Progress in Neuro-Psychopharmacology & Biological Psychiatry 76 (2017) 101–106

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Pharmacokinetic considerations in antipsychotic augmentation strategies: How to combine risperidone with low-potency antipsychotics

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ARTICLE INFO

Article history:
Received 22 December 2016
Accepted 12 March 2017
Available online 14 March 2017

Keywords:
Antipsychotics
Risperidone
Psychopharmacology
Pharmacokinetics
Therapeutic drug monitoring

ABSTRACT

Objectives: To investigate in vivo the effect of low-potency antipsychotics on metabolism of risperidone (RIS).
Methods: A therapeutic drug monitoring database containing plasma concentrations of RIS and its metabolite 9-OH-RIS of 1584 patients was analyzed. Five groups were compared; a risperidone group (n = 842) and four co- medication groups; a group co-medicated with chlorprothixene (n = 67), a group with levomepromazine (n = 32), a group with melperone (n = 46), a group with pipamperone (n = 63) and a group with prothipendyl (n = 24). Plasma concentrations, dose-adjusted plasma concentrations (C/D) of RIS, 9-OH-RIS and active moiety (RIS + 9-OH-RIS; AM) as well as the metabolic ratios (9-OH-RIS/RIS; MR) were computed.
Results: Differences in plasma concentrations were detected for AM and RIS. Pairwise comparisons revealed significant findings; RIS plasma concentrations were higher in co-medication groups than in monotherapy group. Chlorprothixene- and prothipendyl- medicated patients demonstrated no other differences. In the levomepromazine and melperone group plasma and C/D concentrations of AM and RIS were higher, while MRs were lower. For pipamperone, differences included higher C/D values of RIS and lower MRs.
Conclusions: Alterations of risperidone metabolism suggest pharmacokinetic interactions for levomepromazine and melperone. In the pipamperone-group, lower MRs as well as higher plasma and C/D levels of RIS suggest potential interactions.

1. Introduction

Anxiety, agitation and sleep disturbances are common symptoms in patients with psychiatric disorders such as schizophrenia (Goodwin et al., 2003; Naidu et al., 2014). Besides the concomitant use of benzodiazepines for anxiolytic effects in acute states, a very common clinical practice implies the addition of low-potency antipsychotics (Higashima et al., 2004). Combining low-potency antipsychotics with first or second generation antipsychotics is lacks the risk of dependence, withdrawal and recurrence of anxiety following cessation of the treatment (Sim et al., 2015). Moreover, possible pharmacodynamic interactions including amplified dopaminergic and noradrenergic blockade may prevent psychotic relapses (Nishikawa et al., 1985). Widely prescribed low-potency antipsychotics include chlorprothixene, levomepromazine, melperone, pipamperone and prothipendyl. These drugs show an efficient sedative potential and are often incorporated into a tailored antipsychotic treatment regimen (Waldfahrer, 2013). However, psychopharmacological treatment strategies may give rise to pharmacokinetic drug-drug interactions (DDI) that prominently increase the likelihood of adverse drug reactions, not only demonstrated by case reports (Chandran et al., 2003; Sarro, 2011). Consequently, knowledge about both, pharmacodynamic as well as pharmacokinetic interactions, is mandatory especially in the treatment of elderly patients, who are more vulnerable to unwanted side effects (Juurlink et al., 2003).

Aim of the study was to compare plasma concentrations, dose-adjusted plasma concentrations (C/D) of RIS, 9-OH-RIS and active moiety

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http://dx.doi.org/10.1016/j.pnpbp.2017.03.002
0278-5846/

(RIS + 9-OH-RIS) as well as metabolic ratios between the co-medicated groups and the control group to account for potential pharmacokinetic interactions between low-potency antipsychotics and the CYP 2D6 metabolized risperidone.

Chlorprothixene is a commonly used low-potency first generation tricyclic antipsychotic of the thioxanthene class for the management of agitation, primarily acting as a high affinity antagonist at dopamine D_1-, D_2-, D_3-, serotonin 5-HT_2-, histamine H_1-, α_1-adrenergic- and acetylcholine M_1-receptors (Hiemke and Pfuhlmann, 2012). It has been reported to inhibit cytochrome P450 CYP2D6 as well as P-glycoprotein (Bader et al., 2008; Taur et al., 2012). A case report detected increased serum concentrations of risperidone's active moiety under a concomitant medication with chlorprothixene (Bader et al., 2008).

Levomepromazine, also known as methotrimeprazine, is a low-potency antipsychotic of the phenothiazine class. Its anxiolytic, antiemetic, analgesic and sedative properties lead to its wide usage in palliative care (Bush et al., 2014; Dietz et al., 2013). It is acting with antagonistic properties at H_1-, M_1-, D_2-, α_1- and 5HT_2-receptors (Lal et al., 1993). The α_1-blockade may contribute to its cardiovascular side effects (Sahlberg et al., 2015) that are luckily rarely reported for doses below 100 mg/day. Data support efficacy for the treatment of agitation in patients with schizophrenia (Higashima et al., 2004). The *N*-methylation of levomepromazine is mediated by CYP3A4 (Wojcikowski et al., 2014), while there is evidence for an inhibiting effect of levomepromazine on distinct CYP isoenzymes but primarily on CYP2D6 activity (Balant-Gorgia et al., 1986; Suzuki et al., 1997).

Melperone is a butyrophenone derivative with antipsychotic, anxiolytic and sedative properties. Its main effect includes a weak dopamine D_2-blockade and a strong antiserotonergic activity (5-HT_{2A}) (Meltzer et al., 1989). The metabolic pathway of melperone has not been elucidated yet (Koppel et al., 1988). Regarding interactions in CYP mediated pathways, in vivo data support inhibiting effects on CYP2D6 activity; and data confirm that melperone alters the plasma concentrations of CYP2D6 substrates such as risperidone, nortriptyline and venlafaxine (Grözinger et al., 2003; Hefner et al., 2014; Hefner et al., 2015; Kohnke et al., 2006).

Pipamperone is another low-potency antipsychotic drug of the butyrophenone family. In addition to its weak dopamine D_2-receptor blockade, it exerts a prominent antagonistic effect at 5-HT_2-receptors (Awouters and Lewi, 2007). Neither the mechanisms mediating the metabolism of pipamperone nor pharmacokinetic interactions are known so far (Hiemke and Pfuhlmann, 2012).

Prothipendyl is a tricyclic low-potency antipsychotic of the azaphenothiazine group with sedating, antihistaminergic and antiemetic properties. Due to a very low affinity at the dopamine D_2-receptor, extrapyramidal symptoms are rare even at high doses, while a strong torsadogenic signal may be produced (Raschi et al., 2013). Very little is known about its metabolic pathway and its potential of pharmacokinetic interactions (Hiemke and Pfuhlmann, 2012).

Risperidone (RIS), a benzisoxazole derivative, is a second generation antipsychotic with antagonistic properties at serotonin 5-HT_2- and dopamine D_2-receptors (Janssen et al., 1988). RIS has been used effectively in the treatment of a broad spectrum of psychiatric diseases including schizophrenia (Chouinard and Arnott, 1993; Leucht et al., 1999; Marder et al., 1997). The primary pathway of RIS (half life time 3 h) metabolism is a CYP2D6-catalyzed 9-hydroxylation and the main active metabolite is 9-hydroxyrisperidone (9-OH-RIS) with a much longer half-life time of 21-30 h. In vitro findings have revealed that CYP3A4 and CYP3A5 might be also involved in the metabolism of risperidone (Fang et al., 1999; Xiang et al., 2010; Yasui-Furukori et al., 2001). As 9-OH-RIS is pharmacologically active, 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 (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie), a therapeutic reference range is suggested as 20–60 ng/mL for the active moiety (Hiemke et al., 2011).

2. Experimental procedures

A large TDM database as part of KONBEST, a web-based laboratory information management system for TDM-laboratories (Haen, 2011) containing plasma concentrations of RIS and 9-OH-RIS of 1584 patients was analyzed. Data collection took place between 2006 and 2015 as part of the clinical routine in different institutions as part of the AGATE, 'Arbeitsgemeinschaft Arzneimitteltherapie bei psychischen Erkrankungen', a cooperation for drug safety in the treatment of psychiatric diseases, (for details: www.amuep-agate.de). Retrospective analysis of clinical data for this study was in accordance with the local regulatory authority of RWTH Aachen University hospital and in alignment with the Declaration of Helsinki.

In this naturalistic database, patients were under medication with risperidone (RIS) for different reasons, only patients with organic mental disorders were excluded. Patients that received depot formulations and patients that were under concomitant medication with possible CYP2D6 inhibitory or CYP3A4 inhibitory or inducing properties were also excluded from analysis as well as samples with missing data of RIS, its pharmacokinetic parameters or clinical response (Hiemke et al., 2011, US Food and Drug Administration, 2014). Finally, 1074 out of 1584 patients met the inclusion criteria. We considered six groups; a group of patients that received RIS without a potentially cytochrome influencing co-medication (control group, R_0), a group receiving a combination of risperidone and chlorprothixene (R_{CHLOR}), a group co-medicated with levomepromazine (R_{LEV}), a group co-medicated with melperone (R_{MEL}), a fourth with pipamperone (R_{PIP}) and a fifth group, co-medicated with prothipendyl (R_{PRO}). No matching processes for age, diagnoses, severity of illness, length or onset of illness were undertaken.

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 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) (Paul et al., 2009), FDA (US Food and Drug Administration) guidances (US Food and Drug Administration, 2001) and ICH (International Conference on Harmonization) requirements (International Conference on Harmonization, 1996). The laboratory regularly runs internal quality controls and participates in external quality assessment schemes by INSTAND (Düsseldorf, Germany, www.instandev.de).

2.2. Statistical analysis

Our primary outcome was the active moiety plasma levels, which are considered of major clinical relevance (Hiemke et al., 2011). We compared the medians and the distributions of the plasma concentration of the parent compound, RIS, the active metabolite, 9-OH-RIS, as well as the active moiety (RIS + 9-OH-RIS) between the defined groups. Further comparisons included the plasma concentration corrected by the daily dose, defined as the dose-adjusted plasma concentration or 'concentration-by-dose', (C/D), and the ratios of 9-OH-RIS/RIS for the identification of the metabolizer status phenotype. Both were calculated in accordance with the AGNP consensus guidelines (Hiemke et al., 2011). Histograms yielded evidence of non-normal distributions, so that a non-parametrical Kruskal-Wallis test (K-W) with a significance level of 0.05 was conducted. To conduct pairwise comparisons (co-medication groups vs control group) a Mann Whitney *U* test with the same significance level was used. Statistical analysis was carried out using IBM SPSS Statistics version 18.0 (IBM GmbH, Ehningen, Germany).