HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2004; **19**: 111–119.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/hup.574

Dosage finding and outcome in the treatment of schizophrenic inpatients with amisulpride. Results of a drug utilization observation study

Michael Linden[1]*, Tabea Scheel[1] and Franz Xaver Eich[2]

[1]*Research Group Psychosomatic Rehabilitation, Charité, University Hospital Benjamin Franklin, Germany*
[2]*Sanofi, Synthelabo Berlin, Germany*

Objectives Amisulpride is an unique neuroleptic drug insofar as it has a dual pharmacodynamic effect. At low doses it blocks selectively presynaptic autoreceptors, and at high doses it blocks postsynaptic D_2/D_3 receptors. This allows the dosage to be adjusted and the treatment tailored to various clinical situations. It is unknown whether this pharmacological property has any bearing for routine treatment. The questions are: which dosages of amisulpride are chosen by physicians in the treatment of schizophrenic inpatients and does this dosage handling deviate from prescription guidelines?; which factors can explain dosage selection, and what is the treatment outcome with different dosages? The study pertains to drug management and dosage finding as principal factors in explaining positive and negative medication results.
Methods In a drug utilization observation study the prescribing of amisulpride for 811 schizophrenic inpatients from 240 psychiatric hospitals was monitored for 8 weeks. Standardized assessment included dosage, the positive and negative symptom scale (PANSS), the clinical global impression rating (CGI), the patients' subjective reaction to amisulpride, psychosocial functioning, EPS and other adverse events. The mean observation period was 49 days.
Results The mean initial daily dose of amisulpride was 361 mg/day. The mean daily dose at day 56 was on average 550 (SD 266) mg/d, ranging from 100 mg to 1600 mg. 17.9% of patients received a maximum dose up to 399 mg/d, 48.1% between 400 and 799 mg/d, and 25.5% 800 mg/d and higher. Higher doses were preferably prescribed for males, patients with involuntary admission, patients with paranoid schizophrenia with acute exacerbation, high CGI and high PANSS-positive scores. Patients with higher doses of amisulpride at the same time received higher rates of additional other neuroleptic drugs. Higher doses yield better results in very severe cases.
Conclusions Prescribed dosages were in the lower range of what is recommended for acute cases. Dosage was significantly influenced by the severity of the illness. Polypharmacy was the rule rather than the exception. Efficacy rates under conditions of routine care were similar to the results from controlled clinical trials, which speaks for their generalizability. Very severe cases profit from higher doses. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — schizophrenia; antipsychotics; neuroleptic drugs; amisulpride; dosage finding; drug utilization; epidemiology of care; quality assurance

INTRODUCTION

The blockade of dopamine D_2 receptors is seen as the essential mechanism for the antipsychotic properties of neuroleptic drugs while other pharmacodynamic actions explain unwanted effects (Soares *et al.*, 2001). A drug with a preferential affinity for dopamine D_2 and D_3 receptors, but none for D_1, D_4 and D_5 receptors, and also with a primary activity in limbic regions of the brain rather than at striatal dopamine receptors is the substituted benzamide amisulpride. Furthermore it has a dual effect insofar as at high doses it blocks postsynaptic D_2/D_3 receptor subtypes and at low doses it selectively blocks presynaptic autoreceptors, enhancing dopaminergic transmission. Amisulpride also has no affinity for adrenergic, serotonergic, histaminergic or muscarinergic receptor systems. Therefore,

* Correspondence to: Professor M. Linden, Rehabilitation Centre Seehof, Lichterfelder Allee 55, 14513 Teltow/Berlin, Germany. Tel: 03328/345678. Fax: 03328/345555.
E-mail: linden@zedat.fu-berlin.de

Contract/grant sponsor: Sanofi Synthelabo, Berlin.

Received 31 July 2003
Accepted 11 December 2003

amisulpride does not cause hypotension, anticholinergic effects, sedation, cognitive impairment, weight increase or EPS. Several authors stress that the safety profile of amisulpride is superior to standard reference compounds (Wetzel *et al.*, 1998; Coulouvrat and Dondey-Nouvel, 1999; Peuskens *et al.*, 1999; Carriere *et al.*, 2000; Legangneux *et al.*, 2000; Rosenzweig *et al.*, 2002). On the other hand, amisulpride can, dose dependently, have a higher incidence of prolactin elevation (Mauri *et al.*, 1996), which might decrease during treatment over 1 year (Schlösser *et al.*, 2002).

There is a great body of evidence for the clinical effectiveness of amisulpride in positive as well as negative and in acute as well as chronic schizophrenic disorders. Reviews of double-blind, randomized controlled clinical trials (Möller *et al.*, 1997; Puech *et al.*, 1998; Wetzel *et al.*, 1998; Peuskens *et al.*, 1999; Blin, 2000; Carriere *et al.*, 2000; Lecrubier, 2000; Leucht *et al.*, 2002) show that amisulpride is at least as efficacious as haloperidol (10–30 mg/d), risperidone (8 mg/d), or flupentixol (25 mg/d) in controlling positive symptoms, but was significantly more effective than haloperidol on secondary negative symptoms. Amisulpride led to a better improvement in the global assessment of functioning, GAF, or quality of life, QLS (Carriere *et al.*, 2000). This efficacy profile makes amisulpride not only a drug of choice in acute but even more in chronic schizophrenic patients with predominantly negative symptoms (Colonna *et al.*, 2000; Lecrubier, 2000).

Referring to the hypothesis that dopaminergic hypofunction is one of the causes of negative symptoms and concordant with the pharmacological peculiarity of blockade of presynaptic autoreceptors, several studies suggest that negative symptoms can especially benefit from lower doses of amisulpride. In a 12-week, multicentre double-blind trial by Danion *et al.* (1999) the efficacy of 50 mg/d and 100 mg/d amisulpride and placebo was compared in the treatment of negative symptoms of schizophrenia. Both amisulpride treatment groups showed significantly greater improvement (measured by the scale for the assessment of negative symptoms/SANS) in primary negative symptoms than the placebo group (independent of improvement of positive symptoms). Similar double-blind placebo-controlled studies, of 6 weeks to 6 months duration, in which schizophrenic patients were selected carefully for the predominance of primary negative symptoms (Boyer *et al.*, 1995; Paillère-Martinot *et al.*, 1995; Loo *et al.*, 1997; Rein and Turjanski, 1997), confirm the efficacy of amisulpride at a dose of 100 mg/d in schizophrenic patients with primary negative or deficit symptoms. No further clinical improvement was obtained when the dose of amisulpride was increased from 100 to 300 mg/d.

When it comes to acute episodes of schizophrenia available pharmacological considerations and empirical clinical evidence speaks for the use of higher doses of amisulpride, i.e. 800–1200 mg/d (Boyer *et al.*, 1994). *In vivo* PET scan data in schizophrenic patients indicate that the optimal 70–80% occupancy of striatal D_2 receptors, suggested as an optimal interval for therapeutic action on positive psychotic symptoms, is reached at doses of 550 to 750 mg/d, while doses beyond 1100 mg/d result in receptor occupancy of more than 80% and are accompanied by increased EPS (Farde *et al.*, 1992; 1995; Martinot *et al.*, 1996). Clinical double-blind studies (Hillert *et al.*, 1994; Puech *et al.*, 1996; Freeman, 1997; Möller *et al.*, 1997) with acutely ill schizophrenic patients show that amisulpride has optimal efficacy at doses between 400 and 800 mg/d. Puech *et al.* (1996) studied in a 4-week, double-blind, randomized trial the dose–response relationship of 100, 400, 800 and 1200 mg/d amisulpride and 16 mg/d haloperidol. Efficacy data (BPRS and PANSS positive subscale) showed a bell-shaped dose-response curve in the amisulpride group, with 400 mg/d and 800 mg/d being the most effective treatments for positive symptoms. Parkinsonism did not increase significantly between baseline and endpoint with amisulpride 400, 800 and 1200 mg/d compared with the amisulpride 100 mg/d group, whereas there was a significant difference in the haloperidol group. Recently published studies (Martin *et al.*, 2002; Sechter *et al.*, 2002) comparing amisulpride with olanzapine or risperidone showed equal efficacy with a better safety profile of amisulpride.

In summary, one of the special characteristics of amisulpride is that it has a large therapeutic range, i.e. from 50 mg/d to 1200 mg/d, depending on the therapeutic problem at hand. This makes it possible to taper the dose to the needs of the individual patient allowing tailored and optimal treatment for many different clinical situations without the need to switch drugs. Lecrubier *et al.* (2001) recommended 800 mg/d as a standard dose in severe and recurrent episodes and especially in hospital settings. In the case of an insufficient response, the dose can be increased to 1200 mg/d. In acute outpatients the initial dose should be 400 mg/d and in the case of an insufficient response it can be increased to 800 mg/d by 200 mg/d steps. In maintenance treatment, modulation of the dose as a function of symptoms is recommended. For patients who no longer manifest positive symptoms, a dose reduction of 200 mg every 2–3 months is recommended with 400 mg/d as the target. For patients with

predominantly negative symptomatology the dose should be reduced to 100–300 mg/d, with 100 mg/d being sufficient in most cases.

An open question is to what degree this double pharmacologic action of the drug can be used in routine care. Guidelines such as those from Lecrubier *et al.* (2001) are based on pharmacological data and evidence from controlled clinical trials which are known to differ in many aspects from clinical practice (Linden, 1989). In controlled trials, compared with routine, selected patients are treated by physicians with special expertise under intensive surveillance conditions. Clinical trials ask for efficacy while clinical practice aims at efficiency. Treatment decisions in routine care must not only take into consideration medical information but also cultural, economic or psychological aspects (Linden, 1994). As a consequence, treatment under conditions of routine care can and often must deviate considerably from guidelines. Studies on the epidemiology of care and prescribing modalities of drugs are therefore important to validate and improve treatment guidelines, to assure treatment quality, target possible problems, and also to understand better the process of prescribing (Curran *et al.*, 2002).

So far, to our knowledge, there are no epidemiological studies on the prescribing of amisulpride in routine care. Given the double pharmacological action and the recommendation of the producer for different dosages for different patient groups, empirical data are needed to answer the following questions:

1. Which initial and maximum dose of amisulpride is chosen by physicians in practice for acute schizophrenic inpatients, and does this dosage handling deviate from prescription guidelines?
2. Which factors are correlated with dose, and does this comply with pharmacological theory?
3. Are different doses correlated with different treatment results?

The methods used to study such questions are drug utilization observation studies (DUOS) (Linden, 1992, 1997). These are pharmacoepidemiological studies which prospectively and with standardized assessment instruments monitor physician behaviour without interfering with treatment decisions. The doses are chosen for the individual patient, therefore dosage is the independent variable in this study.

MATERIALS AND METHODS

In a drug utilization observation study the prescribing of amisulpride for schizophrenic inpatients was monitored for 8 weeks. Psychiatrists treated these patients according to their clinical expertise and the needs of the individual patient. Treatment was not influenced by the study. Physicians did not receive any special information on the drug or the treatment. Patients were included in the study if they were between 18 and 65 years of age, fulfilled the DSM-IV criteria for schizophrenic disorder and were prescribed amisulpride for individual reasons. Some 811 schizophrenic inpatients from 240 psychiatric hospitals (23 university hospitals) from all over Germany were included. Cooperating hospitals and physicians were recruited by company representatives of Sanofi-Synthelabo, Germany.

Standardized assessment included sociodemographic variables, patient status, dosage, unwanted events and psychosocial functioning (Table 1). Patient status was measured by the clinical global impression rating (CGI), with score 2 for 'patient is not ill' to score 8 for 'patient is extremely severe ill', and by a modified positive and negative symptom scale (PANSS scores ranged from 1, not observed, to 4, severe symptoms, giving a sum score of 7 to 28 for the positive and the negative subscale; sleep disturbance and anxiety were measured separately). The patient's subjective reaction to amisulpride was assessed by the van Putten questionnaire (van Putten and May, 1978). The presence and severity of extrapyramidal symptoms (parkinsonism, akathisia, dyskinesia) were rated from 1, not observed, to 4, severe symptoms, leading to a total score between 3 and 12; other unwanted events were reported by free text. Psychosocial functioning was measured with four items (work, leisure activities, social interaction, self-care; each rated from 1, good, to 4, severely impaired, total score ranging from 4 to 16).

Assessments of the patient and the treatment were done at day 0, day 28 and day 56. A contract statistical institute (Jung & Jung GmbH) collected the forms and did the data processing and quality control. In all cases where data were missing or inconsistencies had to be clarified, the prescribing physicians were contacted by telephone. Detailed statistical analyses were done by the authors. Data were analysed with the Statistical Package for Social Sciences (SPSS).

Data were analysed descriptively. For further analyses patients were grouped referring to the maximum daily dose during the observation period. The low dosage group includes patients receiving up to 399 mg/d, patients in the medium dosage group received between 400 and 799 mg/d, and 800 mg/d or more was the dose for patients in the high dosage group. The three dosage groups were compared by

Table 1. Comparison of dosage groups

	All groups % resp. mean (SD) $n = 811$[a]	Low dose group[b] % resp. mean (SD) $n = 146$[a]/17.9%	Medium dose group[b] % resp. mean (SD) $n = 390$[a]/48.1%	High dose group[b] % resp. mean (SD) $n = 207$[a]/25.5%	Chi-square resp. F and significance
Female	0%	58.7%	48.3%	47.1%	$\chi^2 = 0.064$
Age (years)	39.9 (11.9)	40.1 (12.8)	40.1 (11.6)	39.2 (11.9)	$F = 0.393$ $p = 0.001$
School					$\chi^2 = 0.778$
No school qualification	7.6%	7.3%	8.5%	6.1%	
Secondary modern school	37.6%	35%	38.8%	37.1%	
Junior high school	28.7%	29.2%	26.9%	32%	
High school diploma	19.4%	19%	19.7%	19.3%	
University	6.6%	9.5%	6.1%	5.6%	
Occupation					$\chi^2 = 0.938$
Continuous work	21.6%	22.5%	21.8%	20.7%	
Unemployed	22.6%	23.2%	23.9%	19.7%	
Retired	38.1%	36.6%	36.7%	41.9%	
Houseman/-wife	7.4%	7%	8%	6.6%	
In education	10.2%	10.6%	9.6%	11.1%	
Family state: patient lives					$\chi^2 = 0.976$
Married/with spouse	25.7%	29.2%	25.3%	24.3%	
With parents	20.6%	17.4%	21.1%	21.8%	
With children	2.7%	3.5%	2.3%	2.9%	
Single	40.1%	41.0%	39.9%	39.8%	
In sheltered home	6.8%	6.3%	7.0%	6.8%	
Others	4.1%	2.8%	4.4%	4.4%	
Family history (psychiatric)	27%	27.7%	27%	26.6%	$\chi^2 = 0.723$
Years since first schizophrenic illness	8.4 (8.6)	8.4 (8.8)	8.1 (8.5)	8.7 (8.6)	$F = 0.283$ $p = 0.001$
Number of inpatient treatments so far (due to schizophrenia)	4.9 (5.6)	3.8 (3.4)	5.3 (6.6)	5.0 (4.9)	$F = 3.475$ $p = 0.002$
Admission state					$\chi^2 = 0.005$
Voluntary accommodation	79.1%	88.7%	75.9%	78.3%	
Forced admittance	17.2%	8.5%	20.1%	17.7%	
Endangering (self/others)	1.4%	1.4%	0.5%	3%	
Paranoid schizophrenia with exacerbation	70.1%	61.6%	69.7%	76.8%	$\chi^2 = 0.023$
CGI severity T1[c]	6.4 (0.8)	6.1 (0.8)	6.4 (0.8)	6.5 (0.7)	$F = 15.293$ $p = 0.000$
CGI severity T3[c] (with covariate T1)	5.0 (1.4)	4.9 (1.4)	5.1 (1.4)	5.0 (1.4)	$F = 0.616$ $p = 0.540$
PANSS positive T1	16.8 (4.1)	15.5 (4.4)	17.0 (4.1)	17.5 (3.7)	$F = 10.185$ $p = 0.028$
PANSS positive T3 (with covariate T1)	10.9 (4.1)	10.1 (3.8)	11.0 (4.0)	11.2 (4.3)	$F = 1.100$ $p = 0.334$
PANSS negative T1	19.1 (4.9)	18.9 (4.9)	19.4 (4.9)	18.8 (5.0)	$F = 1.256$ $p = 0.004$
PANSS negative T3 (with covariate T1)	14.6 (4.8)	13.6 (4.5)	15.1 (4.9)	14.5 (4.8)	$F = 4.286$ $p = 0.014$
EPS T1	3.97 (1.7)	3.68 (1.3)	4.09 (1.7)	3.96 (1.7)	$F = 3.168$ $p = 0.043$
EPS T3 (with covariate EPS T1)	3.59 (1.3)	3.44 (1.2)	3.64 (1.4)	3.59 (1.1)	$F = 0.203$ $p = 0.816$
Psychosocial functioning level T1 (sumscore 1–12)	11.1 (2.8)	10.8 (2.7)	11.1 (2.8)	11.1 (2.8)	$F = 0.606$ $p = 0.002$
Psychosocial functioning level T3 (sumscore 1–12) (with covariate T1)	8.1 (2.9)	7.8 (3.09)	8.2 (2.9)	8.1 (3.0)	$F = 0.640$ $p = 0.528$
Psychopharmacological additional medication	77.8%	64.4%	77.4%	87.9%	$\chi^2 = 0.000$

Continues

Table 1. (*Continued*)

	All groups % resp. mean (SD) $n = 811$[a]	Low dose group[b] % resp. mean (SD) $n = 146$[a]/17.9%	Medium dose group[b] % resp. mean (SD) $n = 390$[a]/48.1%	High dose group[b] % resp. mean (SD) $n = 207$[a]/25.5%	Chi-square resp. F and significance
Neuroleptic additional medication	46.6%	40.4%	43.8%	55.6%	$\chi^2 = 0.006$
1. Atypical neuroleptics	11.0%	17.8%	9.0%	10.1%	$\chi^2 = 0.013$
2. Butyrophenons	15.5%	12.3%	15.1%	18.4%	$\chi^2 = 0.293$
3. Trisyclical neuroleptics	28.5%	17.8%	28.5%	36.2%	$\chi^2 = 0.001$
4. Antidepressives	12.5%	19.9%	11.0%	10.1%	$\chi^2 = 0.011$
5. Tranquilizers	44.4%	29.5%	44.9%	54.1%	$\chi^2 = 0.000$
6. Other psychiatric drugs	0.4%	0%	0.5%	0.5%	$\chi^2 = 0.691$
7. Biperidone	17.9%	9.6%	18.2%	23.2%	$\chi^2 = 0.004$
8. Mood stabilizers	6.5%	4.1%	5.9%	9.2%	$\chi^2 = 0.131$
Unwanted side effects					
T2[c]	13.1%	8%	12.2%	18.3%	$\chi^2 = 0.025$
T3	12.0%	7.4%	11.4%	16.3%	$\chi^2 = 0.044$

[a]*n* per line can vary according to missing data.
[b]Low dose: up to 399 mg/ d; medium dose: 400–799 mg/d; high dose: 800 mg/d and more.
[c]T1: study begin; T2: day 28 of study; T3: study end.

chi-square analyses or univariate analyses of variance. A multiple regression was performed to determine which factor contributes most to the choice of dosage independent from other factors. The maximum dose of amisulpride over the entire course of treatment was taken as the dependent variable. The sum of the positive and the sum of the negative scales of the PANSS at the beginning of the study, the rate of neuroleptic comedication, chronicity, paranoid type, gender and education were chosen as predictors. Another multiple regression was calculated to test whether dosage is related to outcome. The difference between the initial and the final PANSS-positive score was taken as the dependent variable and gender, paranoid type of schizophrenia, clinical global impression (CGI), education, neuroleptic comedication, chronicity and maximum dose as independent variables (Table 3). The same independent variables were chosen for multiple regression with the difference between the initial and the final PANSS-negative score being the dependent variable (Table 4). As outlined above, for theoretical reasons less severe schizophrenic cases should respond best to lower dosages and more severe cases to higher dosages. Therefore analyses of dose–outcome relations were done separately for both groups. A median-split was made for the positive PANSS (16 and less versus 17 and more) and the negative PANSS (19 and less versus 20 and more).

RESULTS

The patient characteristics are summarized in Table 1. 50% were female, the mean age was 39.9 years, 21.6% were in work, 25.7% lived with their spouse while 40.1% were single and 6.8% lived in sheltered homes. 70.1% were suffering from an acute exacerbation of paranoid schizophrenia.

The mean observation period was 49 days. The mean initial daily dose of amisulpride was 361 (SD 217.1) mg/d, ranging from 50 mg to 1200 mg. After 28 days the mean daily dose was 534 (SD 267.9) mg/d, ranging from 50 to 1400 mg. The mean daily dose at day 56 was on average 550 (SD 266) mg/d, ranging from 100 mg to 1600 mg. 17.9% of patients received up to 399 mg/d and therefore belonged to

Table 2. Multiple linear regression (dose prediction)

Predictor	Unstandardized coefficients Beta	Standardized coefficients Beta	T[a]	p[a]
(Constant)	416.753		6.156	0.000
Additional neuroleptic medication	49.967	0.102	2.627	0.009
Sum of PANSS positive scale at begin	8.485	0.144	3.596	0.000

[a]Dependent variable: maximum dose over entire course of treatment. Analysis determined exclusion of the following variables: years since first diagnosis, paranoid type, school, gender, initial sum of PANSS negative scale.
$R = 0.220$; adjusted $R^2 = 0.038$; $F = 4.690$; $p = 0.000$.

Table 3. Multiple linear regression (treatment effect prediction for positive symptoms)

Predictor	Unstandardized coefficients Beta	Standardized coefficients Beta	T^a	p^a
(Constant)	2.140		1.197	0.232
Severity of disease (CGI)	−1.072	−0.174	−4.344	0.000
Paranoid type	−1.216	−0.229	−5.795	0.000

[a]Dependent variable: difference PANSS positive subscale day 0 and day 56.
Analysis determined exclusion of the following variables: additional neuroleptic medication, years since first diagnosis, maximum dose over entire course of treatment, school, gender.
$R = 0.311$; adjusted $R^2 = 0.086$; $F = 9.029$; $p = 0.000$.

the low dosage group, 48.1% belonged to the medium dosage group, and 25.5% were in the high dosage group. The initial mean dose was 165 mg/d for the low dosage group, 397 mg/d for the medium dosage group and 597 mg/d for the high dosage group. At day 28, the respective mean dosages were 197 mg/d, 448 mg/d and 723 mg/d and at day 56 223 mg/d, 509 mg/d and 778 mg/d.

When comparing the three dosage groups, chi-square analyses or univariate analyses of variance showed that higher doses were preferably prescribed for males, patients with involuntary admission, paranoid schizophrenia with acute exacerbation, severity of illness and a PANSS-positive score (Table 1). Patients with higher doses of amisulpride at the same time received higher rates of additional other neuroleptic drugs. Neuroleptic (46.4% of all observed cases) or psychotropic comedication (77.8%) was the rule rather than the exception. The low-dosage group received preferably other atypical neuroleptics and/or antidepressants, while in the high-dosage group butyrophenons, sedating tricyclic neuroleptics or minor tranquillizers were the preferred comedications.

Unwanted events were reported in 7% to 18% of patients depending on the time of assessment and the dosage group (Table 1). There was a significant increase with higher dosages. Also the rate of biperidone comedication increased in parallel with dosage up to 23%. This must be attributed to not only amisulpride but to the overall medication and also the medication history. The EPS sum score, even at the start of the amisulpride medication, in the low dose group (3.7) was significantly lower than in the medium and high dose group (4.1 resp. 4.0, $F = 3.168$; $p = 0.043$*). Other reported adverse effects were gastrointestinal and skin reactions, menstrual disorders, galactorrhoea and prolactin increase.

During the observation period, a reduction of 5.9 was seen for the modified PANSS-positive score and of 4.5 for the modified PANSS-negative score. There was a significant difference between dosage groups only for negative symptoms: patients with low doses showed more improvement than patients with medium or high doses. The severity of illness, measured by CGI, dropped from initially 6.4 on average to 5.0 at the third visit. No significant difference between dosage groups was observed.

Since many of the single factors discriminating the dosage are related, a multiple regression was performed to determine which factor contributes most to the choice of dosage independent from other factors (Table 2). Neuroleptic comedication and the sum of the positive scale of the PANSS at the start of treatment explained 22% (adjusted 3.8%) of the variance of the maximum dose of amisulpride over the entire course of treatment. The initial sum score of the negative scale of the PANSS, chronicity, paranoid type, gender and school had no further significant contribution. Higher doses of amisulpride were prescribed in

Table 4. Multiple linear regression (treatment effect prediction for negative symptoms)

Predictor	Unstandardized coefficients Beta	Standardized coefficients Beta	T^a	p^a
(Constant)	−2.298		−1.326	0.185
Severity of disease (CGI)	−0.510	−0.089	−2.135	0.033

[a]Dependent variable: difference PANSS negative subscale begin and day 56.
Analysis determined exclusion of the following variables: additional neuroleptic medication, years since first diagnosis, maximum dose over entire course of treatment, paranoid type, school, gender.
$R = 0.127$; adjusted $R^2 = 0.004$; $F = 1.371$; $p = 0.215$.

Table 5. Logarithmic regression (treatment effect prediction for positive symptoms)

Predictor	Unstandardized coefficients Beta	Standardized coefficients Beta	T[a]	p[a]
(Constant)	−14.297		−4.277	0.000
Maximum dose for severely ill patients[b]	0.967	0.0957	1.817	0.070

[a]Dependent variable: difference PANSS positive subscale begin and day 56.
[b]Initial PANSS positive sumscore over 16.
$R = 0.09573$; adjusted $R^2 = 0.0064$; $F = 3.302$; $p = 0.070$.

Table 6. Logarithmic regression (treatment effect prediction for negative symptoms)

Predictor	Unstandardized coefficients Beta	Standardized coefficients Beta	T[a]	p[a]
(Constant)	−10.809		−3.996	0.000
Maximum dose for severely ill patients[b]	0.726	0.0904	1.657	0.099

[a]Dependent variable: difference PANSS negative subscale begin and day 56.
[b]Initial PANSS negative sumscore over 19.
$R = 0.09041$; adjusted $R^2 = 0.0052$; $F = 2.705$; $p = 0.099$.

cases with higher severity of positive symptoms and for patients already receiving more neuroleptics in general.

As a result of the multiple linear regression with the reduction of PANSS-positive score as the dependent variable (Table 3), the CGI and the paranoid type of schizophrenia explained 31.1% (adjusted 8.6%) of the variance, i.e. patients with initially higher scores in psychopathology showed larger reductions. The same analysis with reduction of the PANSS-negative score as the dependent variable (Table 4) showed that only the CGI could explain part of the variance (12.7%, adjusted 0.4%).

Analyses of dose-outcome relations were done separately for the less severe and the more severe cases. While there was no adequate regression model for patients with an initial PANSS positive sumscore under 17 and for patients with an initial PANSS negative sumscore under 20, logarithmic regression models for the more severe cases showed a trend such that higher doses were related to a better improvement in positive symptoms ($F = 3.3$, $p = 0.07$; Table 5) and also in negative symptoms ($F = 2.7$, $p = 0.099$, Table 6).

DISCUSSION

This study aims at improving knowledge on the utilization of amisulpride under conditions of routine care. At the same time it also gives information on the utilization of atypical antipsychotics in general and can serve as an important source of evidence for treatment recommendations and guidelines (Balestrieri *et al.*, 2000; Curran *et al.*, 2002), because clinical studies as well as utilization observations each cover unique treatment aspects. The reported data come from a drug utilization observation study, which are an important addition to data from controlled clinical trials, as they describe drug management under conditions of routine care. Only observational data can answer what dosages are used in routine care, for whom and why and with which consequences. They refer to a standardized assessment of a great number of schizophrenic patients who had been admitted to a large number of nationwide inpatient psychiatric units because of an acute exacerbation of their illness. Still, a notice of caution is necessary, as such data can be distorted by sampling or recording biases. The data therefore need replication by other authors and in other settings. So far, this study is the first of this type on amisulpride inpatient prescribing.

The patients who have been treated with amisulpride had been hospitalized because of acute exacerbations of their illness. It is a group of fairly chronic patients with 8 years since their first episode, who already have been hospitalized five times on average, and are out of work in about 80% of cases. The CGI severity of illness was classified as definitely to extremely severe in about 90% of cases. Therefore, in total this is a group of acutely ill schizophrenic patients.

The first question of this study concerned the dosage handling. Daily doses ranged from 50 mg/d to 1600 mg/d, which is a large difference. On average 361 mg/d was prescribed as the initial dose and 550 mg/d was the highest dose in the course of treatment. Does this deviate from guidelines? According

to Farde *et al.* (1992, 1995) and Martinot *et al.* (1996), the optimal interval for therapeutic action on positive psychotic symptoms was reached at doses of 550 to 750 mg/d, or according to Freeman (1997) at doses between 400 and 800 mg/d. Lecrubier *et al.* (2001) recommended doses up to 1200 mg/d for acute psychotic episodes. Therefore, the results of this study show that the selected dosages meet the guidelines but are in the lower range of what is recommended. The predominance of medical reasons for drug prescription as in clinical studies may be accompanied by reasons relevant for practice, such as cultural, economic or psychological reasons or simply polypharmacy. The latter is controlled for in clinical trials, but obviously not in practice.

The second question aims at factors determining dosage. Severity of illness (CGI; PANSS positive score, paranoid type with acute exacerbation) was directly related to dosage. Pharmacological theory explains a need for high dosage for positive symptoms. Also, higher doses for males and patients with involuntary admission are reasonable because of their higher potential for violence, and simply because of the higher body weight of males than of females.

Most relevant for the patient is the correlation of doses and treatment outcomes. There was a tendency for the more severe cases that higher doses were related to a better improvement in positive symptoms and also in negative symptoms. For the less severe cases, this correlation was not found. This supports the notion that in more severe cases higher doses should be prescribed, while in milder cases lower doses may be sufficient, which would be in line with existing prescription recommendations.

When interpreting amisulpride dosages one has to take into account that 46.4% of patients received additional neuroleptic drugs. Our data clearly show that severity of illness had a major impact on dosage selection and also on polypharmacy. The impact of severity on dosage selection is also confirmed by multivariate regression analysis. More severe patients not only received more amisulpride but also more other neuroleptics, i.e. especially sedative ones. These patients had been more often admitted involuntarily, had more chronic courses, and lower grades in psychosocial functioning. It can be speculated that curbing the positive symptomatology is the primary therapeutic target. In contrast, milder cases received lower dosages and as comedication more often antidepressants, the primary therapeutic target probably being depressive or negative symptoms. There is a doubling of unwanted effects in the high dose group, which must be attributed to the overall rate of neuroleptics. In general, no unexpected serious adverse events could be observed. Whether the observed neuroleptic comedication style is therapeutically beneficial or not can not be answered by our data. Instead, this is an important question which needs further research.

Within 8 weeks of treatment there was a reduction of the modified positive PANSS score of 5.9, i.e. 35%, and a reduction of the negative symptoms score of 4.5, i.e. 24%. The reduction of CGI score was 1.4, i.e. 20%. These data are not proof of efficacy by themselves, but give important information in the context of the existing literature. They show that the same rate of change can be observed under conditions of routine treatment as in controlled clinical trials. This result therefore can be interpreted as confirmation and validation of these experimental studies. They speak for the assumption that they can be generalized to everyday practice and against the hypothesis that results from controlled clinical trials are only valid for selected patient groups and treatment settings.

ACKNOWLEDGEMENT

This research was supported by Sanofi Synthelabo, Berlin Germany.

REFERENCES

Balestrieri M, Vampini C, Bellantuono C. 2000. Efficacy and safety of novel antipsychotics: a critical review. *Hum Psychopharmacol* **15**: 499–512.

Blin O. 2000. L′amisulpride: quelle place dans la réinsertion du patient schizophrène présentant des exacerbations aiguës. *L′Encéphale* **26**(Spec 1): 7–11.

Boyer P, Lecrubier Y, Puech AJ, *et al.* 1995. Treatment of negative symptoms in schizophrenia with amisulpride. *Br J Psychiatry* **166**: 68–72.

Boyer P, Lecrubier Y, Rein W. 1994. Amisulpride, new data in the treatment of schizophrenia. *Neuropsychopharmacology* **10**: 3S–804S.

Carpenter WT, Heinrichs DW, Wagman AMI. 1988. Deficit and non-deficit forms of schizophrenia: the concept. *Am J Psychiatry* **145**: 578–583.

Carriere P, Bonhomme D, Lemperiere T. 2000. Amisulpride has a superior benefit/risk profile to haloperidol in schizophrenia: results of a multicentre, double-blind study. The Amisulpride Study Group. *Eur Psychiatry* **15**: 321–329.

Curran S, Harris L, Macdonald A, *et al.* 2002. Antipsychotics in clinical practice: guidelines for safe and effective use. *Hum Psychopharmacol* **17**: 75–82.

Colonna L, Saleem P, Dondey-Nouvel L, *et al.* 2000. Long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. *Int Clin Psychopharmacol* **15**: 13–22.

Coulouvrat C, Dondey-Nouvel L. 1999. Safety of amisulpride (Solian): a review of 11 clinical studies. *Int Clin Psychopharmacol* **14**: 209–218.

Danion JM, Rein W, Fleurot O. 1999. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. *Am J Psychiatry* **156**: 610–616.

Farde L, Nordström AL, Karlsson P, *et al.* 1995. Positron emission tomography studies on dopamine receptors in schizophrenia. *Clin Neuropharmacol* **18**(Suppl. 1): S121–S129.

Farde L, Nordström AL, Wiesel FA, *et al.* 1992. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side-effects. *Arch Gen Psychiatry* **49**: 538–544.

Freeman HL. 1997. Amisulpride compared with standard neuroleptics in acute exacerbations of schizophrenia: three efficacy studies. *Int Clin Psychopharmacol* **12**(Suppl. 2): S11–S17.

Hillert A, Philipp M, Gattaz WF, *et al.* 1994. Amisulpride versus flupenthixol in the treatment of schizophrenia with predominant positive symptomatology: a controlled double-blind study [abstract]. *Neuropharmacology* **10**(Suppl. 3, part 2): S31.

Lecrubier Y. 2000. Is amisulpride an 'atypical' atypical antipsychotic agent? *Int Clin Psychopharmacol* **15**(Suppl. 4): S21– S26.

Lecrubier Y, Azorin M, Bottai T, *et al.* 2001. Consensus on the practical use of amisulpride, an atypical antipsychotic, in the treatment of schizophrenia. *Neuropsychobiology* **44**: 41–46.

Legangneux E, Mc Ewen J, Wesnes KA, *et al.* 2000. The acute effects of amisulpride (50 mg and 200 mg) and haloperidol (2 mg) on cognitive function in healthy elderly volunteers. *J Psychopharmacol* **14**: 164–171.

Leucht S, Pitschel-Walz G, Engel RR, *et al.* 2002. Amisulpride, an unusual 'atypical' antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry* **159**: 180–190.

Linden M. 1989. Die Phase IV der Therapie-Evaluation. *Nervenarzt* **60**: 453–461.

Linden M. 1992. Epidemiological methods in the evaluation of drugs. Field studies in the post-marketing phase. *Pharmacopsychiatry* **25**: 67–68.

Linden M. 1994. Therapeutic standards in psychopharmacology and medical decision-making. *Pharmacopsychiatry* **27**(Suppl.): 41–45.

Linden M. 1997. Phase IV research and drug utilization observation studies. *Pharmacopsychiatry* **30**: 1–3.

Loo H, Poirier-Littre MF, Théron M, *et al.* 1997. Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. *Br J Psychiatry* **170**: 18–22.

Martin S, Ljo H, Peuskens J, *et al.* 2002. A double-blind, randomized comparative trial of amisulpride versus olanzapine in the treatment of schizophrenia: short-term results at two months. *Curr Med Res Opin* **18**: 355–362.

Martinot JL, Paillère-Martinot ML, Poirier MF, *et al.* 1996. *In vivo* characteristics of dopamine D2 receptor occupancy by amisulpride in schizophrenia. *Psychopharmacology* **124**: 154–158.

Mauri MC, Bravin S, Bitetto A, *et al.* 1996. A risk-benefit assessment of sulpiride in the treatment of schizophrenia. *Drug Saf* **14**: 288–298.

Möller HJ, Boyer P, Fleurot O, *et al.* 1997. Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison to haloperidol. *Psychopharmacology* **132**: 396–401.

Paillère-Martinot M-L, Lecrubier Y, Martinot J-L, *et al.* 1995. Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. *Am J Psychiatry* **152**: 130–133.

Peuskens J, Bech P, Moller HJ, *et al.* 1999. Amisulpride vs. risperidone in the treatment of acute exacerbations of schizophrenia. Amisulpride Study Group. *Psychiatry Res* **88**: 107–117.

Puech A, Fleurot O, Rein W. 1998. Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. The Amisulpride Study Group. *Acta Psychiatr Scand* **98**: 65–72.

Puech A, Fleurot O, Rein W, *et al.* 1996. Amisulpride in the treatment of acute exacerbations of subchronic or chronic schizophrenia: a dose-range finding study [abstract]. *Eur Psychiatry* **11**(Suppl. 4): 280S.

Rein W, Turjanski S. 1997. Clinical update on amisulpride in deficit schizophrenia. *Int Clin Psychopharmacol* **12**(Suppl. 2): S19–S27.

Rosenzweig P, Canal M, Patat A, *et al.* 2002. A review of the Pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers. *Hum Psychopharmacol* **17**: 1–13.

Schlösser R, Gründer G, Anghelescu I, *et al.* 2002. Long-term effects of the substituted benzamide derivative amisulpride on baseline and stimulated prolactin levels. *Neuropsychobiology* **46**: 33–40.

Sechter D, Peuskens J, Fleurot O, *et al.* 2002. Amisulpride vs. risperidone in chronic schizophrenia: results of a 6-month double-blind study. *Neuropsychopharmacology* **27**: 1071–1081.

Soares BGO, Fenton M, Chue P. 2001. Sulpiride for schizophrenia (Cochrane Review). In *The Cochrane Library*, Issue 3. Update Software: Oxford.

van Putten T, May PR. 1978. Subjective response as a predictor of outcome in pharmacotherapy: the consumer has a point. *Arch Gen Psychiat* **35**: 477-480.

Wetzel H, Grunder G, Hillert A, *et al.* 1998. Amisulpride versus flupentixol in schizophrenia with predominantly positive symptomatology—a double-blind controlled study comparing a selective D2-like antagonist to a mixed D1-/D2-like antagonist. The Amisulpride Study Group. *Psychopharmacology* **137**: 223–232.

