title

Lopinavir/ritonavir and rifampin: is coadministration possible?

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summary

The necessity of concomitant treatment of tuberculosis and HIV infection in the same patient creates a therapeutic challenge due to drug-drug interactions. The most problematic issue is coadministration of rifamycins with protease inhibitor (PI) – based antiretroviral regimens. One of the PIs, commonly used in Poland is lopinavir/ritonavir (LPV/r), and the only rifamycin directly available is rifampin. It is well known that rifampin dramatically decreases lopinavir plasma levels. In the view of different studies, coadministration of LPV/r with rifampin, despite attempts to compensate the interaction with dosage adjustment or additional ritonavir, is not advisable because of toxicity. In such situations, rifabutin should be a drug of choice. It can be taken as 1/4 of normal dosage. LPV/r dosage does not need to be changed. In Poland, rifabutin can be obtained through special importing procedure.

key words

lopinavir, ritonavir, rifamycins, rifampin, rifampicin, rifabutin, drug interactions

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The necessity of concomitant treatment of tuberculosis and HIV infection in the same patient is not a rare situation. Both infections require the use of combined therapy for the same reason: to prevent resistance. In either case, it means at least three agents given together. This leads to unavoidable problem of drug interactions.

In antiretroviral-naive patient with CD4+ count >50 cells/mm^3 and active tuberculosis, the DHHS Guidelines [1] recommend starting four-drug (rifampin or rifabutin, isoniazid, pyrazinamide, and ethambutol or streptomycin) antimycobacterial treatment, then to initiate antiretroviral regimen 4 to 8 weeks later. Such approach helps identify the causes of adverse reactions which are common in this group of patients; also, after this delay period, the number of antimycobacterials can be usually reduced to one of the rifamycins plus isoniazid. In patients already on antiretroviral therapy, a four-drug regimen is recommended for first 2 months, followed by 4-7 month therapy with rifampin/rifabutin plus isoniazid; therefore, the potential risk of drug interactions during first weeks of anti-tuberculosis therapy in these patients is even higher.

The most troublesome drugs are these metabolized via P450 cytochrome system (CYP450). Unfortunately, two basic anti-tuberculosis drugs: rifampin and isoniazid, are either metabolized that way, or at least they are CYP450 inducers. Among antiretrovirals, the situation is not better. Most potent agents – protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) – are all CYP450-dependent. In case of first-line NNRTI, efavirenz, it is possible to overcome the interaction with +33% dose adjustment; however, this simple approach does not work well with the PIs [1, 2].

One of the PIs, commonly used in Poland is lopinavir/ritonavir (LPV/r), and the only rifamycin directly available is rifampin (=rifampicin). The purpose of this paper is to review the current knowledge about possibility of coadministration of these agents.

Rifampin and other rifamycins

Rifampin is one of the rifamycins, the group of antibiotics active mostly against Gram(+) and acid-fast bacteria, including *Mycobacterium tuberculosis*. It is a first-line antimycobacterial agent, acting by inhibition of DNA-dependent RNA polymerase of mycobacteria. It is cheap, relatively safe and readily available worldwide, also as a fixed-dose combination with isoniazid, as both drugs can be given orally.

Rifampin is a potent CYP3A inducer, and this induction accelerates elimination of most other compounds which are metabolized by the same enzyme. Interestingly, rifampin metabolism itself does not depend on CYP3A [3, 4]. Adult dose of rifampin is 600 mg once daily (QD).

The compound which is chemically related to rifampin, and exhibits very similar antimycobacterial activity, is rifabutin. It is a relatively weak inducer of CYP3A, however, its metabolism is dependent on it; therefore, inhibition of this cytochrome leads to increase of rifabutin pharmacokinetic parameters [3, 4]. Adult rifabutin dose is 300 mg QD [5].

Third important member of rifamycin group, rifapentine, has very prolonged elimination, enabling twice-weekly dosage at 2-months initiation period, then once-weekly at maintenance therapy [6]. However, it proved to be inferior vs. rifampin in clinical trials due to high relapse rate [6], and currently it is not recommended in HIV+ patients because of resistance and adherence concerns [1]. Rifapentine is a strong CYP3A4 inducer [3, 4].

Lopinavir/ritonavir

Lopinavir (LPV), a HIV protease inhibitor, is metabolized mainly by CYP3A4. Ritonavir, another PI, is a strong inhibitor of this cytochrome. Therefore, coadministration of these compounds (with ritonavir given in much lower dose than lopinavir – the ratio is 1:4) enhances the pharmacokinetics of lopinavir, resulting in elevated and sustained LPV plasma levels. This beneficial interaction, occurring also between ritonavir and most other PIs, is known as "ritonavir-boosting", and is employed in a number of antiretroviral regimens. In case of lopinavir, it ended with the development of convenient, co-formulated tablet containing both lopinavir and ritonavir (LPV/r 200/50 mg). Adult daily dose of LPV/r is 800 mg of lopinavir and 200 mg of ritonavir, given as two tabs twice daily (BID) [7].

Ritonavir, given in low dose as a pharmacokinetic booster, exhibits no antiviral activity of its own.

Lopinavir/ritonavir and rifampin

First studies [8] of the pharmacokinetic interaction between rifampin and LPV/r showed that the area under the pharmacokinetic curve (AUC) and the minimum concentration in plasma (C_{min}) for lopinavir in healthy subjects were decreased by 75 and 99%, respectively, as a result of coadministration of rifampin at 600 mg QD with standard dose of LPV/r. This results from strong induction of CYP3A by rifampin, which overcomes the inhibition of this enzyme by low-dose ritonavir. It is clear that rifampin, combined with standard-dose LPV/r, makes the latter drug almost completely inactive.

The next major study by la Porte et al. [9] tried to establish whether modifying the LPV and ritonavir dosage could overcome the interaction with rifampin. In standard-dose regimen, they basically confirmed the results of Bertz et al. [8]: LPV C_{min} levels in steady-state have dropped by 93%. However, in their study, the observed lopinavir exposure was substantially higher compared to the historical data [8]. The dosage adjustment investigated by the authors (LPV/r BID, respectively: 667/167 mg, 800/200 mg, 400/300 mg, 400/400 mg; rifampin always 600 mg QD) showed that while the concentrations of lopinavir could be significantly increased, especially in 400/400 mg BID group, it could not be demonstrated that these regimens were equivalent – particularly with respect to C_{min} – to the standard dose of LPV/r without rifampin. This indicates that the simple dose adjustment (either with LPV/r ratio maintained, or ritonavir dose increased to 1:1 with LPV) may not be capable of complete compensation for the accelerated metabolism of lopinavir by rifampin. Moreover, in order to approach LPV plasma levels achievable without rifampin, the authors had to administer 800 mg of ritonavir daily; due to nonlinear pharmacokinetics of ritonavir, this resulted in unproportionally high ritonavir exposure [9]. According