Ritonavir Enables Combined Therapy with Rifampin and Saquinavir

As recently discussed in this journal, the treatment of individuals coinfected with HIV-1 and *Mycobacterium tuberculosis* poses a difficult problem for physicians [1]. The current standard of care for the treatment of HIV-1 infection involves a backbone of 2 nucleoside reverse-transcriptase inhibitors in combination with a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor [2]. A dramatic decrease in the systemic exposure of protease inhibitors and nonnucleoside reverse transcriptase inhibitors to subtherapeutic levels has been reported, which can be explained by the inducing effect of rifampin on metabolizing enzymes in the gut wall and liver [1, 3]. This was confirmed in 1 of our patients, who concomitantly used saquinavir and rifampin, as shown in figure 1 (patient 1).

In practice, this drug-drug interaction severely limits therapeutic options for the concomitant treatment of *M. tuberculosis* and HIV-1 infections [1, 4]. The HIV-1 protease inhibitor ritonavir is a potent inhibitor of cytochrome P450 enzymes and causes an unprecedented 20-fold increase of saquinavir exposure during concomitant use. The combination of ritonavir and saquinavir, each at a dosage of 400 mg b.i.d., is therefore widely applied and leads to a powerful antiretroviral response [5, 6].

We hypothesized that the strong inhibiting effect of ritonavir on saquinavir metabolism might compensate for the enzyme-inducing effect of rifampin. Therapeutic concentrations of saquinavir may thus be reached when it is combined with ritonavir and rifampin. On the basis of this concept, 2 HIV-1–infected patients (1 male, 1 female) received the combination of saquinavir (hard gelatin capsules), ritonavir, and rifampin. Steady-state drug concentrations were determined after 4 weeks of therapy.

The pharmacokinetic profiles of saquinavir are shown in figure 1 (patients 2 and 3). Saquinavir concentrations were high and correspond with the therapeutic levels observed when the drug is combined with ritonavir (without rifampin) [5]. The exposure to ritonavir (maximum concentrations were 3.6 and 9.4 mg/L) was within the expected range [5]. Maximum rifampin concentrations were in the therapeutic range of 8–24 mg/L. The combination of saquinavir, ritonavir, and rifampin was well tolerated, and HIV viremia remained controlled (<1000 HIV-1 RNA copies/mL) during the treatment period.

Our results demonstrate that ritonavir enables the treatment of coinfection by HIV-1 and *M. tuberculosis* with saquinavir and rifampin. This strategy may be of paramount importance for HIV-1–infected individuals and needs further investigation, with regard to not only saquinavir but also the other protease inhibitors (e.g., indinavir).

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References