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Therapeutic drug monitoring for optimizing amisulpride therapy in patients with Schizophrenia

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Abstract

Amisulpride is a clinically effective antipsychotic drug in a broad dose range with low propensity for extrapyramidal symptoms (EPS). Daily doses and plasma levels of amisulpride were analyzed within a large-scale therapeutic drug monitoring (TDM) survey to find plasma level ranges for optimized treatment under naturalistic conditions. Data of 378 schizophrenic patients treated with amisulpride (100–1550 mg) were included (40% female). Amisulpride plasma levels were analyzed at steady state; assessment comprised improvement (CGI-I) and side-effects, particularly EPS. For detection of cut-off values regarding non-response or EPS, receiver operating characteristics (ROC) curves were applied and the area under the ROC curve (AUC) was calculated. Amisulpride daily doses (594 ± 262 mg) and plasma levels (315 ± 277 ng/ml) were significantly correlated ($r = 0.53$; $P < 0.0001$). Patients with non-response to amisulpride (8.9%) had significantly ($P < 0.05$) lower plasma levels (248 ± 291 ng/ml) than patients with at least moderate improvement (316 ± 253 ng/ml) despite comparable amisulpride doses (628 ± 253 vs. 590 ± 263 mg). Patients with EPS (14.6%) had significantly ($P < 0.05$) higher amisulpride plasma levels (377 ± 290 ng/ml) than patients without EPS (305 ± 274 ng/ml) despite similar doses in both groups (595 ± 266 vs. 594 ± 246 mg). ROC analyses revealed significant predictive properties of amisulpride plasma levels ($P < 0.05$) for non-response (AUC $= 0.65 \pm 0.05$) and EPS (AUC $= 0.62 \pm 0.05$), respectively. Daily amisulpride doses did not significantly predict non-response or EPS. Optimal amisulpride plasma level values to avoid non-response and EPS were $\geqslant 100$ or $\leqslant 320$ ng/ml, respectively. Analysis of clinical utility revealed that blood levels must be analyzed in 7 patients until one patient benefits from the TDM procedure by avoiding non-response or EPS. Although our results were mainly explorative, TDM of amisulpride seems very useful for clinical decision making.

Keywords: Amisulpride; Therapeutic drug monitoring; Schizophrenia

1. Introduction

Amisulpride, a selective dopamine D2/D3-receptor antagonist with assumed preferentially extrastriatal binding (Vernaleken et al., 2004; Xiberas et al., 2001a,b) is clinically effective in schizophrenia in a broad dose range with low propensity for extrapyramidal symptoms (EPS) (Correll et al., 2004; McKeage and Plosker, 2004; Mortimer et al., 2004; Mota et al., 2002; Müller and Benkert, 2002). Studies with positron emission tomography (PET) in schizophrenic patients using different tracers to detect D2-receptor occupancy in striatal and extrastriatal brain regions have shown a close association of amisulpride plasma levels and striatal D2-receptor occupancy (Vernaleken et al., 2004;

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Xiberas et al., 2001a,b). Combined with findings derived from PET studies with conventional and atypical antipsychotics (Fitzgerald et al., 2000; Gründer and Wong, 2003), it can be assumed that clinically obtained amisulpride plasma levels correspond to treatment-related EPS propensity. From a clinical perspective, this relationship could be beneficially used for the treatment of schizophrenic patients if an optimal therapeutic range can be established predicting a low propensity for EPS with an – at the same time – high probability for response. However, such studies directly translating findings from basic research into clinical decision making (from the bench to the bed) have rarely been carried out (Fitzgerald et al., 2000; Kasper et al., 1999).

The only so far published study on the relationship of amisulpride daily doses and plasma levels (Bergemann et al., 2004) has demonstrated a substantial linear correlation ($r = 0.50$) in a cohort of more than 100 patients with schizophrenia, whereas these authors did not investigate the relationship between amisulpride doses or plasma levels and clinical outcome.

In a TDM study, we analyzed amisulpride doses and plasma levels in relation to clinical response and EPS, to propose an optimum therapeutic range. The utility of daily doses in comparison with plasma levels should be elucidated to test the possible benefits of routine amisulpride plasma level determination.

2. Methods

This large-scale naturalistic study was carried out in accordance with the German Law (PsychKG), and retrospective analysis of TDM data was approved by the local Ethics committee. Data of patients who were under treatment with amisulpride were included. For these patients, TDM was requested for treatment optimization according to the decision of the treating psychiatrist. The patients fulfilled the following criteria: in- and outpatients with schizophrenia (DSM-IV 295.x, not 295.7), neuroleptic monotherapy with amisulpride of at least 100 mg, and at least five days fixed dose amisulpride treatment prior to plasma level determination. From an original sample of 544 patients with amisulpride plasma level determination, 82 (15.1%) were excluded due to a diagnosis other than schizophrenia; of the remaining 462 patients with schizophrenia, 72 (15.6%) had a second neuroleptic treatment in addition to amisulpride and were also excluded.

Blood samples were collected between 7 and 9.00 a.m., at least 14 h after the last amisulpride intake. Trough amisulpride plasma levels were analyzed at steady state after at least 5 days fixed dose treatment using column switching coupled with high-performance liquid chromatography (HPLC) with spectrophotometric detection as described previously (Sachse et al., 2003). As reported previously (Sachse et al., 2003), the inter-assay reproducibility (coefficient of variation) of quality control samples was between 2.8% and 11.3%. Inaccuracy was between 20.6% and 19.1%. The performance of daily calibration standards revealed an imprecision always below 15% and maximum inaccuracy of 7.7%. In case of repeated assessments across the course of clinical treatment, only one (i.e., the first) set of data for an individual patient was used for analyses. Smoking status was not assessed. All patients underwent routine psychiatric and neurological examination. Clinical assessments comprised illness severity (CGI-S) and clinical response (CGI-I) (clinical global impression; CGI) (Guy, 1976), side-effects (UKU) (Lingjaerde et al., 1987), and comedication. The CGI-I was used for definition of clinical response (1, very good response; 2, moderate response; 3, slight improvement and 4, unchanged or worsened). Non-response was defined as 4 points on the CGI-I. Clinical ratings were carried out by treating psychiatrists who were blind to plasma levels. The UKU comprised questions on the absence or presence of specific side-effects including EPS (yes/no); EPS comprised dystonia, motor rigidity, hypokinesia/akinesia, tremor and akathisia. Additionally, the global severity of side-effects was assessed with a 4-point scale (0, no side-effects; 1, mild; 2, moderate and 3, severe). Non-EPS side-effects were analyzed in all patients; for analyses of EPS, patients receiving anticholinergic drugs were excluded.

For detection of optimal cut-off values (amisulpride dose, plasma levels) regarding clinical non-response and prevalent side-effects and EPS, receiver operating characteristics (ROC) curves were applied and the area under the ROC curve (AUC) was calculated (Cook and Sackett, 1995; Hanley and McNeil, 1982; MedCalc Software, 2005; Zweig and Campbell, 1993). For ROC-derived optimal cut-off values, clinically meaningful parameters (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], relative risk reduction [RRR] and the number needed to treat [NNT]) were calculated (Cook and Sackett, 1995; Sinclair and Bracken, 1994). Optimal cut-off values are the values corresponding with the highest accuracy (i.e., with minimal false negative and false positive results). Spearman rank correlations were used for calculating associations between variables; for group comparisons, Mann–Whitney *U*-tests (MWU) were performed; the level of statistical significance was set at $\alpha = 0.05$.

3. Results

Data of 390 patients with schizophrenia (DSM-IV) and neuroleptic monotherapy with amisulpride at daily doses $\geqslant 100$ mg and at least 5 days without dose changes (fixed dose) were initially included. The final sample comprised 378 patients; data of 12 (3.1%)