Effect of smoking on risperidone pharmacokinetics – A multifactorial approach to better predict the influence on drug metabolism

Georgios Schoretsanitis, Ekkehard Haen, Benedikt Stegmann, Christoph Hiemke, Gerhard Gründer, Michael Paulzen

Department of Psychiatry, Psychotherapy and Psychosomatics, JARA – Translational Brain Medicine, RWTH Aachen University, Aachen, Germany

Clinical Pharmacology, Dept. of Psychiatry and Psychotherapy, Dept. of Pharmacology and Toxicology, University of Regensburg, Regensburg, Germany

University Hospital of Psychiatry, Bern, Switzerland

Department of Psychiatry and Psychotherapy, Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center of Mainz, Germany

Abstract

Purpose: To disentangle an association between tobacco smoking, smoking habits and pharmacokinetic patterns such as plasma concentrations of risperidone (RIS), its active metabolite 9-hydroxyrisperidone (9-OH-RIS) and the active moiety, AM, (RIS + 9-OH-RIS) in a naturalistic sample.

Methods: Plasma concentrations, dose adjusted plasma concentrations (C/D) of RIS, 9-OH-RIS and AM in patients out of a therapeutic drug monitoring (TDM) database were compared between smokers (n = 401) and non-smokers (n = 292).

Results: Daily dosage of risperidone differed significantly with smokers receiving higher doses than patients in the control group (p = 0.001). No differences were detected in plasma concentrations of the active moiety, AM, (RIS + 9-OH-RIS) in a naturalistic sample.

Conclusions: Apart from the well-known induction of CYP1A2 activity by polycyclic aromatic hydrocarbons, smoking might exert an effect on other CYP isoenzymes as well. A possible interpretation proposes a slight inducing effect of smoking on risperidone metabolism most likely via CYP3A4.

1. Introduction

Consistent epidemiologic data report a higher prevalence of smoking in patients with severe mental illnesses and especially schizophrenia than in the general population (Cook et al., 2014; Cage and Munafo, 2015). Furthermore, severe nicotine dependence seems to be preponderant in patients with schizophrenia (Salokangas et al., 2006). Excessive smoking rates in schizophrenic patients have been associated with increased risk of cardiovascular diseases or strokes (Liang et al., 2016) and consequently with a higher mortality (Ringen et al., 2014). Consequently, smoking may alter the disposition of numerous psychotropic drugs including various antipsychotics and antidepressants (Seppala et al., 1999; Wu et al., 2008). The clinical significance of such alterations has been highlighted by a plethora of case reports describing adverse reactions in case of smoking cessation or changes in smoking habits in schizophrenic patients (Derenne and Baldessarini, 2005; McCarthy, 1994). Notably, the inductive effect of smoking on CYP1A2 is reversible; various models of the temporal course of this reversibility have been...
suggested [Meyer, 2001]. Various data suggest that the inducing effect of smoking may be dose- and/or genotype-dependent [Suzuki et al., 2011] with a critical impact of the number of smoked cigarettes per day [Haslmo et al., 2006]. Literature data suggest some evidence for clinically relevant effects of smoking on the activity of other CYP isoenzymes than CYP1A2. More recent findings support inducing effects of smoking on CYP3A4 activity [Rahmioglu et al., 2011]. Kang and colleagues reported an accelerated clearance of the primarily via CYP3A4/5 metabolized verapamil in smokers compared to non-smokers [Kang et al., 2003] suggesting a CYP3A4/5-mediated, inducing effect of smoking. Further effects of smoking on distinct cytochrome P450 isoenzymes include and induction of CYP2E1 [Benowitz et al., 2003] and CYP2B6 [Washio et al., 2011], while some rather conflicting data suggest an effect of smoking on uridine 5′-diphospho-glucuronosyltransferases (UGT) enzymes [Petros et al., 2012].

Risperidone (RIS) is a second generation antipsychotic (SGA) with selective antagonistic properties at serotonin 5-HT2- and dopamine D2 receptors. It has been used effectively in the treatment of a broad spectrum of psychiatric diseases with a low incidence of extrapyramidal symptoms (EPS) and a lack of anticholinergic effects [Leucht et al., 1999; Schoretsanitis et al., 2016b]. The primary pathway of RIS metabolism is a CYP2D6-catalyzed 9-hydroxylation and the main active metabolite is 9-hydroxyrisperidone (9-OH-RIS). In vitro findings have revealed that CYP3A4 and CYP3A5 might be also involved in the metabolism of risperidone [Xiang et al., 2010; Yasui-Furukori et al., 2001]. Pre-clinical studies indicated that 9-OH-RIS has approximately 70% of the pharmacological activity of RIS [Heykants et al., 1994]. Therefore, clinicians consider the combined concentration of RIS and 9-OH-RIS (active moiety, AM) as the most relevant measure. According to the AGNP consensus guidelines, a so called therapeutic reference range is suggested as 20–60 ng/ml for the active moiety [Hiemke et al., 2011].

The therapeutic drug monitoring (TDM) is a specific method of clinical pharmacology that can be successfully used to guide psychopharmacological treatment in clinical routine by determining plasma concentrations of applied drugs. TDM databases are a valuable source to promote the safety and tolerability of pharmacotherapy in a clinical setting [Schoretsanitis et al., 2016b, 2016c].

Regarding the effect of smoking on the metabolism of risperidone, data is rare and has been rather conflicting [Bowskill et al., 2012; Feng et al., 2008]. Accordingly, further studies are demanded and our aim was to unravel the effect of smoking on risperidone metabolism in a naturalistic sample. We therefore compared pharmacokinetic parameters such as plasma concentrations of RIS, 9-OH-RIS and the active moiety as well as the ratio of 9-OH-RIS/RIS and the so called dose-adjusted plasma concentration (C/D) between a group of risperidone treated patients that were smoking and a group of non-smoking patients.

2. Materials and methods

The present study was conducted as a cooperation between the Department of Psychiatry, Psychotherapy and Psychosomatics of RWTH Aachen University Hospital, Aachen, Germany, and the Department of Psychiatry and Psychotherapy at the University of Regensburg, Germany. A large TDM database containing plasma concentrations of RIS and 9-OH-RIS of 1584 orally medicated adult in- and outpatients with a broad spectrum of psychiatric diseases (exception: organic mental disorders, where lower therapeutic dosages of risperidone are invariably prescribed) was analyzed. Data collection took place between 2005 and 2015 as part of the clinical routine as part of the AGATE, (Arbeitsgemeinschaft Arzneimitteltberieh bei psychischen Erkrankungen), a cooperation for drug safety in the treatment of psychiatric diseases (for details: www.amuep-agate.de). Our database has been analyzed addressing different aspects of risperidone metabolism and pharmacokinetic patterns [Paulzen et al., 2016a, 2016b, 2016c; Schoretsanitis et al., 2016a, 2016b, 2016c]. Retrospective analysis of clinical data for this study was in accordance with the local regulatory authority as well as latest version of the Declaration of Helsinki. Informed consent of participants was not necessary.

Out of this naturalistic database, we considered two groups; a group of smokers (RS) and a group of non-smokers (R0, control group). No matching processes for age, diagnoses, severity of illness, length or onset of illness were undertaken. Patients under concomitant medication with possible CYP2D6 inhibitory or CYP3A4 inhibitory or inducing properties such as various psychotropic agents (for more details see list; US and Administration, 2014) were excluded. Patients under long acting injectable form of risperidone were also excluded. Furthermore, we excluded patients receiving risperidone in terms of acute psychiatric interventions, i.e. rapid tranquilization, so that only patients under steady state conditions were included. In case of missing pharmacokinetic or demographic data (including smoking habits) patients were not included. Finally, when multiple plasma concentrations were available for one patient, we included only the most recent value.

2.1. Quantification of risperidone and 9-OH-risperidone

Blood was asked to be drawn just before drug administration (trough concentration) at steady state (>5 elimination half-lives under the same drug dose). Risperidone and 9-OH-risperidone concentrations were determined by high performance liquid chromatography (HPLC) with ultraviolet detection (HPLC/UV) [Bader et al., 2005]. The method was validated according to DIN 32645 (Deutsche Industrie Norm 32645, described in guidelines of GTFCh (Society of Toxicology and Forensic Chemistry) in consideration of ISO 5725 (International Organization for Standardization), FDA (US Food and Drug Administration) guidelines (US and Administration, 2001) and ICH (International Conference on Harmonization) requirements (ICH, 1996)). The laboratory regularly runs internal quality controls and participates in external quality assessment schemes by INSTAND (Düsseldorf, Germany, www.instandev.de).

2.1.1. Statistical analysis

We compared the distributions of the plasma concentration of RIS, 9-OH-RIS and the active moiety (RIS + 9-OH-RIS) between the group of smokers (RS) and the group of non-smokers (R0) as the control group. Further comparisons included the plasma concentration corrected by the daily dose, the so called ‘concentration-by-dose’, (C/D), and the ratios of 9-OH-RIS/RIS for identification of the CYP2D6 metabolizer status (de Leon et al., 2005). To investigate the influence of smoking habits, we focused on the plasma concentration of the active moiety, which is widely accepted as of clinical significance [Hiemke et al., 2011]. Furthermore, other parameters of pharmacokinetic relevance were analyzed. For the comparisons we applied a non-parametrical Mann Whitney U test (M-W-U) with a significance level of 0.05, since histograms indicated that data was not normally distributed. Due to the non-normal distribution of the pharmacokinetic parameters, the assumptions for applying a traditional analysis of co-variance were violated. Subsequently, we selected bootstrapping as a reliable method for deriving robust estimates of standard errors and confidence intervals for measures of central tendency as well as association. A robust bootstrapping analysis of covariate (ANCOVA) with the same significance level (p = 0.05) was conducted in order to control for confounding factors. This approach was undertaken to maintain the naturalistic character of the sample thereby avoiding to match study samples for demographic characteristics. Finally, we arbitrarily split our sample in patients treated with relatively high doses above 6 mg (R0) and equal lower as 6 mg doses of risperidone (RS) and repeated the comparisons between smokers and non-smokers. Statistical analysis was carried out using IBM SPSS Statistics version 18.0 (IBM GmbH, Echingen, Germany).

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