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Plasma amisulpride levels in schizophrenia or schizoaffective disorder

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Abstract

The atypical antipsychotic drug amisulpride is a benzamide with specific antagonistic properties, which target dopamine D_2 and D_3 receptors, preferentially in the limbic system. Amisulpride is readily absorbed from the gastrointestinal tract, distributed to all body systems with little binding to plasma proteins. Elimination occurs mainly through the kidneys as unchanged drug. In contrast, hepatic metabolism is of minor significance and primarily yields two inactive metabolites. Very little is known about the plasma concentrations of amisulpride in patients at varying oral doses or about clinically relevant interactions with co-medication. The aim of the present investigation was to elucidate the factors, which affect amisulpride levels in schizophrenic patients. The plasma amisulpride levels of 85 patients with schizophrenia or schizoaffective disorder (mean age: 34.0 ± 11.4 years; 40 women, 45 men) were assessed by high-performance liquid chromatography (HPLC) with fluorometric detection. The average daily dose of amisulpride was 772.3 mg (S.D. 346.7 mg) and the mean amisulpride plasma concentration was 424.4 ng/ml (S.D. 292.8 ng/ml). The interindividual variance of the amisulpride plasma concentration was high; furthermore, the plasma concentration increased linearly with the daily oral dose ($r = 0.50$, $p < 0.001$). Age and gender showed a significant effect on the dose-corrected amisulpride plasma concentrations – older patients and women had higher dose-corrected amisulpride plasma concentrations than younger patients and men. However, cigarette consumption had no effect on the amisulpride plasma concentrations. Regarding co-medication with lithium and/or clozapine, significantly higher amisulpride plasma concentrations were found as compared to monotherapy, whereas other co-medications such as benzodiazepines and various conventional antipsychotics had no effect on the amisulpride plasma concentrations. The results, the possible pathomechanisms and the clinical relevance are discussed. The findings need to be confirmed in larger patient samples and with a wider range of co-medications.

Keywords: Amisulpride; Plasma concentration; Drug interaction; Schizophrenia

1. Introduction

The second-generation (atypical) antipsychotic amisulpride is a substituted benzamide derivative demonstrating a specific antagonism for dopamine D_2 and D_3 receptors, preferentially in the limbic system rather than in the striatum (Curran and Perry, 2001). It has no affinity for other receptors or transporter systems (Schoemaker et al., 1997).

At low doses, amisulpride binds preferentially to presynaptic receptors, increasing dopaminergic transmission, and at high doses the postsynaptic receptor blockade induces a decrease in dopaminergic transmission. In clinical studies, amisulpride, at high doses, was shown to be effective in treating positive symptoms of schizophrenia (Peuskens et al., 1999; Lecrubier et al., 2000; Davis et al., 2003). Recent studies have also proven the efficacy of low doses of amisulpride in the treatment of primary negative schizophrenic symptoms (Danion et al., 1999; Colonna et al., 2000; Müller et al., 2000; Leucht et al., 2002).

There are indications that amisulpride is superior to conventional antipsychotics both in the acute phase of a psychosis, in the sense of producing a more rapid response, and as a prophylactic for recurrence. The recommended starting dose for amisulpride in acute schizophrenic inpatients is 800 mg/day (Lecrubier et al., 2000).

A meta-analysis by Coulouvrat and Dondey-Nouvel (1999) indicated that the safety profile of amisulpride was satisfactory.

Amisulpride is rapidly resorbed after oral intake, reaching two maxima of plasma concentration after approximately 1 and 3–4 h, with a bioavailability of about 48% because of its

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low first-pass metabolization. The drug shows a rate of protein binding of about 16%. A steady state is reached after 2–3 days. The elimination half-life has been found to be 12 h. Amisulpride is metabolized in the liver to only a minor degree, yielding only two inactive metabolites. The drug is predominantly eliminated via the kidneys (Lambert and Naber, 1999).

To date, little is known about the significance of plasma concentrations of amisulpride for therapy (cf. Caccia, 2000) and whether there is any correlation with clinical effectiveness in patients at various oral doses.

The aim of the present study was to elucidate the factors, which affect amisulpride plasma concentrations in schizophrenic patients. For this purpose, the following questions were addressed:

1. What amisulpride plasma concentration ranges are observed when therapy is guided by clinical impression?
2. How do daily dose and plasma levels of amisulpride correlate?
3. How do the variables gender, age, cigarette consumption and relevant co-medications affect the amisulpride plasma concentration?

2. Methods

2.1. Study sample

Plasma levels of amisulpride were determined at regular intervals in 85 in-patients being treated at the Department of Psychiatry at the University of Heidelberg (age: mean ± standard deviation [$M \pm$ S.D.] = 34.0 ± 11.4 years, range 18–64 years; 40 women, 45 men).The patients were receiving amisulpride for treatment of either a schizophrenic psychosis (ICD 10: F20.0–20.9) or a schizoaffective disorder (ICD 10: F25.0–25.9). Of the patients, 34 were smokers and 46 non-smokers (no information for 5 patients). For each patient, 1 up to a maximum of 29 tests were carried out ($M \pm$ S.D. = 6.5 ± 5.8)–in a few patients, a large number of tests were carried out because they were hospitalized for a long period or because of a relapse and re-hospitalization; for some of them, repeated measurements were carried out over a longer period of time on an outpatient basis. All in all, 504 test results are available, 51 under amisulpride monotherapy.

For 64 patients, the most recent result from examinations performed close to discharge, and thus representative of a stable clinical improvement, was used for further analysis. In the remaining patients, amisulpride was discontinued because of adverse side effects ($n = 3$: extrapyramidal side effects, galactorrhea and weight gain) or due to lack of effectiveness ($n = 7$); 11 patients were still receiving treatment in the hospital and tolerating the medication well. There was no difference in the amisulpride plasma concentration among these four groups.

2.2. Blood specimens and laboratory analysis

Blood was drawn for drug monitoring under steady-state conditions, i.e., the daily dose had not been changed for at least 7 days, between 8 and 9 a.m., i.e., 10–24 h after the last oral dose of amisulpride.

The plasma amisulpride concentrations were assessed after solid phase extraction by high-performance liquid chromatography (HPLC) with fluorometric detection as described by Malavasi et al. (1996; cf. Bohbot et al., 1987). The chromatographic equipment consisted of a HD2-400 pump (Besta, Wilhelmsfeld, Germany), a 5-μm Hypersil C18 column (150 × 4.6 mm I.D., Ziemer Chromatographie, Mannheim, Germany), a spectrofluorometric LC detector model Shimadzu Rf-551 equipped with a 12-μl quartz cell and a HPLC data processor model Shimadzu C-R5A. Spiked human plasma samples were used to validate the assay. Detection limit was 2 ng/ml. Linear calibration curves were obtained from 2 to 800 ng/ml. Samples containing higher concentrations were diluted prior to the assay. The intraassay precision was determined by analyzing five spiked plasma samples at different concentrations, ranging from 20 to 800 ng/ml. Intraassay accuracy was always between 93% and 108%, and intraassay precision was always better than 9%. The amisulpride recovery from spiked samples was 79.8 ± 2.2% and 81.9 ± 2.5% at 50 and 400 ng/ml. The pharmacokinetics of the two enantiomers and the racemic mixture have been shown to differ for amisulpride, which is a chiral drug (Rosenzweig et al., 2002). The analytical method applied in the present study is an achiral procedure; thus, our data do not distinguish between the two enantiomers and represent plasma levels of the amisulpride racemate.

2.3. Biometrics

In addition to descriptive statistics, a covariance analysis was carried out to analyze the effects of gender and cigarette smoking behavior as independent variables on the dose-corrected amisulpride plasma concentration, using age as a covariate. For comparison of the dose-corrected amisulpride plasma levels of patients under different co-medication and/or amisulpride monotherapy, Mann–Whitney tests were carried out. The Pearson correlation coefficient was used for bivariate analysis of the relationship between amisulpride daily dose and plasma level of amisulpride.

3. Results

The average daily dose of amisulpride in the 85 patients enrolled in the study was 772.3 mg (S.D. 346.7 mg); the range was 150–1600 mg/day. The mean plasma level of amisulpride amounts to 424.4 ng/ml (S.D. 292.8), ranging

from 20 to 1.904 ng/ml (dose-corrected amisulpride plasma concentration: $M \pm$ S.D. = 0.59 ± 0.42 ng/ml:mg).

The correlation of $r = 0.50$ indicates a linear relationship between the daily dose of amisulpride and the plasma concentrations (Fig. 1); this result is statistically significant ($p < 0.001$).

Of particular importance are the mean amisulpride daily dose and the mean amisulpride plasma concentration with respect to their clinical effectiveness, the amisulpride plasma concentrations having been measured close to discharge from the hospital and thus being representative of stable clinical improvement; at this point in time, the amisulpride daily dose was 671.9 mg (S.D. = 317.5, range 200–1600 mg/day, $n = 64$) and the amisulpride plasma concentration was 367.6 ng/ml (S.D. = 265.1, range 34–1208 ng/ml, $n = 64$; dose-corrected amisulpride plasma concentration: $M \pm$ S.D. = 0.56 ± 0.32 ng/ml:mg).

3.1. Effects of age, gender and cigarette smoking on plasma concentrations

Women received significantly *lower* daily doses of amisulpride than men ($M \pm$ S.D. = 719.3 ± 340.0 vs. 817.9 ± 346.4 mg/day, $p = 0.009$), but showed significantly *higher* dose-corrected amisulpride plasma concentrations than men ($M \pm$ S.D. = 0.67 ± 0.40 vs. 0.52 ± 0.42 ng/ml:mg, $p = 0.008$).

Furthermore, smokers received significantly *higher* daily doses of amisulpride than non-smokers ($M \pm$ S.D. = 841.0 ± 360.1 vs. 725.2 ± 324.5 mg/day, $p = 0.015$).

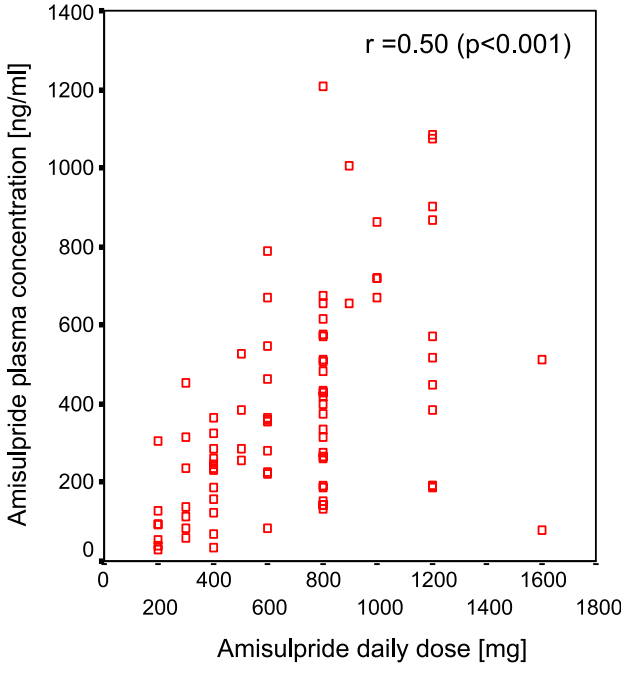

Fig. 1. Correlation between amisulpride daily dose and amisulpride plasma concentration ($n = 85$).

Table 1
Effect of gender and cigarette consumption on the dose-corrected amisulpride plasma concentration: descriptive statistics

	Smoker	Dose-corrected amisulpride plasma concentration, $M \pm$ S.D. (ng/ml:mg)	N
Men	Yes	0.41 ± 0.35	18
	No	0.55 ± 0.29	23
	Total	0.49 ± 0.32	41
Women	Yes	0.67 ± 0.33	16
	No	0.67 ± 0.32	23
	Total	0.67 ± 0.32	39

Age had no effect on the prescribed daily dose, but a moderate correlation between age and dose-corrected amisulpride plasma concentration could be seen ($r = 0.26$, $p = 0.018$).

Because of a significant correlation between age and cigarette consumption ($r = 0.29$, $p = 0.01$), a covariance analysis was carried out to evaluate the effects of gender and cigarette consumption (as independent variables) and age (as covariable) on the (dose-corrected) plasma concentration. An effect of smoking could only be seen in men: smokers had lower dose-corrected amisulpride plasma concentrations than non-smokers; in women, there was no difference in the plasma concentrations between smokers and non-smokers (Table 1). In the covariance analysis, the effect of age on the dose-corrected plasma concentration was significant with $p = 0.022$ ($df = 1$, $F = 5.51$); the effect size as a measure of practical significance according to Cohen (1988, 1992) was $d = 0.27$ and therefore in a middle range ($\varepsilon^2 = 0.068$). The effect of gender was also significant with $p = 0.011$ ($df = 1$, $F = 6.82$); the effect size d was 0.30 and accordingly also in a middle range ($\varepsilon^2 = 0.082$). Smoking had no significant effect on the dose-corrected plasma concentration ($p = 0.772$, $df = 1$, $F = 0.82$). None of the interactions calculated – gender × smoking, gender × age and smoking × age – reached statistical significance.

3.2. Effects of various co-medications on the amisulpride plasma concentration

Fifty-one plasma concentrations were assessed while patients received amisulpride as monotherapy. In some other cases, the plasma concentration was measured while the patient received one other medication. Plasma concentrations were considered only when data from at least three patients were available.

The dose-corrected amisulpride plasma concentration under the co-medication of lithium was significantly higher than under monotherapy (Mann–Whitney test, $p = 0.006$); the same was true for co-medication with clozapine (Mann–Whitney test, $p = 0.009$). Trimipramine, classical antipsychotics and benzodiazepines had no effect on the dose-corrected amisulpride plasma concentrations (Table 2).

Table 2
Amisulpride plasma concentration during amisulpride monotherapy and various co-medications

Co-medication	Measurements, *n*	Patients, *n*	Amisulpride dose (mg/day), $M \pm$ S.D.	Amisulpride plasma concentration (ng/ml), $M \pm$ S.D.	Dose-corrected amisulpride plasma concentration (ng/ml:mg), $M \pm$ S.D.	*p**
Amisulpride monotherapy	51	13	934 ± 350	372 ± 255	0.44 ± 0.29	–
Lithium	3	3	567 ± 252	731 ± 449	1.23 ± 0.25	0.006
Clozapine	26	7	571 ± 374	392 ± 425	0.86 ± 1.01	0.009
Trimipramine	8	5	988 ± 275	408 ± 222	0.41 ± 0.18	n.s.
Classical antipsychotics	8	4	850 ± 227	304 ± 359	0.34 ± 0.30	n.s.
Benzodiazepine	7	4	629 ± 309	228 ± 161	0.33 ± 0.14	n.s.

* Mann–Whitney test based on the dose-corrected amisulpride plasma concentration data; n.s. = not significant.

The mean daily dose of clozapine and the mean clozapine plasma concentration was 330 mg (S.D. = 148 mg) and 452 ng/ml (S.D. = 260 ng/ml), respectively.

4. Discussion

In amisulpride therapy guided by clinical efficacy, patients received a mean daily amisulpride dose of 772.3 mg; at discharge, the patients were receiving a mean daily dose of 671.9 mg. A high interindividual variance in amisulpride plasma concentrations was observed in these patients. The mean amisulpride plasma concentration was 424.4 ng/ml, at discharge 367.6 ng/ml (dose-corrected amisulpride plasma concentration: 0.59 and 0.56 ng/ml:mg, respectively).

Gender and age had a significant effect on the dose-corrected amisulpride plasma concentration–older patients and women had higher dose-corrected amisulpride plasma concentrations than younger patients and men. These findings are in line with results from Hamon-Vilcot et al. (1998). Cigarette consumption had no effect on the dose-corrected amisulpride plasma concentrations; interestingly, smokers received significantly higher doses of amisulpride than non-smokers. This may be a consequence of an increase in mesolimbic dopamine release due to the nicotine (Clarke, 1998; Imperato et al., 1986), which competes with the drug for receptor binding. Women received significantly *lower* daily doses of amisulpride than men, but showed significantly *higher* dose-corrected amisulpride plasma concentrations than men. Since amisulpride is nearly exclusively eliminated by renal secretion, this observation obviously demonstrates gender differences in renal clearance of the drug, in particular a greater effectiveness of the kidneys in men (Cerrutti et al., 2001). The age-related increase in dose-corrected concentrations is likely to be due to a combination of reduced volume of distribution and reduced clearance, as already shown for other drugs (Sproule et al., 2000).

Some of the effects described may be partly explained by differences in weight in the subgroups. As the elimination of amisulpride by the liver is low and as it has a relatively high volume of distribution, weight should also be considered as a variable in further studies because it may affect the plasma level of amisulpride.

Among the co-medications investigated, lithium and clozapine showed an effect on the dose-corrected amisulpride plasma concentrations. Lithium leads to a highly significant increase in the dose-corrected amisulpride plasma concentrations, clozapine to a moderate increase.

These results are remarkable because a combination of amisulpride with clozapine is clinically advantageous (Matthiasson et al., 2002; Ziegenbein et al., 2003), and amisulpride is of particularly high value for patients with depressive symptoms such as schizoaffective disorder or delusional depression (c.f. Freeman, 1997), both indications for lithium.

Neither effect has been reported in the literature so far. Renal interaction may account for the increase in the plasma concentration under co-medication with lithium (cf. Markowitz et al., 2000). Toxic nephropathy is known under lithium medication, tubular atrophy and interstitial fibrosis, in particular, less often glomerulosclerosis. Jorkasky et al. (1988), for example, reported on a prospective study of 65 patients receiving lithium who showed a significant decline in creatinine clearance as early as 1 year after initiation of therapy. On the other hand, a direct pharmacokinetic interaction between lithium and amisulpride cannot be entirely excluded, since such an interaction with lithium has already been observed for the renal clearance of other drugs (Troy et al., 1996; Sugihara et al., 1985). Future studies on pharmacokinetic interactions following coadministration of amisulpride and lithium, e.g., in studies with healthy volunteers (Breuel et al., 1995), may help to understand the observed pharmacokinetic interference of the two drugs.

Amisulpride, in humans, is considered to undergo only low metabolism and, consequently, most of it can be recovered as unmodified drug from the urine (Coukell et al., 1996; Lambert and Naber, 1999). The exact mechanism of renal amisulpride excretion is still unclear. Interestingly, its rate of renal excretion is about 2.5-fold higher than might be expected from mere glomerular filtration (Dufour and Desanti, 1988). Thus, active secretion of the drug via cation–proton–antiporters is likely (Pritchard et al., 1997). Since clozapine and its major metabolites, clozapine *N*-oxide and *N*-desmethylclozapine, are considered substrates of the same transporter family (Schaber et al., 1998), competitive inhibition of active renal elimination of amisulpride by clozapine and its metabolites may explain the observed

effects of clozapine co-medication on amisulpride plasma levels. This assumption is also supported by investigations on the renal clearance of sultopride, a deaminated derivative of amisulpride in rats where the renal elimination of the drug is also competitively inhibited by organic cations (Kamizono et al., 1993).

After intravenous administration to healthy volunteers, most of the drug appeared unchanged in the urine and only a small portion as metabolites (Coukell et al., 1996), indicating that only a minor amount of amisulpride is metabolized hepatically. On the other hand, after oral administration, urinary excretion of unchanged drug was reported to be even lower (Malavasi et al., 1996), suggesting that biotransformation, like *N*-dealkylation and oxidation (Coukell et al., 1996), may significantly contribute to the drug's metabolism. Therefore, we cannot entirely exclude that the increase under the co-medication of clozapine may be at least partially attributed to an interaction of the two compounds via the cytochrome P450-system during hepatic metabolism. In in vitro studies, no inhibition of cytochrome P450 isozyme by amisulpride could be seen (Gillet et al., 2000). However, the details of its interactions with cytochrome P450 isozymes have not been fully elucidated and, most importantly, clinical studies on this issue are lacking (Caccia, 2000).

Little experience with therapeutic drug monitoring of amisulpride has been reported to date. Although the results presented here may be preliminary, they point out possible pitfalls associated with amisulpride medication. In order to confirm a broad clinical relevance of our results, the sample size needs to be increased to provide further evidence for our observations.

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