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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