JPP Journal of Pharmacy and Pharmacology

JPP 2001, 53: 409–412

Received March 28, 2000
Accepted October 26, 2000
ISSN 0022-3573

Effect of indinavir on the pharmacokinetics of rifampicin in HIV-infected patients*

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Abstract

Indinavir, an antiretroviral agent, has an influence on the pharmacokinetics of other drugs by acting as an inhibitor of cytochrome P450-mediated drug metabolism. The incidence of tuberculosis has increased dramatically in the past decade because of an epidemic of HIV infection. Rifampicin is still one of the most valuable drugs for the standard treatment of tuberculosis. The objective of this study was to investigate the effects of indinavir on the pharmacokinetics of rifampicin in man. Our study was conducted in eleven HIV-infected patients. All patients received a 600-mg single dose of oral rifampicin on day 1 and 15- and 800-mg oral indinavir three times a day from day 2 to day 15. Rifampicin pharmacokinetic studies were carried out on day 1 and day 15. The results showed that rifampicin concentrations were higher when it was administered with indinavir than when it was administered alone. With concomitant indinavir medication, the mean AUC_{0-24} of rifampicin was increased by 73%. Therefore, we conclude that indinavir has an inhibitory effect on the metabolism of rifampicin.

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Acknowledgement and Funding: This work was supported by a Faculty grant from Faculty of Medicine, Prince of Songkla University. We thank Mrs Shari L. Hunter for her English consultation services.

* This paper was presented at the 21st International Congress of Chemotherapy, Birmingham, UK, 4–7 July 1999.

Introduction

Drugs are often administered concomitantly to patients, especially AIDS patients, and are occasionally continued for the duration of their lives. Those patients may receive a variety of agents, either therapeutically or prophylactically, for infections. Therefore, it is important to investigate drug interactions between agents given to patients, because interactions may influence efficacy.

Rapid advances in the treatment of HIV infection have resulted directly in dramatic declines in morbidity and mortality (Palella et al 1998). These are due to the widespread use of potent combination therapy. Protease inhibitors and reverse transcriptase inhibitors, when used as part of combination drug regimens, can profoundly suppress viral replication with consequent repletion of CD4+ cell counts. Therefore, the highly active antiretroviral therapy including a protease inhibitor is the current standard of HIV patient's care (Carpenter et al 1998). However, protease inhibitors have an influence on the pharmacokinetics of several other drugs by acting as inhibitors of cytochrome P450-mediated drug metabolism (Piscitelli et al 1996). Thus, they can interact with other drugs commonly used to treat opportunistic infections in AIDS patients.

The incidence of tuberculosis has increased dramatically in the past decade, especially in developing countries. One of the primary reasons is the epidemic of HIV infection (Sathe & Reichman 1989). Rifampicin is still one of the most valuable drugs for the standard treatment of tuberculosis and its metabolism is mediated by hepatic cytochrome P450 enzymes (Mandell & Petri 1996). However,

until now we have had no data to demonstrate the effects of indinavir on the pharmacokinetics of rifampicin in AIDS patients. Therefore, the aim of this study was to provide such data.

Materials and Methods

Subjects

The Ethics Committee of Songklanagarind Hospital approved the protocol for the study and written informed consent was obtained from each patient.

Eleven HIV-infected patients participated in this study, of whom four were male and seven were female. The mean age was 28.27 ± 7.55 years (range 20–48) and their mean weight was 51.09 ± 6.94 kg (range 41.5–60). The mean CD4+ cell count was 256.18 ± 154.25 cell $(mm^3)^{-1}$ (range 10–410). Patients were excluded from the study if they were pregnant or considered unlikely to survive for more than two weeks. They were also excluded if they had evidence of liver dysfunction, creatinine clearance rate of less than 50 mL min^{-1}, vomiting or diarrhoea, or a history of rifampicin and indinavir intolerance. All patients received treatment with a variety of drugs including cotrimoxazole, zidovudine and lamivudine, none of which are known to interact with the pharmacokinetics of rifampicin.

Drugs and chemicals

Indinavir (Crixivan) was purchased from Merck Sharp & Dohme and rifampicin was purchased from Lederle (Thailand). Rifampicin pure powder was purchased from Sigma Chemical Company (St Louis, MO). All of the solvents were high-performance liquid chromatography (HPLC) grade.

Study design and sample collection

All patients received a 600-mg single dose of oral rifampicin on day 1 (phase I), which served as the control day, and on day 15 (phase II), and 800-mg oral indinavir three times a day from day 2 to day 15. Rifampicin pharmacokinetic studies were carried out on days 1 and 15. Before each rifampicin treatment, patients underwent an overnight fast of at least 8 h, which was continued for a further 4 h after rifampicin administration. Blood samples (approximately 5 mL each) were obtained by direct venepuncture at the following times: before (time 0) and every 15 min for 3 h, every 30 min for 2 h, then 6, 7, 8, 12, 18 and 24 h after the rifampicin dose. All blood samples were allowed to clot and then centrifuged at 2000 *g*. The serum obtained was stored at $-80°C$ until analysis.

Rifampicin assay

The concentration of rifampicin was determined by reversed-phase HPLC. The samples were extracted by the method of Darouiche et al (1990) and 50 μL of the samples were injected, using an automated injection system (Waters 717 plus Autosampler, Waters Associates, Milford, MA), onto a Bondapak C18 column (Waters Associates). The mobile phase was 50 mmol L^{-1} potassium dihydrogen phosphate/acetonitrile (62:38, v/v) pH 4.7, at a flow rate of 1 mL min^{-1}. The column effluent was monitored by UV detection (Waters 486, Waters Associates) at 340 nm. The peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates, Milford, MA). The limit of detection of rifampicin was 2.5 ng per injection.

Pharmacokinetic parameters

The maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were determined by visual inspection of the individual plasma concentration–time profiles. AUC_{0-24} were the areas under the concentration vs time between 0 and 24 h calculated using the trapezoidal rule. These standard parameters were used for statistical comparisons. Results were expressed as mean $\pm$ s.d. and statistical comparisons were made using the Wilcoxon signed-ranks test.

Results

The mean serum rifampicin concentration–time data for the two phases are depicted in Figure 1. The concentrations were higher when rifampicin was administered with indinavir (phase II) than when administered alone (phase I). With concomitant indinavir medication, the mean AUC_{0-24} of rifampicin was increased by 73% ($P < 0.05$; Table 1).

The mean C_{max} for phase II was 8.78% higher than that for phase I, but this was not statistically significant ($P > 0.05$; Table 1). The mean t_{max} for phase I and II were equal (Table 1).

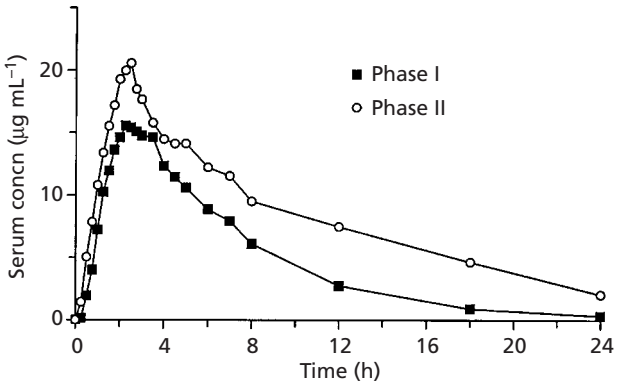

Figure 1 Mean serum rifampicin concentration–time data in 11 HIV-infected patients following administration of a 600-mg single dose of oral rifampicin alone (phase I) or after 800-mg oral indinavir three times a day for 14 days (phase II).

Table 1 Pharmacokinetic parameters of 600-mg oral rifampicin when it was administered alone (phase I) and after treatment with indinavir for 14 days (phase II).

Parameter	Phase I	Phase II
AUC_{0-24} (μg h mL^{-1})	112.40 ± 27.26*	194.26 ± 46.75*
C_{max}(μg mL^{-1})	21.19 ± 6.02	23.05 ± 8.33
t_{max} (h)	2.61 ± 0.90	2.61 ± 0.85

*$P < 0.05$.

Discussion

Studies to define pharmacokinetic drug interactions between agents used as part of a multidrug regimen are important because the interaction may have influence on drug efficacy. Multidrug regimens are often administered to patients with AIDS for the duration of their lives. One of the most important mechanisms of drug interactions is enzyme inhibition, which results in elevated levels of the parent drug, prolonged pharmacological effects and an increased incidence of drug-induced toxicity.

Indinavir, a protease inhibitor, has been shown to be a potent inhibitor of cytochrome P450 3A4-mediated drug metabolism (Piscitelli et al 1996). Although the inhibitory effect of indinavir is less potent than ritonavir, it can interfere with hepatic metabolism of several other coadministered medications. Previous studies in man showed that coadministration of indinavir and rifabutin resulted in a 204% increase in the AUC of rifabutin (Indinavir Pharmacokinetic Study Group 1996). Therefore, when patients receive this drug combination, an adjustment in the dose of rifabutin to one-half of the standard dose is recommended. This study has shown that rifampicin concentrations were higher when it was administered with indinavir than when it was administered alone. The mean AUC of rifampicin was increased significantly by approximately 73%. These findings demonstrated the pharmacokinetic interactions between the two drugs. The possible explanation of this drug interaction is that indinavir has a potent inhibitory effect on the metabolism of rifampicin. Therefore, coadministration of indinavir and rifampicin requires caution because high plasma concentrations of rifampicin may increase the risk of adverse effects. However, the inhibitory effect of indinavir on drug metabolism can be used to enhance the pharmacokinetics of some other drugs. McCrea et al (1997a) showed that the concomitant administration of indinavir and saquinavir resulted in a 500% increase in the AUC of saquinavir. This combination of two protease inhibitors has the advantage of pharmacokinetic enhancement and an increase of antiviral activity.

Rifampicin is one of the potent inducers of hepatic cytochrome P450 oxidative enzyme in man and a number of drugs have been reported to be affected by rifampicin (Mandell & Petri 1996). Indinavir is also metabolized in the liver primarily by the isoenzyme cytochrome P450 3A4. Therefore, it is prone to significant drug interactions caused by cytochrome P450 inducers, such as rifampicin and rifabutin, which accelerate the clearance of indinavir. These drug interactions result in a reduction in the efficacy and may lead to the development of resistance to indinavir. McCrea et al (1997b) reported that concomitant administration of indinavir and rifampicin in man resulted in a 92% decrease in the AUC of indinavir.

In conclusion, this study has shown the inhibitory effect of indinavir on the metabolism of rifampicin. Conversely, previous studies in man have shown that indinavir can itself be affected by the inducing effect of rifampicin (McCrea et al 1997b). Therefore these two drugs should not be administered concomitantly; however, if this cannot be avoided, the two drugs should be used with caution.

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