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Short Communication

Effect of fosamprenavir/ritonavir on the pharmacokinetics of single-dose olanzapine in healthy volunteers

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ABSTRACT

Psychosis and other mental illnesses are common in HIV-infected patients. Olanzapine is one of the preferred antipsychotic agents for the treatment of schizophrenia. Olanzapine is primarily metabolised by CYP1A2 and uridine diphosphate glucuronosyltransferase (UGT). High-dose ritonavir has been shown to increase olanzapine elimination through induction of CYP1A2 and/or UGT, but the effect of low-dose ritonavir on olanzapine pharmacokinetics is unknown. Fosamprenavir is an HIV protease inhibitor that is boosted by low-dose ritonavir. To compensate for the induction of olanzapine metabolism by fosamprenavir/ritonavir, we hypothesised that a dose increase of olanzapine to 15 mg with fosamprenavir/ritonavir would lead to a similar area under the concentration–time curve (AUC) compared with olanzapine 10 mg alone. An open-label, randomised, two-period, cross-over, single-centre trial was conducted in 24 healthy volunteers. Subjects were randomised to one of the following treatments: (A) fosamprenavir/ritonavir 700/100 mg twice daily (b.i.d.) for 16 days with a single dose of olanzapine 15 mg on Day 13, a wash-out period of 31 days and a single dose of olanzapine 10 mg on Day 48; or (B) the same medication in reverse order. Twenty subjects completed the trial. The geometric mean ratios (90% CI) of olanzapine AUC_{last}, maximum drug concentration (C_{max}) and apparent elimination half-life ($t_{1/2}$) when taken with fosamprenavir/ritonavir versus olanzapine alone were 1.00 (0.93–1.08), 1.32 (1.18–1.47) and 0.68 (0.63–0.74), respectively. Fosamprenavir/ritonavir 700/100 mg b.i.d. appeared to induce olanzapine metabolism. We therefore propose a 50% dosage increase of olanzapine when combining with a ritonavir-boosted protease inhibitor.

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Introduction

Mental disorders such as schizophrenia frequently occur in patients infected with human immunodeficiency virus (HIV). The prevalence of HIV infection in patients with a mental disorder is estimated to vary from 3% up to 23% depending on the population studied and the methodology used [1]. These high rates of co-morbidity of HIV infection in people with mental disorders can be partly explained by the risk behaviour of patients with a mental disorder, such as promiscuous behaviour and intravenous drug use [1]. Furthermore, awareness of the potential risks of HIV appears to be lower in patients with mental disorders compared with the general population [2].

Up to 15% of patients with a pre-existing HIV infection develop new-onset psychosis [3]. Possible mechanisms are the presence of HIV in the central nervous system [1,3] and provocation of psychiatric disorders by antiretroviral agents (e.g. zidovudine, efavirenz and nevirapine) [4].

Olanzapine is one of the preferred atypical antipsychotics for the treatment of schizophrenia, but there is little experience with olanzapine in treating schizophrenia in HIV/AIDS patients. Ritonavir, an antiretroviral protease inhibitor (PI), inhibits the cytochrome P450 (CYP) isoenzymes CYP2D6 and CYP3A4 and thereby the metabolism of most antipsychotic agents. Olanzapine has a distinct metabolic profile compared with the other atypical antipsychotic agents: it is primarily metabolised by CYP1A2 and uridine diphosphate

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glucuronosyltransferase 1A4 (UGT1A4). Therefore, olanzapine could be an attractive antipsychotic agent in HIV/AIDS patients with schizophrenia.

Previous research showed that ritonavir at a dose of 500 mg twice daily (b.i.d.) reduced the mean area under the concentration–time curve (AUC) of olanzapine by 53%, probably due to induction of CYP1A2 and/or UGT [5]. Nowadays, ritonavir is used only as a booster of other PIs at a much lower dose (100–200 mg once or twice daily) by inhibiting the metabolism of the second PI (e.g. fosamprenavir). Previous studies have shown that a low dose of ritonavir may still have an inducing effect on CYP1A2 [6] or UGT enzymes [7,8]. The effect of low-dose ritonavir in combination with a PI on the pharmacokinetics of olanzapine has not been investigated.

In this study, the effect of the combination fosamprenavir/ritonavir on the pharmacokinetics of single-dose olanzapine in healthy volunteers was studied. We hypothesised that a dose increase of olanzapine to 15 mg in combination with fosamprenavir/ritonavir would lead to a similar AUC compared with olanzapine 10 mg alone.

Materials and methods

General study information

This open-label, randomised, two-period, cross-over, single-centre trial in 24 healthy volunteers was conducted at the Clinical Research Center of the Radboud University Nijmegen Medical Center (Radboudumc) (Nijmegen, The Netherlands). The study (ClinicalTrials.gov identifier NCT00977301) was approved by the Investigational Review Board of the Radboudumc. The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Informed consent was obtained from all subjects before enrolment.

Study population

Healthy male and female volunteers aged 18–55 years with a body mass index (BMI) of 18–30 kg/m^2 were included. Subjects had to be in a good age-appropriate health condition. The main exclusion criteria were a documented history of sensitivity/idiosyncrasy to medicinal products or excipients, a positive HIV, hepatitis B or hepatitis C test, pregnancy or breast-feeding, and therapy with any drug other than acetaminophen from 2 weeks preceding the study and during the study.

Study design

Subjects were randomised to one of the following treatments: (A) fosamprenavir/ritonavir 700/100 mg b.i.d. for 16 days with a single dose of olanzapine 15 mg on Day 13, a wash-out period of 31 days and subsequently a single dose of olanzapine 10 mg on Day 48; or (B) the same medication in reverse order (Table 1). The 10 mg dosage of olanzapine is the recommended starting dose in patients with schizophrenia; a 50% higher dose (15 mg) was chosen when combining olanzapine with fosamprenavir/ritonavir to compensate for the expected effect of the induction of olanzapine metabolism by ritonavir. The 15 mg dosage of olanzapine is within the registered dose range of olanzapine of 5–20 mg/day [9]. The used dose of fosamprenavir/ritonavir (700/100 mg b.i.d.) is the recommended dose for these agents for use as antiretroviral therapy [10,11].

Fosamprenavir (Telzir® tablet 700 mg; ViiV Healthcare UK Ltd., Brentford, UK) and ritonavir (Norvir® capsules 100 mg; Abbott Laboratories Ltd., Maidenhead, UK) were taken twice daily. Subjects visited the research centre every other day where fosamprenavir/ritonavir intake was observed. Outside of these times, subjects took the fosamprenavir/ritonavir doses at home. Drug intake at home was monitored by the use of MEMS® (Medication Event Monitoring System) caps (Aardex, Sion, Switzerland), recording the time of opening of the medication bottle. Furthermore, subjects wrote the exact times of medication intake in a booklet.

Olanzapine (Zyprexa®; Eli Lilly Nederland BV, Houten, The Netherlands) intake was supervised at the research centre 5 min after finishing a standardised breakfast, although food is not expected to affect olanzapine pharmacokinetics.

Smoking (CYP1A2 induction) and caffeine use (CYP1A2 substrate) could influence olanzapine metabolism, which is mainly metabolised by CYP1A2. Because smoking and caffeine use are very common among psychiatric patients, smoking and the use of caffeine were not prohibited in the study. Subjects were asked to adhere to their normal smoking habits and caffeine intake from 4 weeks before the start of the study until the end of the trial.

Pharmacokinetic sampling, analytical procedure and safety assessments

Blood was collected just before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 72 and 96 h after olanzapine intake. Plasma concentrations of olanzapine, amprenavir (the active metabolite of fosamprenavir) and ritonavir were determined at the Department of Pharmacy of Radboudumc. Olanzapine concentrations were determined using a validated high-performance liquid chromatography (HPLC) method. The analytical range of the olanzapine assay was 0.5–250 μg/L.

Amprenavir and ritonavir concentrations were determined using a validated ultraperformance liquid chromatography (UPLC) method with ultraviolet detection. The analytical range was 0.1–30 mg/L for the amprenavir assay and 0.045–30 mg/L for the ritonavir assay.

During the use of fosamprenavir/ritonavir, serum biochemistry, haematology and adverse events were assessed every other day. Because prolongation of the QT_c interval is an adverse effect of olanzapine [9], an electrocardiogram was recorded in all subjects

Table 1
Treatment schedule.

	Days 1–12	Day 13	Days 14–16	Days 17–35	Days 36–47	Day 48	Days 49–51
Treatment A	FPV/RTV 700/100 mg b.i.d.	FPV/RTV 700/100 mg b.i.d. + OLZ 15 mg	FPV/RTV 700/100 mg b.i.d.	Wash-out	Wash-out	OLZ 10 mg	–
Treatment B	–	OLZ 10 mg	Wash-out	Wash-out	FPV/RTV 700/100 mg b.i.d.	FPV/RTV 700/100 mg b.i.d. + OLZ 15 mg	FPV/RTV 700/100 mg b.i.d.

FPV/RTV, fosamprenavir/ritonavir; b.i.d., twice daily; OLZ, olanzapine.

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