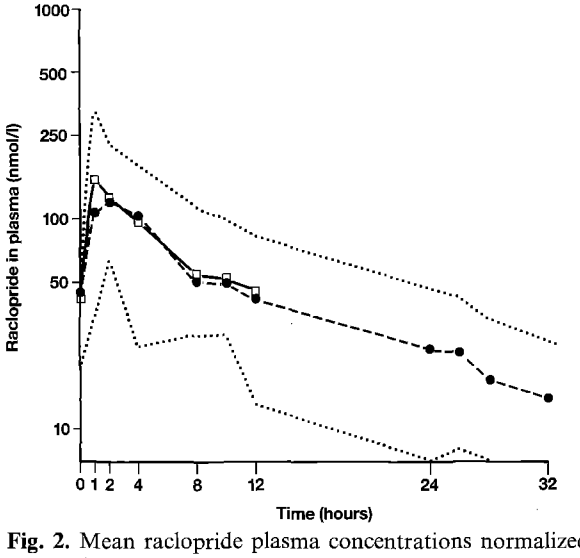


Fig. 2. Mean raclopride plasma concentrations normalized to the 4 mg b.i.d. dose level ($n=10$). □—□ 2 weeks: 4 mg ×2; ●—● 4 weeks; 4 mg ×2; ····· 4 weeks: max/min conc

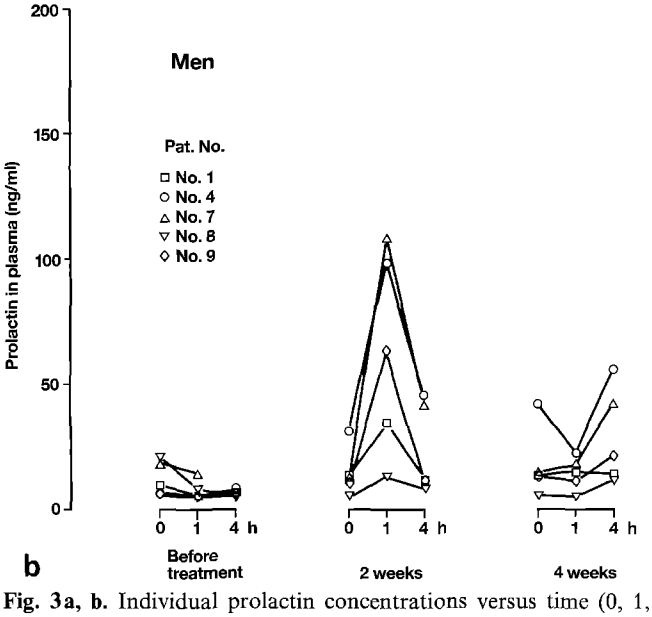


Fig. 3a, b. Individual prolactin concentrations versus time (0, 1, 4 h) before treatment, after 2 and after 4 weeks of treatment. *Above:* female patients ($n=5$) and *below:* male patients ($n=5$)

Cardiovascular assessments. In two patients, No. 3 and No. 10, borderline postural hypotension was recorded on one occasion. There was a decrease in systolic blood pressure of 20 mm Hg when the patient rose from lying to standing position. The corresponding increase in pulse rate was 10 and 18 beats/min.

In nine of the ten patients the ECG was normal throughout the study. Patient No. had occasional monofocal ventricular extrasystoles (VES) after 2 and 3 weeks of treatment. The ECG was normal after 4 weeks.

Clinical chemistry and hematology. Patient No. 8 had a slight increase in S-aspartate aminotransferase to 0.9 μkat/l after 1 and 2 weeks of raclopride 3 mg b.i.d (upper limit 0.7 μkat/l). S-Alanine aminotransferase was 0.75 on admission (upper limit 0.7 μkat/l), increased to 1.5 μkat/l after 2 weeks and was reduced to1.1 μkat/l after 4 weeks of treatment. The cause of these deviations is uncertain. S-Bilirubin, creatine kinase, creatinine and alkaline phosphatase values were normal in this patient. Patient No. 7 had increased S-bilirubin on admission and through treatment. This deviation was probably caused by Morbus Gilbert. No other deviations from normal values in clinical chemistry or hematology were considered to be caused by raclopride treatment.

Adverse events. The most frequently recorded adverse event was mild drowsiness or mild tiredness, that occurred in five patients. In patient No. 2 the drowsiness was rated moderate on one occasion 1 h after drug intake.

In patient No. 3 dyskinesia of the tongue was both reported and observed after 2 weeks (4 mg b.i.d.). The dyskin-

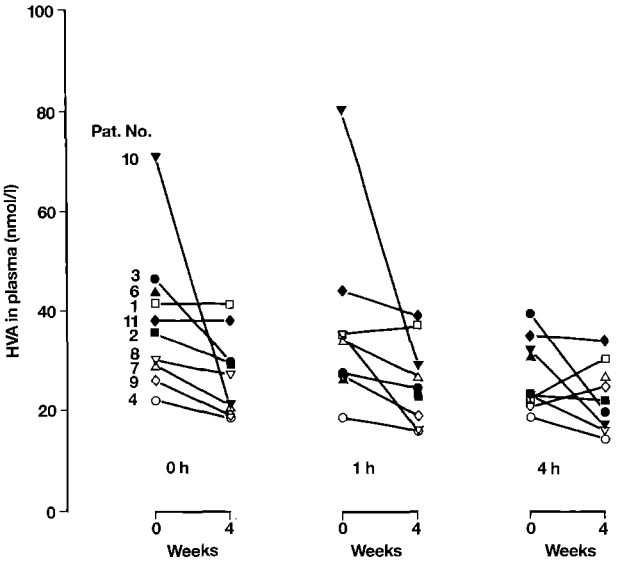


Fig. 4. Individual plasma HVA concentrations versus time (0, 1, 4 h) before treatment and after 4 weeks of treatment

esia disappeared after 2 mg biperiden. The dose of raclopride was reduced to 2 mg b.i.d. without the reappearance of adverse symptoms.

In Patient No. 6 mild akathisia was rated after 3 weeks on raclopride (3 mg b.i.d.). The dose of raclopride was increased to 4 mg b.i.d. On this dose, moderate akathisia was rated and as the patient did not improve, raclopride treatment was stopped.

In patient No. 7 akathisia of moderate severity was rated after raclopride 4 mg b.i.d. The akathisia disappeared after dose reduction to 3 mg b.i.d. after 2 weeks.

Patient No. 8 erroneously took 8 mg raclopride as a single dose on day 19 (weekend leave). He reported limb dystonia and took occasional doses of biperiden. The patient continued in the study on raclopride 3 mg b.i.d. without any extrapyramidal side effects.

A mild "chilly sensation" was reported by patient No. 1 on two occasions. All other adverse events were rated mild, reported only once and by one patient. They were considered not to be treatment emergent.

Ratings of psychopathology. According to CGI three patients were "very much improved" four were "much improved", two were "minimally improved" and in one there was "no change" at the end of raclopride treatment.

The mean BPRS score was 31.4 (SD 7.9) at baseline and declined to 11.4 (SD 5.5) after 4 weeks of treatment, corresponding to a 64% reduction. The reduction of the BPRS score from baseline to the last available rating (i.e. including patient No. 6 who was excluded after 3 weeks), was 55%. In Fig. 1, the BPRS score is plotted versus time for each patient.

The mean score of the 12 CPRS items was 12.9 (SD 3.3) at baseline, 8.1 (SD 3.7) after 2 weeks and 4.1 (SD 3.1) after 4 weeks of treatment, corresponding to a 68% reduction. The reduction at the last rating, including patient No. 6, was 62%.

Plasma raclopride concentration. Maximal plasma concentrations of raclopride were in most cases obtained 1 h after drug intake. In patient No. 10 maximal drug concentration was reached after 4 h after both 2 and 4 weeks of treatment. Mean plasma concentrations are presented in Fig. 2. The mean maximal plasma drug concentration (C_{max}), was 171 (SD = 38) after 2 weeks and 160 nmol/l (SD = 77) after 4 weeks. The steady state concentrations (C_{min}) were 45 (SD = 24) after 2 weeks and 41 (SD = 22) nmol/l after 4 weeks. The mean area under the plasma drug concentration versus time curve (AUC) was 967 (SD = 369) after 2 and 928 (SD = 362) $\text{nmol} \times 1^{-1} \times \text{h}$ after 4 weeks of raclopride treatment. There was a threefold interindividual variability in AUC values during steady-state conditions. The elimination half-life of raclopride ranged from 6 to 13 h (median = 11).

Plasma prolactin concentration. An increase in PRL concentrations of short duration was observed in both male and female patients (Fig. 3). In males, the mean PRL concentration was 63.5 (SD = 40.8) ng/ml, 1 h after drug intake dur-

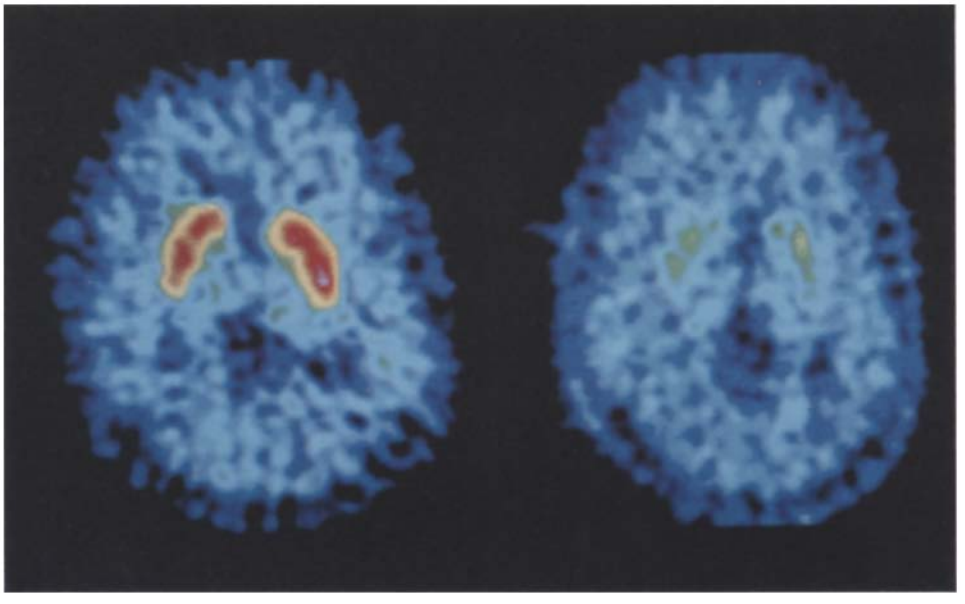


Fig. 5. PET images through the caudate putamen level of patient No. 4. Before *(left)* and during *(right)* treatment with raclopride 4 mg b.i.d. The images show radioactivity accumulated from min 10 to 51 after the injection of ^{11}C-raclopride

ing the 2nd treatment week ($P<0.05$). After 4 weeks, however, no significant increase in PRL was observed 1 h after drug intake (14.1, SD=6.6), when compared to before treatment (7.4, SD=4.0). After 4 h, there was a slight increase in PRL concentrations after both 2 and 4 weeks. Due to the limited number of samples at this time point ($n=4$ at baseline), the significance of this increase was not tested. In females there was a significant increase ($P<0.05$) in PRL concentrations 1 h after drug intake after both 2 (86.2 ng/ml, SD=76.1) and 4 weeks (89.1 ng/ml, SD=62.6) of treatment.

Plasma HVA concentrations. After 2 weeks of treatment with raclopride, there was no consistent change in HVA levels. After 4 weeks there was a significant decrease ($P<0.05$) from a mean baseline value of 38.4 (SD=14) to 27.2 (SD=28.2) nmol/l. This fall in HVA was mainly due to the fall in patient No. 10 (Fig. 4). The decrease in HVA after 4 weeks was also significant ($P<0.05$) at 1 h but not at 4 h after raclopride administration.

Positron emission tomography. Before raclopride treatment there was a high uptake of radioactivity in the caudate nucleus and the putamen after the injection of ^{11}C-raclopride in patient No. 4 (Fig. 5). After 4 weeks of treatment with raclopride 4 mg b.i.d. a PET experiment was made 6 h after the last dose intake. At this experiment, there was a conspicuous reduction of radioactivity in the caudate nucleus and putamen (Fig. 5). The calculated receptor occupancy was 72%.

In the second patient, treated with 3 mg b.i.d., there was also a low uptake of ^{11}C-raclopride. The calculated receptor occupancy was 68% when compared to the drug-naive schizophrenic patients.

Discussion

Raclopride was well tolerated by most patients. Nine of the ten patients completed the study. In no patient was the treatment stopped because of side effects. Most side effects recorded were of the extrapyramidal type but no signs or symptoms of parkinsonism were reported or observed. Few side effects were recorded on the Adverse Event Checklist. This checklist includes effects mediated by drug interaction with cholinergic, adrenergic and histaminergic effector systems. The specificity of raclopride for D2-dopamine receptors accordingly seems to be a clinical advantage, taking the pattern of side effects into account.

In animal studies raclopride has been shown to interact selectively with D2-dopamine receptors (Ögren et al. 1986). Raclopride exhibits a marked separation between the dose that induces catalepsy and the dose that blocks apomorphine-induced hyperactivity or stereotypies. A high ratio between these two doses has been suggested to indicate a separation between the doses causing extrapyramidal side-effects and antipsychotic effect in patients (Fuxe et al. 1977). Two cases were interesting in this respect. In patient No. 7 akathisia was recorded daily during the first 2 weeks when he was treated with 4 mg b.i.d. He had only improved slightly with regard to psychopathology. The dose was reduced to 3 mg b.i.d. and the akathisia disappeared. However, the major improvement according to the BPRS was recorded during the 4th week of treatment, when he had been on the 3 mg b.i.d. dose level for nearly 2 weeks (Fig. 1). Patient No. 8 had responded well after 3 weeks of raclopride 4 mg b.i.d. (Fig. 1). No side effects were recorded. He then erroneously took raclopride 8 mg instead of 4 mg and reported a leg dystonia that occurred 2 h after dose intake. These two case reports suggest that an individual dose level of raclopride may be found where there is an antipsychotic effect in the absence of extrapyramidal side effects.

The reductions recorded in CGI, BPRS and CPRS are similar to those obtained for established antipsychotics such as haloperidol (Silverstone et al. 1984) or zuclopenthixol (Mann et al. 1985). The reductions in rated scores therefore indicate that racloprice has a marked potential as an antipsychotic. Since raclopride is a highly selective D2-dopamine receptor antagonist, evidence was also obtained for the hypothesis that the antipsychotic effect is mediated by a blockade of D2-dopamine receptors.

After 4 weeks of treatment according to the protocol, patient No. 11 was continued on raclopride 3 mg b.i.d. for 3 months on a named patient basis. The patient remained "very much improved" during the prolonged treatment period. No adverse events were recorded. Two weeks after withdrawal from raclopride treatment she reported the reccurrence of symptoms that were reported before treatment. She was then treated with perphenazine 8 mg b.i.d. and the symptoms disappeared again.

The plasma concentrations and elimination characteristics of raclopride in schizophrenic patients are in good agreement with our previous results in healthy male volunteers (Farde et al. manuscript in preparation). The interindividual variability in AUC for raclopride was small in comparison with other antipsychotic drugs such as chlorpromazine, thioridazine or haloperidol (Dahl 1986). The elimination rate demonstrated should allow a b.i.d. dosage regimen with the present formulation of raclopride.

In a previous study in male volunteers (Farde et al. manuscript in preparation) a transient increase in PRL concentration was demonstrated 1 h after single doses up to 16 mg. The PRL concentrations were reduced to normal values after 4 h. After administration of sulpiride or chlorpromazine to schizophrenic patients, higher peak concentrations of prolactin have been demonstrated in females than in males (Härnryd et al. 1984b). After 2 weeks of raclopride treatment an increase of short duration in the prolactin peak concentration was found both in females and in males. Galactorrhea was not reported or observed in any of the subjects. After 4 weeks the peak concentration of prolactin remained the same in females, but there was no marked increase in prolactin concentrations in males (Fig. 3). Since the pharmacokinetic parameters were similar at 2 and 4 weeks in both sexes, this lack of prolactin response in males indicates the development of pharmacodynamic tolerance.

A decrease in plasma HVA levels that was correlated to clinical improvement in schizophrenic patients after 5 weeks of treatment with fluphenazine has been reported by Pickar et al. (1984). In this study a significant decrease ($P<0.05$) in plasma HVA levels was obtained after 4 but not 2 weeks of treatment. The mechanism of this decrease in plasma HVA levels remains to be clarified.

The PET experiments with ^{11}C-raclopride indicated that the D2-dopamine receptors in the putamen of schizophrenic patients were occupied to 65–75% during treatment with raclopride 3–4 mg b.i.d. This receptor occupancy was similar to that found using the same methodology in patients

treated with several classes of conventional neuroleptics (Farde et al. 1986, 1987b). The finding that antipsychotic doses of raclopride produce a similar D2-dopamine receptor occupancy to clinical doses of other antipsychotic drugs supports the view that raclopride is an antipsychotic drug.

In the present open study of raclopride in schizophrenic patients the drug was safe and well tolerated. The treatment response justifies further analysis of the antipsychotic potential of raclopride by controlled clinical studies.

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References

Bergström M, Boethius J, Eriksson L, Greitz T, Ribbe T, Widen L (1981) Head fixation device for reproducible positron alignment in transmission CT and positron emission tomography. J Comput Assist Tomogr 8:74–87

Braude WM, Barnes TRE, Gore SM (1983) Clinical characteristics of akathisia. A systematic investigation of acute psychiatric inpatient admissions. Br J Psychiatry 143:139–150

Creese I, Burt DR, Snyder SH (1976) Dopamine receptor binding clinical and pharmacological potencies of antischizophrenic drugs. Science 192:481–483

Dahl SG (1986) Plasma level monitoring of antipsychotic drugs: Clinical utility. Clin Pharmacokinet 11:36–61

ECDEU Manual – Assessment Manual for Psychopharmacology (1976) US Department of Health, Education and Welfare

Edlund PO (1986) Automated analysis of homovanillic acid and 5-hydroxyindole-3-acetic acid in biological fluids by coupled-column liquid chromatography and dual coulometric-amperometric detection J Pharm Biomed Anal 4:641–652

Farde L, Ehrin E, Eriksson L, Greitz T, Hall H, Hedström C-G, Litton J-E, Sedvall G (1985) Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. Proc Natl Acad Sci USA 82:3863–3867

Farde L, Hall H, Ehrin E, Sedvall G (1986) Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. Science 231:258–261

Farde L, Halldin C, Stone-Elander S, Sedvall G (1987a) PET analysis of human dopamine receptor subtypes using ^{11}C-SCH 23390 and ^{11}C-raclopride. Psychopharmacology 92:278–284

Farde L, Wiesel F-A, Halldin C, Sedvall G (1987b) Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatry (in press)

Farde L, Wiesel F, Hall H, Halldin C, Stone-Elander S, Sedvall G (1987c) PET-determination of striatal D2-dopamine receptors in drug-naive schizophrenic patients. Arch Gen Psychiatry 44:671–672

Fuxe K, Ögren S-O, Fredholm B, Agnati L, Hökfelt T, Perez de la Mora M (1976) Possibilities of a differential blockade of central monoamine receptors. In: de Ajuriaguerra J, Tissot R (eds) Rhinencephale neurotransmetteurs et psychoses. Symposium Bel-Air V, Georg & Cie, Geneve, pp 253–289

Härnryd C, Bjerkenstedt L, Björk K, Gullberg B, Oxenstierna G, Sedvall G, Wiesel F-A, Wik G, Åberg-Wistedt A (1984a) Clinical evaluation of sulpiride in schizophrenic patients – a double-blind comparison with chlorpromazine. Acta Psychiatr Scand [Suppl] No 311, 69:7–30

Härnryd C, Bjerkenstedt L, Gullberg B, Oxenstierna G, Sedvall G, Wiesel F-A (1984b) Time course for effects of sulpiride and chlorpromazine on monoamine metabolite and prolactin levels in cerebrospinal fluid from schizophrenic patients. Acta Psychiatr Scand [Suppl] 311, 69:75–92

Jenner P, Testa B, van de Waterbeemd, Marsden (1982) Interaction of substituted benzamide drugs with cerebral dopamine receptors. In: Ackenheil M, Matussek N (eds) Special aspects of psychopharmacology

Köhler C, Hall H, Ögren S-O, Gawell L (1985) Specific in vitro and in vivo binding of ^{3}H-raclopride. A potent substituted benzamide drug with high affinity for dopamine D-2 receptors in the rat brain. Biochem Pharmacol 34:2251–2259

Mann BS, Moslehuddin KS, Owen RT, Clayton AR, Rohatgi KK, Sud P, Vaddadi KS (1985) A clinical assessment of zuclopenthixol dihydrochloride (clopixol tablets) in the treatment of psychotic illness. Pharmatherapeutica 4:387–392

Montgomery SA, Taylor P, Montgomery D (1978) Development of a schizophrenia scale sensitive to change. Neuropharmacology 17:1061–1063

Ögren S-O, Hall H, Köhler C, Magnusson O, Sjöstrand S-E (1986) The selective dopamine D2 receptor antagonist raclopride discriminates between dopamine-mediated motor functions. Psychopharmacoloty 90:287–294

Overall JE, Gorman DR (1962) The brief psychiatric rating scale. Psychological reports, Southern Universities Press 10:799–812

Pickar D, Labarca R, Linnoila M, Roy A, Hommer D, Everett D, Paul S (1984) Neuroleptic-induced decrease in plasma homovanillic acid: Correlation with antipsychotic activity in schizophrenic patients. Science 225:954

Peroutka SJ, Snyder SH (1980) Relationship of neuroleptic drug effects at brain dopamine, serotonin, adrenergic and histamine receptors to clinical potency. Am J Psychiatry 137:1518–1522

Sedvall G, Farde L, Persson A, Wiesel FA (1986) Imaging of neurotransmitter receptors in the living human brain. Arch Gen Psychiatry 43:995–1005

Seeman P, Lee T, Chau-Wong M, Wong K (1976) Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 261:717–719

Silverstone T, Levine S, Freeman HL, Dubini A (1984) Zetidoline, a new antipsychotic – first controlled trial in acute schizophrenia. Br J Psychiatry 145:294–299

Toru M, Schimazonon Y, Miyasaka M, Kokubo T, Mori Y, Nasu T (1972) A double-blind comparison of sulpiride with chlorpromazine in chronic schizophrenia. J Clin Pharmacol 12:221–229

Wagner HN, Burns HD, Dannals RF, Wong DF, Långström B, Duelfer T, Frost JJ, Raert HT, Links JM, Rosenblom SB, Lukas SE, Kramer AV, Kuhar MJ (1983) Imaging dopamine receptors in the human brain by positron tomography. Science 221:1264–1266

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