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ORIGINAL INVESTIGATION

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Amisulpride versus flupentixol in schizophrenia with predominantly positive symptomatology – a double-blind controlled study comparing a selective D_2-like antagonist to a mixed D_1-/D_2-like antagonist

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Abstract The benzamide amisulpride (ASP) is a selective D_2-like dopamine antagonist, while flupentixol (FPX), a thioxanthene, blocks D_2-like, D_1-like and 5-HT_2 receptors. To evaluate efficacy and safety of ASP and to investigate the importance of an additional D_1-like antagonism for antipsychotic effects and extrapyramidal tolerability, a randomized double-blind multi- center study versus FPX as reference drug was performed for 6 weeks in 132 patients suffering from acute schizophrenia (DSM-III-R) with predominant positive symptomatology. Doses were initially fixed (ASP: 1000 mg/day; FPX: 25 mg/day) but could be reduced by 40% in case of side effects (mean daily doses: ASP: 956 mg; FPX: 22.6 mg). Intention-to-treat evaluation demonstrated significant improvement under both medications. The difference between the mean BPRS decreases of both treatment groups was 5.6 points (95% CI: 0.55; 10.65) in favour of ASP. According to CGI, 62% of patients in either drug group were treatment responders. ANCOVA analysis showed that reductions of BPRS (ASP: −42%; FPX: −32%) and SAPS (ASP: −78%; FPX: −65%) were more pronounced under ASP. Due to adverse events, significantly fewer ASP patients (6%) were withdrawn from the study (FPX: 18%). Extrapyramidal tolerability was better in the ASP group, as demonstrated by smaller increases in the Simpson-Angus Scale, the AIMS, and the Barnes Akathisia Scale in ANCOVA analyses with dosage as covariate. ASP appears to be as effective as FPX with regard to antipsychotic effects on positive schizophrenic symptomatology, while extrapyramidal tolerability is better. These conclusions have to be drawn cautiously, as dosage effects on outcome parameters cannot be entirely ruled out. The present results question the notion that additional blockade of D_1-like receptors may be necessary to achieve sufficient antipsychotic effects or to improve extrapyramidal tolerability.

Key words Amisulpride · Flupentixol · Schizophrenia · Antipsychotic efficacy · Extrapyramidal tolerability · Atypical neuroleptic · Dopamine · Selective D_2-like antagonism · Mixed D_1-/D_2-like antagonism

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Introduction

Although many neuroleptics with different pharmacodynamic actions are available, there is still a need to develop new antipsychotic compounds due to several limitations to the currently available antipsychotic drugs in schizophrenic disorders (Wetzel and Benkert 1993). Conventional neuroleptics have only a limited efficacy in negative symptomatology, and about 10–25% of schizophrenic patients are neuroleptic-resistant. Moreover, conventional neuroleptics cause a typical pattern of extrapyramidal side effects. In this respect, the risk for tardive dyskinesia is still a major

restriction to long-term administration. For these reasons, more effective antipsychotics with superior efficacy and/or fewer side effects and better long-term tolerability have to be developed.

To explain the atypical neuroleptic response pattern of clozapine, several hypotheses have been forwarded. It has been suggested that a stronger 5-HT_2 than D_2-like receptor antagonism may be responsible for a lower liability in inducing extrapyramidal symptoms (Meltzer et al. 1989). Clozapine's antagonism of D_1-like and D_2-like dopamine receptors is about equal with K_i values of 100–200 nM for both receptor subgroups (Richelson et al. 1984; Sunahara et al. 1991) while at the D_4 receptor, a D_2-like subtype, clozapine is a more potent antagonist (Van Tol et al. 1991). It has been postulated that clozapine's D_1-like blocking properties may contribute in a relevant manner to its superior clinical efficacy and beneficial side effect profile (Gerlach 1991). Unlike typical neuroleptics and similar to atypical antipsychotics, D_1-like antagonists induce only small increases in striatal dopamine release and metabolism (Altar et al. 1988). From animal experiments with the D_1 antagonist SCH 39166, it has been concluded that by an additional D_1 receptor blockade an antipsychotic effect without or with only little extrapyramidal side effects (McHugh and Coffin 1991) might be achieved. However, open pilot studies with D_1-like antagonists like SCH 39166 (Karlsson et al. 1994; De Beaurepaire et al. 1995), SCH 23390 (Gessa et al. 1991) and NNC 01-0687 (Karle et al. 1995) did not result in any improvement of positive schizophrenic symptomatology, while for negative symptoms some beneficial effects were reported (Den Boer et al. 1995).

Amisulpride as an investigational drug

Amisulpride is a selective dopamine antagonist at D_2-like dopamine receptors. At the cloned dopamine receptor subtypes, amisulpride displays affinity constants between 1.7 nM for D_2 and 3.8 nM for D_3 receptors (Sokoloff et al. 1990). There is no interaction with D_1 or D_5 receptors, and virtually no antagonism of D_4 receptors ($K_i > 1000$ nM). Apart from a very low affinity to α_2-receptors ($K_i = 1600$ nM) (Coche and Chopin 1986), amisulpride does not antagonize other neurotransmitter receptors, including α_1- and β-adrenoceptors and binding sites for serotonin, acetylcholine, histamine, benzodiazepines and various neuropeptides.

Amisulpride consists of a 50:50 racemic mixture of the *S*-(−) and the *R*-(+) enantiomer, the former being 50–300 times more pharmacologically active than the latter (W. Rein, G. Perrault, personal communication).

In acute schizophrenia with predominant positive symptomatology, amisulpride demonstrated antipsychotic properties in dose ranges of 500–1000 mg and 800–1200 mg per day, respectively, in double-blind trials (Pichot and Boyer 1988; Delcker et al. 1990). In schizophrenic patients with negative symptomatology, amisulpride at a dosage of 100–300 mg/day was significantly superior to placebo (Boyer et al. 1995; Paillère-Martinot et al. 1995).

Flupentixol as a reference drug

Flupentixol is a high-potency thioxanthene with well-established antipsychotic properties. In receptor binding experiments, its affinity at cloned dopamine receptors has been established (Leysen et al. 1993). For *cis*-(*Z*)-flupentixol, the K_i values for D_2 and D_1 receptors is 6.4 nM and 4.0 nM, respectively. While for D_3 and D_4 receptors, to our knowledge affinity or inhibition constants have not been established, the K_i for D_5 receptors was found to be 8 nM. Since *cis*-flupentixol is among those neuroleptics which have the most pronounced D_1-blocking effect, it can be characterized as a mixed D_1-like/D_2-like antagonist. Moreover, *cis*-flupentixol is also a 5-HT_2 antagonist, the K_i being as low as 2.5 nM. The affinity of *cis*-flupentixol to α_1 adrenoceptors is low, and the drug does not have substantial anticholinergic actions.

The oral application of flupentixol consists of a racemic mixture of the *cis* and *trans* isomers at equal parts. The *trans*-(E) isomer is of no relevance for antipsychotic drug action, receptor effects of the *trans*-(E) isomer being 50–700 times weaker (Jörgensen 1980).

In a double-blind study, oral *cis*-(Z) flupentixol has been shown to be significantly more effective than placebo in acute schizophrenics at a mean dose of 9 mg/day (Johnstone et al. 1978), which would correspond to a daily dose of 18 mg with respect to the racemic mixture. Likewise, flupentixol at a mean oral dose of 20 mg (50:50 racemic mixture of *cis* and *trans* isomers) has been demonstrated to be of comparable antipsychotic efficacy to pimozide in another double-blind study (Scottish Schizophrenia Research Group 1987).

Aim of the study

To evaluate amisulpride's efficacy and extrapyramidal tolerability in the treatment of acutely ill schizophrenic in-patients, we performed a study against flupentixol as an established reference neuroleptic. Moreover,the comparison of a selective D_2-like antagonist with a mixed D_2-like/D_1-like antagonist should serve to test preclinical assumptions that D_1-like blocking properties of a neuroleptic might add to its clinical efficacy and may be a relevant factor for a more beneficial extrapyramidal side effect profile.

With regard to other selective D_2-antagonistic benzamide antipsychotics, amisulpride is about 4–6 times

more potent in antagonizing D_2 and D_3 receptors than sulpiride with a somewhat higher D_2/D_3 ratio (Sokoloff et al. 1990). It has a slightly higher bioavailability and a somewhat longer elimination half-life than its congener (Dufour and Desanti 1988). Due to higher lipophilicity, it is more able to penetrate the blood-brain barrier. Amisulpride has a considerably higher affinity to D_2 and especially D_3 dopamine receptors than remoxipride (Malmberg et al. 1993), and in contrast to remoxipride demonstrated substantial anti-dopaminergic activity in the absence of catalepsy (Perrault et al. 1997).

To test the widely held notion that benzamide antipsychotics might be less useful in acute schizophrenic subtypes with productive psychotic features, patients with a predominant positive symptomatology rather than a prevailing negative or deficit syndrome were included. For both drugs, high fixed starting doses were chosen to avoid reduced therapeutic response due to insufficient dosage, and to obtain a sufficient D_1-like antagonism in case of flupentixol.

Materials and methods

Study design

A multi-centre, randomized, parallel group design, double-blind comparative clinical trial with fixed doses of amisulpride and flupentixol at 11 German centers was conducted under the guidelines of the current version of the Declaration of Helsinki (Hongkong, 1989), the study protocol being reviewed and approved by the appropriate ethics committees at each clinical site. All patients gave written informed consent before entering the study. Patients under legal guardianship were not eligible for the study. At the time of inclusion, usually after a screening period of 1–3 days after admission to the hospital, all psychotropic medications were discontinued, and patients entered a single-blind placebo washout period of 1–9 days duration (ASP patients: 3.23 ± 2.28 days; FPX group: 3.18 ± 2.05 days; mean $\pm$ SD). Patients were then randomly assigned to either amisulpride (1000 mg/day) or flupentixol (25 mg/day) for a treatment duration of 6 weeks.

Selection criteria

Inclusion criteria

Acutely admitted in-patients of either sex aged 18–65 years with a primary diagnosis of schizophrenia, paranoid type (295.3), or undifferentiated type (295.9) according to DSM-III-R, were eligible for the study. Patients were required a score of at least 36 points on the Brief Psychiatric Rating Scale (BPRS; item score 1–7) (Overall and Gorham 1962) at pre-study screening and at baseline evaluations. Moreover, a written informed consent had to be obtained. For women of childbearing potential, a negative pregnancy test and the use of an adequate contraception was required.

Eligible patients underwent a pre-study evaluation which included a psychiatric interview, a psychiatric and medical history, a complete physical examination, vital signs, laboratory evaluations, an ECG, an EEG, and a urine screen.

Exclusion criteria

Exclusion criteria comprised diagnosis of a schizoaffective disorder or other axis I disorder like dementia or organic brain disorder, prevailing negative schizophrenic symptomatology as assessed by a Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983a) composite score (i.e. observer-rated items without subjective and global ratings) above 55 points, history of alcohol or substance dependence or abuse, suicidal ideations, Parkinson's disease, epilepsy, narrow-angle glaucoma, prostate hypertrophy, urinary retention, severe hypotonia or arteriosclerosis, severe liver or kidney dysfunction, other serious somatic co-morbid disorders, significant laboratory, ECG or EEG abnormality, pregnancy or lactation, necessity of other psychotropic medication, participation in another clinical trial with any investigational drug within the last 30 days, and depot neuroleptic medication within a time period of 3 months prior to study inclusion.

Drug schedule

Study medication was administered under double-blind conditions following a double-dummy protocol as identical capsules of amisulpride and flupentixol. For this study, a dose of 5 mg flupentixol was defined to be equivalent to 200 mg amisulpride. Both amisulpride and flupentixol were given as a racemate containing both the *cis* and the *trans* isomer in equal parts of 50% while only S-(−)-amisulpride and *cis*-flupentixol, respectively, are pharmacologically active.

Study drugs were given on a twice-daily regimen under supervised conditions with an initial fixed-dose administration of amisulpride 1000 mg/day versus flupentixol 25 mg/day. Dosage could be adjusted in case of side effects to a minimal dose of amisulpride 600 mg/day and flupentixol 15 mg/day. Before neuroleptic dose reduction due to extrapyramidal side effects, concommitant anticholinergic medication with biperiden should be administered.

Both drugs were administered at rather high dosages, the dose range especially for flupentixol being at the upper end regarding previously quoted controlled studies. However, according to manufacturer's specifications, for acute schizophrenic symptomatology an oral daily dose of 10–60 mg flupentixol (i.e. 5–30 mg *cis*-flupentixol) was recommended.

After study inclusion, no other psychotropic drug was allowed with the exception of diazepam up to a dose of 20 mg/day (during placebo washout up to 40 mg/day) as sedative- hypnotic medication, and biperiden (up to 12 mg/day) as anticholinergic compound in case of drug-induced acute dystonic reactions or parkinsonism. Other medications such as beta blockers were also prohibited.

Assessment procedures

Treatment response was assessed by the BPRS, the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1983b), the Global Assessment Scale (GAS; Endicott et al. 1976), and the Clinical Global Impression (CGI; Guy 1976). Each scale was administered on day 0, i.e. the day prior to beginning study medication, and on days 7, 14, 21, 28, 35, and 42. The mental status was scored by the same evaluator whenever possible.

Extrapyramidal symptoms were evaluated using the Simpson-Angus scale (Simpson and Angus 1979), the Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Scale (BAS) (Barnes 1989), while other adverse effects were assessed with the UKU side effects scale (Lingjaerde et al. 1987). Rating scales were administered at baseline and on weekly intervals thereafter up to day 42.

Routine laboratory tests (hematology, electrolytes, liver enzymes, alkaline phosphatase, creatinine, uric acid, cholesterol,

triglycerides), and prolactin were performed prior to study begin and at 2-week intervals thereafter until day 42. Blood pressure and heart frequency were registered daily, weight at weekly intervals. ECG and EEG were recorded at baseline and at study termination. Moreover, the physical examination was repeated at the end of the study.

Statistical methods

The comparability among the two treatment groups was assessed for demographic parameters and baseline characteristics. For continuous variables (baseline ratings, safety parameters, age, height, weight, etc.), a *t*-test for independent samples was performed. Categorical parameters (e.g. sex, schizophrenia subtype) were submitted to a χ^2-test.

Confirmatory statistical analyses of efficacy, tolerability and safety parameters were conducted as an intention-to-treat analysis. For all 132 patients under neuroleptic treatment, an intention-to-treat analysis could be performed because all had at least one efficacy and safety evaluation after randomization. Therefore, the last observation was carried forward to day 42 (LOCF42), using an analysis of variance (ANOVA). In case of significant differences of efficacy and safety parameters at baseline, an analysis of covariance (ANCOVA) was performed, using the respective baseline value as covariate. Since dosage emerged to be reduced differentially in both treatment groups, in the statistical analyses of the efficacy and tolerability parameters ANCOVA analyses were performed with doses as covariates. For ordinally scaled parameters, the Mantel-Haenszel test was performed, while for dichotomic variables the χ^2-test was used. Treatment by center interactions were tested by analysis of covariance using least means squares.

The aim of the study was to demonstrate approximate antipsychotic efficacy of amisulpride versus flupentixol and, in case of non-rejection of the null hypothesis with regard to efficacy, to compare the extrapyramidal side effects of the two antipsychotics in order to test for superiority with regard to extrapyramidal tolerability. Key outcome parameters for efficacy, tolerability and the order of hypotheses as outlined above were designated a priori. The level of significance was defined as $\alpha = 0.05$. The key outcome parameter for efficacy was the change in the BPRS total score. All other efficacy parameters, like SAPS, SANS, CGI and GAS, were considered secondary.

As to statistical analysis of antipsychotic efficacy, testing for equivalence between the two treatment conditions was performed one-sided. Equivalence was defined as a comparable therapeutic outcome not exceeding the smallest amount in the BPRS total score to the disadvantage of amisulpride that would be either of clinical relevance or might distinguish between discrete levels of severity. As such a change in the BPRS total score, a difference Δ of 6 points was defined. With regard to the sample sizes needed, to accept or to reject the null hypothesis with a power of $1-\beta = 0.8$ and a significance level of $\alpha = 0.05$ (one-tailed), assuming a clinically relevant difference of $\Delta = 6$ points for the BPRS and an estimated mean standard deviation $\sigma = 14$ points for the BPRS total score, 67 patients in either group would be required (Pocock 1983).

Outcome parameters for safety and tolerability were changes of the Simpson-Angus scale, the AIMS and the BAS. For these parameters, in case of a non-rejection of the null hypothesis with regard to efficacy, a two-sided confirmatory statistical analysis was performed with $\alpha = 0.05$ as significance level to test for superiority of one of the two drugs. Because of multiple comparisons, the α level was adjusted according to a hierarchy as $\alpha = 0.05/2$ for the Simpson-Angus scale, $\alpha = 0.05/4$ for the AIMS, and $\alpha = 0.05/4$ for the BAS. By this stepwise procedure according to an a priori weighting of the extrapyramidal target variables, it should be ensured that a total significance level of 5% was not exceeded (Bauer 1991).

Results

Patient characteristics

In the intention-to-treat population, there was no statistically significant difference as to sociodemographic and diagnostic parameters (Table 1). With regard to premedication, 39 of the amisulpride patients (56%) and 34 of the flupentixol patients (55%) were pretreated with psychotropic drugs. In most cases, patients were on neuroleptics (amisulpride group: 30 patients, 43%; flupentixol group: 26 patients, 42%) and/or benzodiazepine tranquilizers (amisulpride group: 18 patients, 26%; flupentixol group: 13 patients, 21%). Less than 10% in either medication group were pretreated with antidepressants, anticholinergics or other drugs.

Despite randomized assignment to treatment groups, statistically significant differences for some outcome parameters were detected at baseline. Amisulpride patients as a whole presented with significantly higher BPRS and SANS scores. Moreover, total scores for the SAPS and BAS total scores showed a statistical trend to be more pronounced in the amisulpride group (Table 2).

Table 1 Patients' characteristics: sociodemographic and diagnostic parameters

	Amisulpride	Flupentixol
Number of patients	70	62
Gender (m/w)	36/34	38/24
Age (years)	35 ± 11	33 ± 9
(Range)	18–64	18–58
Height (cm)	171 ± 10*	175 ± 9
Weight (kg)	72.6 ± 16.9	69.9 ± 13.6
Pretreatment		
Neuroleptics	30 (43%)	26 (42%)
Benzodiazepines	18 (26%)	13 (21%)
Schizophrenic subtype		
Paranoid	37 (53%)	35 (56%)
Undifferentiated	33 (47%)	27 (44%)

*$P < 0.05$

Table 2 Patients' characteristics with respect to baseline scores of efficacy and tolerability outcome parameters. *$P < 0.05$

	Amisulpride	Flupentixol
BPRS total score	56.1 ± 10.8*	49.8 ± 9.4
SAPS total score	59.2 ± 23.4	52.8 ± 18.4
SANS total score	41.7 ± 15.9*	32.0 ± 14.3
GAS score	35.3 ± 9.9	34.1 ± 9.7
CGI degree of severity	5.4 ± 0.7	5.3 ± 0.8
Simpson-Angus total score	1.1 ± 2.6	1.0 ± 2.4
AIMS total score	0.9 ± 2.5	0.7 ± 2.5
BAS total score	1.0 ± 1.6	0.5 ± 1.3

*$P < 0.05$

Table 3 Reasons for and numbers of drop-outs during double-blind treatment period. *$P < 0.05$

	Amisulpride	Flupentixol
Insufficient response	5 (7.1%)	8 (12.9%)
Adverse events	4 (5.7%)*	11 (17.7%)
"serious"	2 (2.9%)	0
Lack of cooperation	6 (8.5%)	4 (6.5%)
Complete remission and dismission from hospital	2 (2.9%)	1 (1.5%)
Other events	2 (2.9%)	1 (1.5%)
Total number of drop-outs	19 (27.1%)	25 (40.3%)

*$P < 0.05$

Early terminations

Ten of 142 patients included dropped out during the placebo washout phase. The remaining 132 patients as the intention-to-treat population were randomized to study medication: 70 patients received amisulpride, and 62 were administered flupentixol. Eighty-eight patients completed the whole study duration of 42 days of treatment. In the amisulpride group, 19 patients were withdrawn from the study, while in the flupentixol group, 25 patients terminated the study prematurely. The reasons for drop-outs are given in Table 3. Notably, with regard to study withdrawals due to adverse events, there was a significant difference between the two treatment groups (ASP: four patients, 5.7%; FPX: 11 patients, 17.7%; $P = 0.030$).

In the amisulpride group, there were two premature discontinuations due to serious adverse events. One patient attempted suicide while another suffered from a deep venous phlebothrombosis of the leg. The latter patient had had venous thromboses before and has suffered from a post-thrombotic syndrome since. In addition to amisulpride, she was given a contraceptive agent (estradiol and desogestrel in combination). Both of these factors might be more responsible than the neuroleptic treatment for this specific adverse event.

Dose regimen

All patients started with a fixed daily dosage of 1000 mg amisulpride or 25 mg flupentixol. The dosages administered during the consecutive weekly time intervals of the whole treatment duration are depicted in Fig. 1. The mean daily dosage ± SD for the whole study period was 956 ± 105 mg/day for amisulpride (i.e. a dose decrease of 11% of the possible dose reduction range), and 22.6 ± 3.4 mg/day for flupentixol (i.e. a dose decrease of 24% of the possible dose reduction range). At week 4, the mean daily dose was 939 ± 154 mg/day for amisulpride, and 21.8 ± 4.6 mg/day for flupentixol. At the end of week 6, the respective values were 907 ± 177 mg/day for amisulpride, and 19.5 ± 6.0 mg/day for flupentixol. With regard to the mean daily dose for the whole study period and the mean daily dosages

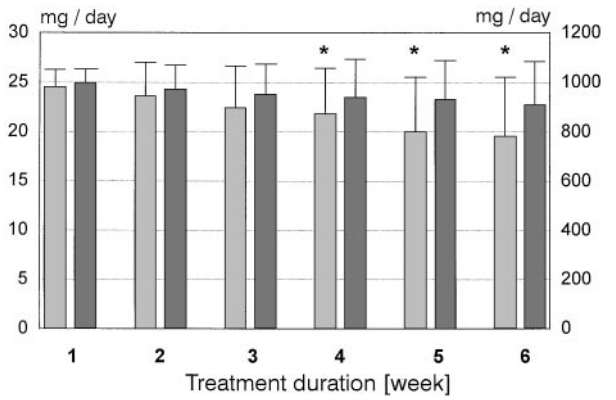

Fig. 1 Changes of mean daily dose during treatment period. *$P < 0.05$. ▫ Flupentixol, ▪ amisulpride

at weeks 4–6, the differences between the treatment groups were statistically significant ($P < 0.05$). Therefore, in all efficacy and tolerability analyses, ANCOVA procedures were applied with percentage dose reduction as covariate.

In the amisulpride group, dosage was decreased in 35 patients (50.0%) while in the flupentixol group, dose reduction was performed in 45 patients (72.6%). Due to side effects, dosage was decreased in 20 amisulpride patients (27.8%) and in 31 flupentixol patients (50.0%) ($P = 0.09$).

Efficacy

Intention-to-treat analysis

Intention-to-treat-analysis showed that both medications significantly improved the acute psychotic symptomatology. Concerning the key efficacy parameter, BPRS total scores decreased from 56.1 ± 10.8 (baseline; mean ± SD) to 32.4 ± 15.4 points (LOCF42) in the amisulpride group. The corresponding BPRS scores for the flupentixol group were 49.8 ± 9.3 at the beginning versus 33.3 ± 15.6 points at LOCF day 42 or treatment termination. Since the BPRS mean total scores were significantly greater in the amisulpride patients at baseline (Table 2), an analysis of covariance was performed with the treatment group as factor and the respective baseline value as covariate in order to perform confirmatory statistical evaluation. There was no difference in efficacy between the two treatment groups to the disadvantage of amisulpride. In fact, when the difference of the mean BPRS decreases of the two treatment groups and the standard deviation of this difference was calculated using outcome data from ANCOVA analysis with BPRS baseline and dosage reduction as covariates, the difference was 5.6 points in favour of amisulpride (95% confidence limits: 0.55; 10.65).

ANCOVA analysis of the BPRS mean total scores revealed a trend in favour of amisulpride ($P = 0.059$).

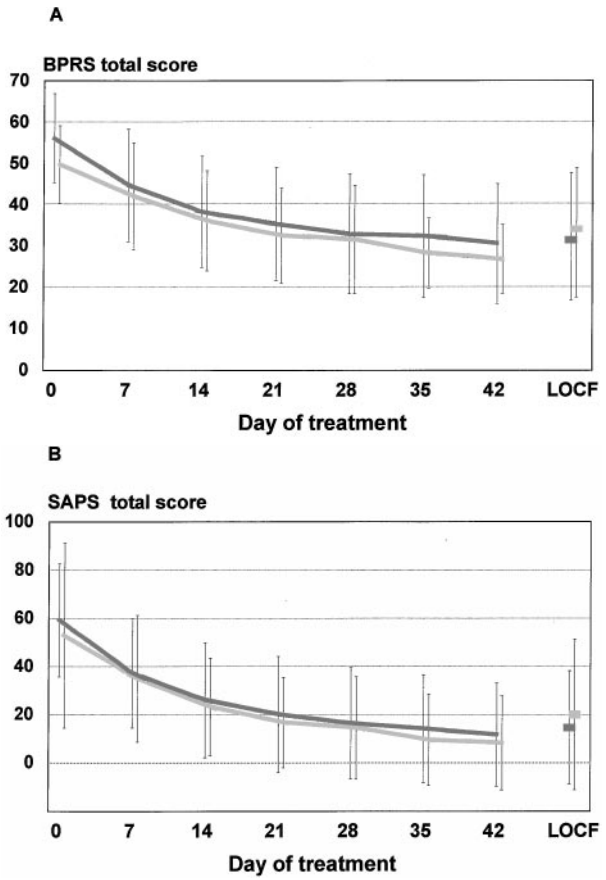

Fig. 2 **A** Time course of BPRS total score during treatment period. **B** Time course of SAPS total score during treatment period. ■ Amisulpride, □ flupentixol

When the statistically different dose reduction in both treatment groups was also taken into consideration, amisulpride was statistically superior to flupentixol with regard to reduction of BPRS total scores ($P = 0.037$). As the statistical comparison between the treatment conditions was intended to be performed one-sided to test for equivalence of amisulpride, these latter ANCOVA differences are only reported in a descriptive manner.

When a categorical response criterion was defined as a reduction of at least 40% of the BPRS total score, 39% of the amisulpride patients and 30% of the flupentixol patients met this requirement. When a responder was defined as presenting with a CGI final improvement score of "very much better" or "much better", 62% of the patients in both treatment groups fulfilled this criterion.

The time course of the BPRS mean total scores during the treatment period is shown in Fig. 2A. There was no difference in the time course of improvement or in the onset of response between the two treatment groups. When a Cox proportional hazard regression analysis with regard to the time needed to reach a 40% reduction in the BPRS total score was performed, there was no difference between the amisulpride and the flupentixol groups.

Table 4 Changes of BPRS subscores during treatment period (LOCF42 versus baseline). Figures refer to the mean decrease under drug treatment. BPRS subscores: *ANDP* anxiety/depression; *ANER* anergia; *THOT* thought disturbance; *ACTV* activation; *HOST* hostile suspiciousness

	Amisulpride	Flupentixol	*P* value ANCOVA
BPRS-ANDP	−5.6 ± 3.7	−3.6 ± 4.6	0.0656
BPRS-ANER	−2.5 ± 3.3	−1.0 ± 3.4	0.1817
BPRS-THOT	−8.1 ± 4.5	−5.9 ± 4.8	0.1080
BPRS-ACTV	−4.2 ± 3.7	−3.1 ± 3.6	0.0903
BPRS-HOST	−2.6 ± 3.8	−2.6 ± 3.9	0.9636

As for the BPRS total score, the amisulpride group had higher symptom ratings than the flupentixol patients with regard to three BPRS subscores at baseline, i.e. anxiety/depression (ANDP; $P = 0.035$), anergia (ANER: $P = 0.001$) and thought disturbance (THOT: $P = 0.008$). Descriptive intention-to-treat ANCOVA analysis of the BPRS subscore changes during treatment with baseline subscores as covariate revealed that there was a trend for a more favourable outcome in the factors "anxiety/depression" and "activation" for the amisulpride treatment group (Table 4).

SAPS scores of the amisulpride patients were reduced from 59.2 ± 23.4 to 14.7 ± 23.4 points at LOCF42 while for the flupentixol group the corresponding SAPS values were 52.8 ± 18.4 at baseline vs. 20.1 ± 31.1 points at LOCF up to day 42. Again, descriptive analysis by ANOVA of this secondary outcome parameter demonstrated a trend to a more marked decrease under amisulpride ($P = 0.069$). Considering the different dose reduction across treatment groups as an independent factor in ANCOVA analysis, there was still a difference in favour of amisulpride ($P = 0.028$). The time course of the SAPS mean total scores during treatment demonstrated fairly parallel curves (Fig. 2B).

For the amisulpride group, SANS scores showed a decrease from 41.7 ± 15.9 at baseline to 22.8 ± 19.4 points at LOCF day 42. The respective SANS data for the flupentixol patients were 32.0 ± 14.3 versus 22.3 ± 22.0 points. Amisulpride patients presented with significantly higher SANS scores at baseline (Table 2). The amisulpride group started from a higher baseline and ended up in a slightly lower LOCF score but ANCOVA analysis demonstrated that this difference did not reach the level of statistical significance ($P = 0.132$).

Despite higher baseline ratings for BPRS and SANS scores, the CGI degree of severity rating was not different in both treatment groups (Table 2). In the amisulpride group, the CGI degree of severity index decreased by 2.5 ± 1.5 points (−46%), while the respective reduction was 2.0 ± 1.6 points (−37%) for the flupentixol group ($P = 0.079$). Likewise, the GAS

score did not differ between the two treatment groups at baseline. The increase of the GAS scores was similar under both amisulpride (+ 28.7 ± 14.7 points) and flupentixol (+ 26.5± 20.4 points).

Completer analysis

In order to account for drop-outs in the beginning of drug administration, patients who had been treated with the study medication for less than the first 26 days were excluded from a supplementary analysis. The remaining 105 patients (57 patients in the amisulpride group and 48 patients in the flupentixol group) were then analysed separately as "completer-evaluable patient population".

As to the primary outcome criterium, the BPRS total score decreased from 55.1 ± 10.7 to 30.1 ± 14.1 in the amisulpride group (mean absolute improvement: + 46 ± 19%), while for flupentixol the respective values were 49.0 ± 9.8 and 28.9 ± 11.0 (mean improvement: + 40 ± 21%). Covariate analysis (factors: group, dosage reduction; covariate: baseline) did not differ significantly between these two groups ($P = 0.321$). Likewise, when a responder was defined as a patient with a final CGI score of "very much better" or "much better", there were 68% responders on amisulpride and 66% on flupentixol ($P = 0.790$).

Time to response, defined as a reduction of at least 40% in the BPRS total score, did not differ significantly between these two groups ($P = 0.513$).

Safety and tolerability

Extrapyramidal symptom ratings

At baseline, between the two treatment groups there was no significant difference in the three extrapyramidal side effect rating scales (Table 2). Inter-group comparisons by intention-to-treat analysis revealed significant treatment effects in the changes from scores at baseline versus LOCF42. In all extrapyramidal outcome parameters, i.e. in the Simpson-Angus scale, the AIMS and the BAS, amisulpride caused significantly fewer motor side effects as compared to flupentixol ($P < 0.01$, respectively). Notably, in the AIMS and the BAS virtually no increase of score values was found during amisulpride treatment. The significant differences found in favour of amisulpride with ANOVA analysis were still highly significant when ANCOVA analysis was applied with dosage and dose reduction at LOCF42, respectively, as covariate (Table 5).

Using the UKU scale, 70% of the amisulpride patients versus 79% in the flupentixol group were rated to suffer from extrapyramidal symptoms of any severity degree at least once during the treatment period.

Table 5 Changes of extrapyramidal side effects during treatment period (LOCF42 versus baseline) as assessed by the Simpson-Angus scale, the AIMS and the BAS. Figures refer to the mean increase under drug treatment

	Amisulpride	Flupentixol	*P* value ANOVA	*P* value ANCOVA
Simpson-Angus	1.1 ± 3.7	3.8 ± 5.9	0.0026	0.0007
AIMS	0.0 ± 2.8	1.8 ± 4.4	0.0063	0.0085
BAS total score	0.2 ± 1.9	1.6 ± 2.4	0.0001	0.0001

Table 6 Treatment-emergent adverse events during treatment period (i.e. one or more adverse events newly registered at at least one time point after baseline as assessed by the UKU scale. Figures refer to the percentage of patients affected. [1] Percentage of female patients only. [2] Percentage of male patients only. *$P < 0.05$

Adverse event	Amisulpride (%)	Flupentixol (%)
Sedation	45.7	54.8
Inner unrest	27.8	29.0
Concentration difficulty	24.3	24.2
Increased duration of sleep	22.9	38.7*
Weight gain	21.4	22.6
Headache	20.0	8.1
Emotional indifference	18.6	27.4
Accomodation disturbance	18.6	27.4
Increased salivation	17.1	22.6
Constipation	17.1	9.7
Increased sweating	14.3	9.7
Orthostatic dizziness	12.9	17.7
Menorrhagia	14.7[1]	14.2[1]
Galactorrhea	5.7	4.8
Gynecomastia	2.9	3.2
Ejaculatory dysfunction	5.5[2]	5.3[2]
Erectile dysfunction	2.5[2]	13.2[2]
Any adverse event	87	92

Concomittant anticholinergic and sedative/hypnotic medication

Fewer patients needed biperiden co-medication under amisulpride (ASP: 43%; FPX: 61%). The average daily biperiden dose given as calculated by LOCF42 intention-to-treat analysis was significantly smaller in the amisulpride group (3.0 ± 2.2 mg/day) than under flupentixol (5.4 ± 4.3 mg/day; $P < 0.05$) while the average duration was similar (ASP: 22.3 days; FPX: 27.3 days).

The number of patients requiring diazepam (ASP: 70%; FPX: 66%) and the average duration of administration (ASP: 17.7 days; FPX: 17.1 days) were comparable across the treatment groups. There was no difference in the average daily dose of diazepam between the amisulpride patients (6.8 ± 5.5 mg/day) and the flupentixol group (11.0 ± 11.8 mg/day).

Other adverse events

Apart from the extrapyramidal side effects, treatment-emergent adverse events (i.e. one or more adverse events

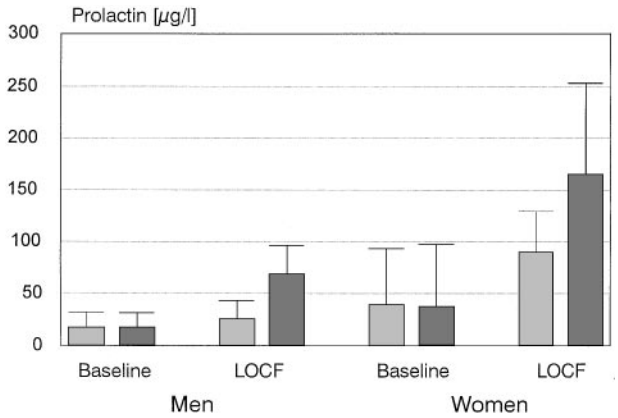

Fig. 3 Prolactin plasma concentrations during treatment period. ▫ Flupentixol (M:17; W:12), ▪ amisulpride (M:18; W:11)

newly registered at least one time point after baseline) mentioned as assessed by the UKU scale were found in 87% of the amisulpride patients and 92% of the flupentixol patients (Table 6).

Other tolerability parameters

Systolic and diastolic blood pressure as well as heart rate were reduced by a minor and insignificant degree by both drugs. Mean weight gain was 1.0 ± 3.9 kg under amisulpride and 2.2 ± 3.5 kg under flupentixol (NS).

Likewise, routine laboratory parameters and ECG and EEG registrations did not show relevant pathological changes under either drug treatment. In both groups, eosinophilia or elevations of cholesterol, triglycerides and creatinine were rarely found as treatment-emergent changes of laboratory parameters without any particular cause for concern.

Prolactin plasma levels

In 29 amisulpride patients (18 men, 11 women) and 29 flupentixol patients (17 men, 12 women), prolactin levels were measured at baseline and after 4 weeks treatment in the morning in the fasting patient. In men, under amisulpride prolactin levels increased from 17.9 ± 13.7 µg/l to 68.8 ± 27.5 µg/l while for flupentixol the respective values were 18.0 ± 14.1 and 26.1 ± 17.0 µg/l. In women, under amisulpride, prolactin levels raised from 37.6 ± 59.5 µg/l to 165.5 ± 87.3 µg/l while for flupentixol, prolactin concentrations of 39.2 ± 53.9 µg/l at baseline and 90.2 ± 39.3 µg/l after 4 weeks treatment were found (Fig. 3). ANCOVA analysis between the treatment groups with sex and baseline prolactin concentration as covariates demonstrated that prolactin levels were significantly more elevated in amisulpride patients ($P < 0.001$).

As to the incidence of "neuroendocrine" side effects, there was no clinically relevant difference with regard to possibly prolactin-related adverse events between the treatment conditions.

Discussion

From the extensive evaluations in this trial, amisulpride emerges as an effective and safe antipsychotic drug. In the relatively high dose range chosen, there were less extrapyramidal side effects and fewer drop-outs due to adverse events with amisulpride as compared to flupentixol. The treatment-emergent incidence and severity of parkinsonism, dyskinesia, and akathisia was lower with amisulpride than with flupentixol. Nevertheless, there were extrapyramidal and other side effects in a substantial number of patients which might not have occurred to this extent if lower doses would have been applied. However, a dose-finding study with different fixed dosage ranges for both amisulpride and flupentixol in order to assess optimal dosages was beyond the scope of this study.

While prolactin levels were higher in the amisulpride group, adverse events such as galactorrhea, gynecomastia, and menorrhagia were reported to an extent not significantly different across both treatment groups.

This was a short-term neuroleptic trial according to the widely held clinical practice that the efficacy of an antipsychotic in acute schizophrenic symptomatology is evaluable after 4–6 weeks. Since none of the patients was on depot neuroleptic treatment, and a wash-out period of 3 days on the average was required during which no significant improvement should occur, treatment effects measured in this trial might not be confuted by carry-over effects from previous neuroleptic treatment regimes or by spontaneous remission in a significant manner. However, for ethical reasons, no placebo group was used in this population of acutely ill schizophrenic patients. Therefore, it cannot be estimated precisely to what extent placebo effects or factors not related to drug treatment might have contributed to patients' improvement.

With regard to acute schizophrenic disorders with predominant positive symptomatology, in double-blind trials against haloperidol (Pichot and Boyer 1988; Delcker et al. 1990), amisulpride demonstrated comparative antipsychotic properties while extrapyramidal side effects and depressive symptoms were significantly less marked than with the standard neuroleptic. However, in both studies the size of the treatment groups did not allow to sufficiently control the type II error. In this study, equivalent antipsychotic effects were demonstrated for amisulpride in comparison to flupentixol as reference neuroleptic with a power of 80% using one-sided statistical analysis. Moreover, in a recent study with 191 in-patients, amisulpride

(800 mg/day) was at least as effective as haloperidol (20 mg/day) in the treatment of productive schizophrenic symptoms whilst causing fewer extrapyramidal side effects (Möller et al. 1997).

Flupentixol was chosen as comparator in order to evaluate the possible contribution of an additional D_1-like antagonism on antipsychotic efficacy and extrapyramidal side effect liability. While a central role for D_2-like receptors as a target for antipsychotic drugs has been indicated by the relative potency of neuroleptics in receptor binding studies (Creese et al. 1976; Seeman et al. 1976) and by PET investigations in the human brain in vivo (Farde et al. 1988), many data from animal experiments and behavioral models suggested that D_1-like antagonistic properties of a drug might add to its antipsychotic activity without or with relatively few extrapyramidal side-effects or even attenuate the the extrapyramidal effects of a D_2-like blocking drug (Chipkin et al. 1988; Coffin et al. 1989; McHugh and Coffin 1991; Gerlach and Hansen 1993; Waddington 1993). Likewise, from preclinical studies, it has been speculated that the addition of a D_1-like antagonism to a D_2-like receptor blockade would accelerate the onset of response and decrease the time needed for an antipsychotic response. Moreover, D_1-like receptors may interact with and regulate D_2-like receptor activity which might be altered in schizophrenia (Seeman et al. 1989).

In our study, we found no additional benefit of flupentixol with regard to antipsychotic efficacy or onset of action in schizophrenic patients. Rather, differences to the disadvantage of combined D_1-like/D_2-like antagonism were found, especially with respect to extrapyramidal side effects. Therefore, none of the aforementioned hypotheses from preclinical animal data on the relevance of D_1-like antagonism could be substantiated. The present findings, the results of the previously quoted open clinical trials and clinical data of the mixed D_1-/D_2-like receptor antagonist savoxepine (Wetzel et al. 1991) do not suggest a pivotal role for D_1-like receptor antagonism in antipsychotic drug efficacy and may also question the relevance of a combined D_1-/D_2-like receptor blockade for antipsychotic efficacy or extrapyramidal tolerability. However, beneficial effects of a supplementary D_1-like antagonism might have been missed because of an inadequate dose range for flupentixol leading to a too strong D_2-like receptor blockade. In order to obtain substantial D_1-like antagonism, flupentixol was administered at a high dose. In this respect, to test this hypothesis, it might have been more favourable to add a selective D_1-like antagonist as a separate drug in a placebo-controlled manner to a selective D_2-like dopamine receptor blocking neuroleptic at their respective "optimal" doses.

In conclusion, compared to the mixed D_1-/D_2-like antagonist flupentixol, the selective D_2-like antagonist amisulpride proved to be equipotent with regard to overall antipsychotic efficacy and onset of response. In the dose range chosen, amisulpride caused significantly fewer extrapyramidal side-effects than flupentixol. Therefore, amisulpride appears to be an effective antipsychotic agent with a favourable extrapyramidal side-effect profile. Although conclusions have to be drawn cautiously as dosage effects on outcome parameters cannot be entirely ruled out, from a more theoretical neurobiological point of view these results question the notion that for neuroleptics an additional D_1-like antagonism might be of benefit to improve antipsychotic efficacy or extrapyramidal tolerability, or would accelerate the rapidity of onset of antipsychotic drug response.

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