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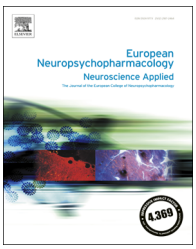

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Changes in psychopathology in schizophrenia patients starting treatment with new-generation antipsychotics: therapeutic drug monitoring in a naturalistic treatment setting

Alexandra Kaufmann[a], Fabienne Wartelsteiner[a], Nursen Yalcin-Siedentopf[a], Susanne Baumgartner[a], Falko Biedermann[a], Monika Edlinger[a], Georg Kemmler[b], Maria A. Rettenbacher[a], Tanja T. Rissanen[a], Christian G. Widschwendter[a], Gerald Zernig[b], W. Wolfgang Fleischhacker[a], Alex Hofer[a,*]

[a]*Medical University Innsbruck, Department of Psychiatry and Psychotherapy, Biological Psychiatry Division, Austria*
[b]*Medical University Innsbruck, Department of Psychiatry and Psychotherapy, General and Social Psychiatry Division, Austria*

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Abstract
Previous studies on the relationship between plasma levels of new-generation antipsychotics (NGAs) and clinical response did not account for inter- and intra-individual variability in drug levels. Therefore, the present study calculated the ratio of observed versus expected NGA plasma levels and investigated its relationship with changes in the Positive and Negative Syndrome Scale (PANSS). Data of patients starting monotherapy with a NGA were collected 2, 4, 8, and 12 weeks after initiation of treatment. Next to the assessment of changes in psychopathology (PANSS) the ratio of observed versus expected plasma level was calculated. A total number of 221 ratios were eligible for analysis. About half of them ranged from 0.5–2 and were considered "normal", whereas the others were considered either "too low" or "too high". Psychopathological symptoms improved over the course of treatment, but changes in PANSS from baseline did not correlate significantly with the ratios of observed versus expected plasma levels at any assessment. The lack of linear correlation can be explained by the fact that 92% of the observed NGA plasma levels were at $\geq$ 50% of the lower limit of the therapeutic reference range, i.e., within the asymptote of the logistic plasma level-effect relationship. Accordingly, our findings indicate that the great majority of patients were treated with NGA doses that led to optimal plasma levels, based on the clinical impression of the treating psychiatrist only. Thus, calculating the ratio of

*Corresponding author. Tel.: +43 512 504 23669; fax: +43 512 504 25267.
E-mail address: a.hofer@i-med.ac.at (A. Hofer).

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observed versus expected plasma level may not be necessary in a routine clinical setting.

1. Introduction

The efficacy of antipsychotic drugs in short-term and maintenance treatment of schizophrenia has been documented in numerous clinical trials over the past decades (Leucht et al., 2012, 2013). However, many patients do not adequately respond to pharmacological therapy, either due to greater metabolic activity or due to poor compliance ("pseudo" drug resistance). In this context, the quantification of drug concentrations in blood plasma or serum (therapeutic drug monitoring, TDM) may represent a valuable tool for tailoring the dosage of the prescribed medication to the individual characteristics of a patient in order to obtain the highest possible probability of response and tolerability (Hiemke et al., 2011; Grunder et al., 2014).

Based on the dosing interval, the clearance, and the bioavailability for a drug in a particular patient TDM calculates the expected dose-related plasma concentration (Hiemke et al., 2011). Of note, inter-individual pharmacokinetic differences caused by age, concurrent diseases, concomitant medication, or genetic variability are of major relevance in this regard. In addition, intra-individual variability due to lifestyle characteristics such as smoking or caffeine use has to be taken into account.

A recent review of the literature on the relationship between plasma concentrations of new-generation antipsychotics (NGA) and clinical response in acute psychosis concluded that a positive correlation between plasma level and clinical response could be found in only 6 of the 11 reviewed clinical trials (Lopez and Kane, 2013). Accordingly, this issue remains unresolved. In daily clinical routine, however, the need to start or switch antipsychotic drug therapy is not only restricted to schizophrenia patients experiencing an acute exacerbation of symptoms but applies also to those who respond insufficiently to ongoing treatment or are affected by side effects. Consequently, in the current study patients with schizophrenia starting monotherapy with a NGA in a naturalistic treatment setting were prospectively followed up for three months, irrespective of baseline symptomatology. Using a pharmacokinetic simulation program, we calculated the ratio of observed versus expected plasma levels of the prescribed NGA and investigated its relationship with changes in psychopathological symptoms. In addition, we studied the impact of clinical and patient characteristics on this issue. Of note, only patients whose expected plasma levels lay within the therapeutic reference range (TRR) were considered in this analysis. According to TDM, the TRR is defined as the range in which the likelihood of clinical response is greatest and the risk of adverse drug effects is minimized (Hiemke et al., 2011).

2. Experimental procedures

In- and outpatients aged between 18 and 65 years and starting monotherapy with a NGA were followed prospectively in a naturalistic drug monitoring program. They met the diagnostic criteria of schizophrenia spectrum disorders and did not suffer from any other axis I disorders according to DSM-IV, including substance abuse. Diagnoses were confirmed using chart information and reports from psychiatrists who had treated these patients. Patients who had been receiving antipsychotic medications and had to switch them because of insufficient efficacy or intolerance underwent a washout period of 3–5 days. They were excluded if they were taking more than one antipsychotic or were taking a long-acting injectable antipsychotic. Antipsychotics were chosen by the psychiatrists treating the patients. Dosing was within the recommended ranges and followed clinical needs. Clinicians were blind to plasma levels. Benzodiazepines were permitted to treat agitation, anxiety or sleep disturbances, and biperiden/propranolol for extrapyramidal symptoms, akathisia as well as hypersalivation. After a complete description of the study, all participants signed informed consent forms in accordance with the local ethics committee.

At baseline, sociodemographic and clinical data were obtained. Follow-up visits were conducted after 2, 4, 8, and 12 weeks of treatment. At each visit, a psychiatrist belonging to a trained schizophrenia research team rated psychopathology by means of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Taking into account that positive symptoms often respond well to antipsychotic treatment, whereas negative symptoms are more difficult to manage (Leucht et al., 2009) subjects were assigned to either of three groups. Group 1 (predominantly positive symptoms) was required to have a baseline score ≥ 4 (moderate) on at least 3 or ≥ 5 (moderately severe) on at least 2 of the 7 positive subscale items of the PANSS (scored on the $1-7$ severity scale), and a score ≤ 21 on the PANSS negative subscale. Correspondingly, group 2 (predominantly negative symptoms) was required to have a baseline score ≥ 4 on at least 3 or ≥ 5 on at least 2 of the 7 negative subscale items of the PANSS, and a score ≤ 21 on the PANSS positive subscale. Patients neither fulfilling the criteria for allocation to groups 1 or 2 were assigned to group 3. All patients were required to have a baseline PANSS total score ≥ 60.

At each follow-up visit, a blood sample was taken and the concentration of the antipsychotic medication in the blood plasma was measured by the ISO 9001 certified psychiatric laboratory using high performance liquid chromatography-tandem mass spectrometry. Blood sampling was conducted before breakfast and before the morning medication. In addition, patients were asked to fill out the Drug Attitude Inventory (Hogan et al., 1983), while the attending psychiatrist quantified side effects using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987). Findings on these issues have been reported previously (Yalcin-Siedentopf et al., 2014).

With all the data collected about the medication regimen, the expected plasma level of the antipsychotic medication the patient received was calculated using AutoKinetic®, version 3.4 (Toennes, 2000). This software is a Microsoft Excel®-based pharmacokinetic simulation program developed by Dr. Stefan W. Toennes at the Institute of Legal Medicine at the Goethe University, Frankfurt/Main, Germany (toennes@em.uni-frankfurt.de). It allows the calculation of individual expected plasma concentration levels for any medication. The required data are the patient's body weight, the period of time to be calculated, and the exact treatment regimen (i.e. the prescribed dose and time of intake). In addition, the drug's