Ritonavir’s Role in Reducing Fentanyl Clearance and Prolonging Its Half-life
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Background: The human immunodeficiency virus protease inhibitor ritonavir is a potent inhibitor of the cytochrome P450 3A4 enzyme, and ritonavir's concomitant administration with the substrates of this enzyme may lead to dangerous drug interactions.

Methods: The authors investigated possible interactions between ritonavir and intravenously administered fentanyl in a double-blind, placebo-controlled, cross-over study in two phases. Twelve healthy volunteers received orally ritonavir or placebo for 3 days; the dose of ritonavir was 200 mg three times on the first day and 300 mg three times on the second. The last dose of ritonavir 300 mg or placebo was given on the morning of the third day. On the second day, 2 h after the afternoon pretreatment dose, fentanyl 5 μg/kg was injected intravenously in 2 min with naloxone to moderate its effects, and 15 timed venous blood samples were collected for 18 h.

Results: Ritonavir reduced the clearance of fentanyl by 67% from 15.6 ± 8.2 to 5.2 ± 2.0 ml·min⁻¹·kg⁻¹ (P < 0.01). The area under the fentanyl plasma concentration-time curve from 0 to 18 h was increased from 4.8 ± 2.7 to 8.8 ± 2.3 ng·ml⁻¹·h⁻¹ by ritonavir (P < 0.01). Ritonavir did not affect the initial concentrations and the steady-state volume of distribution of fentanyl. One subject discontinued participation before fentanyl administration because of severe side effects, and during the study 8 of the remaining 11 subjects reported nausea.

Conclusions: Ritonavir can inhibit the metabolism of fentanyl significantly, so caution should be exercised if fentanyl is given to patients receiving ritonavir medication. (Key words: AIDS; metabolism; opioid; pain management.)

TREATMENT of patients infected with the human immunodeficiency virus (HIV) has changed markedly during the past few years as the new antiretroviral drugs, protease inhibitors, have become available. Inhibition of the HIV protease essential for the proteolytic post-translational cleavage of viral gag and gag-pol polyproteins leads to production of immature noninfectious virions. The protease inhibitors saquinavir, ritonavir, indinavir, and nelfinavir greatly reduce the viral load and increase CD4+ counts, especially if combined with reverse transcriptase inhibitors. Most of the protease inhibitors are also inhibitors of the cytochrome P450 (CYP) 3A4 enzyme, important for the metabolism of several drugs, a fact that increases the probability of pharmacokinetic interactions between protease inhibitors and drugs taken concomitantly. Among HIV protease inhibitors, ritonavir is the most potent inhibitor of CYP3A4 and CYP2D6; it inhibits, to a lesser extent, CYP2C9/10, as well. Fentanyl is a synthetic opioid analgesic widely used as intravenous bolus, as continuous infusions, and, in recent years, also by transdermal route. It is metabolized mainly by CYP3A4, although some studies have suggested that also other CYPs may play a minor role. Because fentanyl has an extraction ratio from 0.8–1.0, its rate of hepatic elimination should be more dependent on liver blood flow than on changes in its intrinsic clearance. In our earlier study, the azole antifungal itraconazole, a potent inhibitor of CYP3A4, did not affect the elimination of fentanyl. Although ritonavir may be an even more potent inhibitor of CYP3A4 than is itraconazole, no information yet exists on the effect of ritonavir on the metabolism of fentanyl in humans. Because pain is a common problem in patients with AIDS and because many patients on ritonavir will be treated with fentanyl at some stage of their disease, we have studied the potential interaction of ritonavir with fentanyl in healthy volunteers.

Materials and Methods

Study Design
We obtained informed written consent from 12 healthy volunteers (eight women, four men, aged 20–33 years).
yr, weighing 48-75 kg) to participate in this study. Based on our previous work, we calculated that at a level of significance of $P = 0.05$ and power of 80%, 10 subjects would be required to demonstrate a 35% difference in fentanyl clearance values.\(^\text{11}\) The subjects were ascertained to be healthy by a clinical examination, a 12-lead electrocardiogram, and laboratory screening including hematologic and biochemical blood tests before entering the study. None was on any continuous medication except five female subjects using contraceptive steroids, and all female subjects were asked to use contraceptive measures other than steroids during the study and for 2 months afterward.

We used a randomized, double-blind, placebo-controlled cross-over study design in two phases with a drug-free interval between the phases of 4 weeks. Subjects were given ritonavir or placebo orally for 3 days. On the first day, ritonavir 200 mg or placebo was given at 8 A.M., 4 P.M., and 11 P.M. to 2 A.M. On the second day, the dose of ritonavir was increased to 300 mg three times with the same timing, and the last dose of 300 mg of ritonavir or placebo was given on the morning of the third day. On the second day, at approximately 6 P.M., 2 h after the afternoon dose of ritonavir or placebo, fentanyl 5 $\mu$g/kg was injected intravenously in 2 min. To prevent the sedative and respiratory depressant effects of fentanyl, 0.1 mg of naloxone was given intravenously 5 min before the fentanyl injection and an additional dose of 0.1 mg with the fentanyl. Additional doses of naloxone were used if needed to counteract the side effects of fentanyl. Peripheral arteriolar oxygen saturation and respiratory rate were monitored until 10 h after the fentanyl injection, and the electrocardiogram was monitored continuously for 2 h. The volunteers fasted for 3 h before the fentanyl and had standard meals 4 h and 12 h afterward. Ingestion of alcohol, coffee, tea, grapefruit juice, or cola was not allowed during the test days, nor was smoking permitted. The study protocol was approved by the Ethics Committee of the Department of Anesthesia, University of Helsinki, as well as by the Finnish National Agency for Medicines.

**Sampling and Drug Analysis**

On the second day of pretreatment, a forearm vein was cannulated, and timed blood samples were drawn into 10-ml EDTA tubes immediately before and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10,12, and 18 h after the fentanyl injection was administered into the opposite arm. Plasma was separated within 2 h and stored at $-20^\circ$C until analysis of ritonavir and fentanyl concentrations.

Fentanyl concentrations were determined by a specific radioimmunoassay method,\(^\text{17}\) and those of ritonavir by a high-performance liquid chromatography.\(^\text{18}\) The quantitation limit for fentanyl was 0.10 ng/ml, and the coefficient of variation was 6.2% at 0.181 ng/ml, 6.5% at 0.604 ng/ml, and 4.2% at 3.02 ng/ml ($n = 3$ at each concentration). Compliance was documented by measurement of ritonavir concentrations in plasma samples taken before fentanyl injection and 2, 4, and 8 h afterward. The quantitation limit for ritonavir was 0.012 $\mu$g/ml, and the coefficient of variation was 3.8, 2.5, and 2.9% at 0.608, 4.72, and 11.16 $\mu$g/ml, respectively ($n = 3$ at each concentration).

**Pharmacokinetic Analysis**

For each subject, the terminal log-linear phase of the fentanyl concentration–time curve was identified visually, and the elimination rate constant ($k_{el}$) was determined by regression analysis of the log-linear part of the curve. The elimination half-life ($t_{1/2}$) of fentanyl was calculated from $t_{1/2} = \ln 2/k_{el}$. The area under the fentanyl concentration curve (AUC) referring to the time from 0 to 18 h after fentanyl injection (AUC0–18) was calculated by use of the trapezoidal rule, and the AUC0–$\infty$ was extrapolated to infinity by use of the $k_{el}$ value. Values for plasma clearance and steady-state volume of distribution ($V_{ss}$) of fentanyl were calculated by noncompartmental methods based on statistical moment theory.\(^\text{19}\) The pharmacokinetic parameters were determined by the MK model, version 5 (Biosoft, Cambridge, UK).

**Statistical Analysis**

One volunteer dropped out before the administration of fentanyl; thus the pharmacokinetic data refer to the remaining 11 subjects who completed the study. We used balanced Latin-square randomization to obtain maximum safety in the study design. Assignments for randomization were generated by the pharmacy of the Helsinki University Central Hospital, which arranged the ritonavir and placebo capsules in coded envelopes to be delivered for the subjects. Pharmacokinetic variables during the two pretreatments were compared with the use of the Student $t$ test for paired data and the chosen significance level was $P < 0.05$. Results were expressed as mean values $\pm$ SD. All the data were analyzed with the statistical program Systat for Windows, version 6.0 (Systat, Evanston, IL).
Results

Plasma concentrations of fentanyl in 11 volunteers as a function of time are presented in figure 1, and the mean ritonavir concentrations in figure 2. One of the female volunteers discontinued the study on the second day of ritonavir pretreatment because of nausea and vomiting. During the ritonavir phase, the mean plasma concentration of fentanyl at 18 h after the injection was at the same level as at 4 h during the placebo phase. Six subjects showed secondary peaks in plasma fentanyl concentrations between 5 and 9 h after fentanyl administration: four of them during the ritonavir phase, and two during the placebo phase. Ritonavir decreased the plasma clearance of fentanyl by 67% ($P < 0.01$). The elimination half-life of fentanyl increased from the control value of 9.4 ± 4.6 h to 20.1 ± 8.4 h ($P < 0.01$) after ritonavir. The $AUC_{0–18}$ of fentanyl increased 81% ($P < 0.01$) and the $AUC_{0–17}$ was increased by 174% ($P < 0.01$) after pretreatment with ritonavir as compared with placebo. Plasma concentrations of fentanyl at 15 and 30 min after injection did not differ significantly between ritonavir and placebo treatments. Ritonavir had no significant effect on the $V_{ss}$ of fentanyl (table 1).

Discussion

Ritonavir profoundly affected the pharmacokinetics of fentanyl by reducing its clearance by 67%. As a result, the $t_{1/2}$ of fentanyl appeared to be prolonged, and the $AUC_{0–\infty}$ was increased by 170%. These changes were most likely caused by an inhibition of the CYP3A4-mediated metabolism of fentanyl. $^5$ Ritonavir had no significant effect on the steady-state volume of distribution of fentanyl, and as the initial concentrations of fentanyl did not differ between the treatments, a difference in the volume of central compartment was also unlikely. However, the relatively few samples drawn immediately after the administration of fentanyl do not allow any absolute conclusions on the events during the initial distribution phase. Because fentanyl has an extraction ratio from 0.8 to 1.0, $^{10}$ its rate of hepatic elimination should therefore be more dependent on liver blood flow than on changes in its intrinsic clearance. $^{12}$ Consistent with this, another...
potent inhibitor of CYP3A4, itraconazole, had no effect on the pharmacokinetics of fentanyl in our previous study,\textsuperscript{11} although in the present study ritonavir decreased the clearance of fentanyl considerably. By use of the “well-stirred” model of hepatic elimination,\textsuperscript{12} we can increased the clearance of fentanyl considerably. By use of the “well-stirred” model of hepatic elimination,\textsuperscript{12} we can

Table 1. Pharmacokinetic Parameters of Fentanyl following Intravenous Administration of 5 μg/kg Fentanyl after Pretreatment with Oral Ritonavir or Placebo for 3 Days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Phase (control)</th>
<th>Ritonavir Phase</th>
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<tbody>
<tr>
<td>CL (mL min(^{-1}) kg(^{-1}))</td>
<td>15.6 ± 8.2</td>
<td>5.2 ± 2.0*</td>
</tr>
<tr>
<td>Relative to control (range)</td>
<td>1</td>
<td>0.33 (0.19–0.65)</td>
</tr>
<tr>
<td>(V_{SS}) (L/kg)</td>
<td>9.3 ± 4.9</td>
<td>7.5 ± 2.1</td>
</tr>
<tr>
<td>Relative to control (range)</td>
<td>1</td>
<td>0.81 (0.37–1.50)</td>
</tr>
<tr>
<td>(t_{1/2}) (h)</td>
<td>9.4 ± 4.6</td>
<td>20.1 ± 8.4*</td>
</tr>
<tr>
<td>Relative to control (range)</td>
<td>1</td>
<td>2.1 (0.91–14.25)</td>
</tr>
<tr>
<td>AUC(_{0-18}) (ng mL(^{-1}) h(^{-1}))</td>
<td>4.8 ± 2.7</td>
<td>8.8 ± 2.3*</td>
</tr>
<tr>
<td>Relative to control (range)</td>
<td>1</td>
<td>1.8 (1.1–3.56)</td>
</tr>
<tr>
<td>AUC(_{0-\infty}) (ng mL(^{-1}) h(^{-1}))</td>
<td>6.6 ± 3.4</td>
<td>18.1 ± 6.5*</td>
</tr>
<tr>
<td>Relative to control (range)</td>
<td>1</td>
<td>2.7 (1.52–5.20)</td>
</tr>
</tbody>
</table>

Values are mean ± SD. On the first day ritonavir 200 mg or placebo was given three times a day, on the second day ritonavir was increased to 300 mg three times a day, and the last dose of ritonavir 300 mg or placebo was given on the morning of the third day. Fentanyl was injected on the second day 2 h after the afternoon dose of ritonavir or placebo.

CL = plasma clearance; \(V_{SS}\) = steady-state volume of distribution; \(t_{1/2}\) = elimination half-life; AUC\(_{0-18}\) = area under fentanyl plasma concentration–time curve 0 to 18 h after fentanyl injection; AUC\(_{0-\infty}\) = area under fentanyl plasma concentration–time curve extrapolated to infinity.

* Significantly different from placebo (\(P < 0.01\)).

As a weak base, fentanyl is excreted in the acidic gastric juice and reabsorbed later from the small intestine, resulting in secondary elevations in fentanyl plasma concentrations.\textsuperscript{20,21} In addition to the liver, CYP3A4 is expressed also in the gut wall.\textsuperscript{22} In the small intestine, fentanyl becomes exposed to duodenal-wall CYP3A4, and therefore CYP3A4 inhibitors may affect the bioavailability of reabsorbed fentanyl both in the intestinal wall and in the liver. In our study somewhat higher secondary peaks of fentanyl concentrations appeared during administration of the ritonavir medication compared with placebo, which may reflect the potent inhibitory effect of ritonavir on CYP3A4 in the gut wall and liver during the absorption of fentanyl.

All volunteers in our study were given naloxone to counteract the effects of fentanyl. Because naloxone is metabolized primarily by glucurononitransferase,\textsuperscript{23} it is unlikely that naloxone would have affected the pharmacokinetics of fentanyl. Our volunteers ingested ritonavir for 3 days only, and the dose of ritonavir was somewhat (25%) smaller than that recommended for HIV patients.\textsuperscript{24} Knowing the high frequency of side effects related to ritonavir, we avoided using medication for any longer period in healthy volunteers. It would also have been unethical to study possible drug interaction in HIV patients during ritonavir monotherapy, because the current standard of care for HIV patients is a three-drug combination.\textsuperscript{2} We measured fentanyl plasma concentrations for 18 h. This means that the elimination half-lives of fentanyl could not be determined with such reliability as usual: normally sampling for three to five half-lives is necessary for the reliable determination of elimination half-life. However, we believe that our results demonstrate that the elimination half-lives are prolonged by ritonavir. Despite these limitations in our study design, the results clearly show a strong interaction between ritonavir and fentanyl and indicate the need for a change in fentanyl dosing, at least at the beginning of ritonavir treatment.

During the past few years, the transdermal route has turned out to be a good alternative for fentanyl administration for chronic cancer pain, especially if other routes are unavailable or have become inconvenient.\textsuperscript{25} It is probable that ritonavir affects the elimination of transdermally administered fentanyl at the same magnitude as that of intravenous fentanyl. It thus can be calculated that ritonavir treatment results in an approximately three-fold increase in fentanyl concentrations. Such an increase is undoubtedly of major clinical significance.
and, if the dose is not reduced and the patients not followed closely, can cause fatal respiratory depression. In conclusion, ritonavir decreases the elimination of fentanyl significantly, and it may dangerously augment and prolong fentanyl-induced respiratory depression. If only small bolus doses of fentanyl are administered during ritonavir treatment, a dose adjustment of fentanyl is probably not needed, because the initial fentanyl concentrations are not affected. However, as the elimination of fentanyl will be slower, it is advisable to maintain respiratory monitoring longer. On more continuous dosing, dosage of fentanyl should be reduced. Further studies are needed to elucidate the effect of long-term ritonavir treatment on fentanyl pharmacokinetics.

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References


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