Accepted Manuscript

Original article

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PII: S0959-289X(13)00122-2
DOI: http://dx.doi.org/10.1016/j.ijoa.2013.08.011
Reference: YIJOA 2229


Accepted Date: 19 August 2013


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ORIGINAL ARTICLE

Effect of ritonavir-induced cytochrome P450 3A4 inhibition on plasma fentanyl concentrations: a pharmacokinetic simulation

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Short Title: Ritonavir and plasma fentanyl concentration

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ABSTRACT

Background: Ritonavir inhibition of cytochrome p450 3A4 decreases the elimination clearance of fentanyl by 67%. We used a pharmacokinetic model developed from published data to simulate the effect of sample patient-controlled epidural labor analgesic regimens on plasma fentanyl concentrations in the absence and presence of ritonavir-induced cytochrome p450 3A4 inhibition.

Methods: Fentanyl absorption from the epidural space was modeled using tanks-in-series delay elements. Systemic fentanyl disposition was described using a three-compartment pharmacokinetic model. Parameters for epidural drug absorption were estimated by fitting the model to reported plasma fentanyl concentrations measured after epidural administration. The validity of the model was assessed by comparing predicted plasma concentrations after epidural administration to published data. The effect of ritonavir was modeled as a 67% decrease in fentanyl elimination clearance. Plasma fentanyl concentrations were simulated for six sample patient-controlled epidural labor analgesic regimens over 24 h using ritonavir and control models. Simulated data were analyzed to determine if plasma fentanyl concentrations producing a 50% decrease in minute ventilation (6.1 ng/mL) were achieved.

Results: Simulated plasma fentanyl concentrations in the ritonavir group were higher than those in the control group for all sample labor analgesic regimens. Maximum plasma fentanyl concentrations were 1.8 ng/mL and 3.4 ng/mL for the normal and ritonavir simulations, respectively, and did not reach concentrations associated with 50% decrease in minute ventilation.

Conclusion: Our model predicts that even with maximal clinical dosing regimens of epidural fentanyl over 24 h, ritonavir-induced cytochrome p450 3A4 inhibition is unlikely to produce plasma fentanyl concentrations associated with a decrease in minute ventilation.

Keywords: Analgesia obstetric, Analgesic techniques extradural, Pharmacokinetics fentanyl, Ritonavir

Introduction

The use of highly active antiretroviral therapy (HAART) in patients with human immunodeficiency virus (HIV) during pregnancy has been shown to lower the vertical transmission rate to 1-2% secondary to a decrease in maternal viral load or post-exposure prophylaxis in neonates. Ritonavir is used as a component of HAART because it is a potent inhibitor of cytochrome P450 (CYP) 3A enzymes. Ritonavir-induced inhibition of CYP3A
enzymes decreases the elimination clearance of other protease inhibitors, resulting in improved clinical efficacy of HAART with lower doses and less frequent dosing. Although ritonavir-induced CYP3A inhibition is advantageous in HIV therapy, it may be detrimental when administering other drugs, such as fentanyl and other synthetic opioids, which are metabolized by CYP3A4. Because ritonavir decreases fentanyl clearance in human volunteers by 67%, it is recommended that intravenous fentanyl doses be reduced during continuous infusions or repeated bolus administration.

Epidural analgesia with continuous or intermittent bupivacaine and fentanyl administration is a mainstay of labor analgesia. It is possible that parturients taking ritonavir may develop elevated plasma fentanyl concentrations during epidural labor analgesia. Given the practical difficulties of conducting a clinical trial, we developed a pharmacokinetic model of epidural fentanyl absorption and systemic disposition using published data. We used the model to perform simulations to determine if, during maintenance of labor analgesia with epidural fentanyl, ritonavir CYP3A4 inhibition results in plasma fentanyl concentrations associated with ventilatory depression. These simulations were conducted using varying fentanyl patient-controlled epidural analgesia (PCEA) dosing regimens over a 24 h period. Such simulations can be helpful not only in deciding whether a clinically significant drug interaction is likely, thus warranting a clinical trial, but also in assessing the “worst case scenario” that may compromise patient safety.

Methods
There are no published pharmacokinetic models of the absorption and systemic disposition of epidural fentanyl. The most detailed pharmacokinetic description of drug absorption from the epidural space is that of the biphasic absorption of both levobupivacaine and ropivacaine. Biphasic fentanyl absorption parameters were estimated by modeling the plasma fentanyl concentration versus time relationship observed in the first 20 min after epidural administration of fentanyl 80 µg in pregnant patients in the first stage of labor using the SAAM II software system (SAAM Institute, University of Washington, Seattle, WA, USA) implemented on a Windows-based (Microsoft, Redmond, WA, USA) computer. Drug absorption was described using two parallel tanks-in-series delay elements to characterize the non-instantaneous appearance of the drug in the central compartment of a three-compartment pharmacokinetic model of systemic drug disposition, which includes plasma, after epidural administration (Fig. 1). The systemic disposition of fentanyl was described using the average parameters of the three-compartment pharmacokinetic model of Scott and Stanski.
Therefore, there were only three parameters (two delay times and the distribution of absorption between the two delays) that were adjusted to fit the model predictions to the reported data. The validity of the resulting absorption-disposition model was assessed by comparing the predicted plasma fentanyl concentrations after epidural fentanyl bolus and infusion dosing with those reported by others (Fig. 2a and 2b). The predictions of the present model are consistent with the results of a previous attempt to describe the systemic pharmacokinetics of epidurally-administered fentanyl (3 µg/kg) in immature pigs in as much as the central venous plasma fentanyl concentration from 2 min until 240 min after its administration were below the lower limit of quantitation of their gas chromatography-mass spectrometry assay of 0.05 ng/mL.

Since the model fitted these data well, it was used to simulate plasma fentanyl concentrations that are produced over 24 h by six sample PCEA regimens, Groups A–F (Table 1), in a patient with normal CYP3A4 activity (normal simulations). The effect of chronic ritonavir therapy was modeled by reducing the fentanyl elimination clearance by 67% (ritonavir simulations). The simulated data were then analyzed to determine if plasma fentanyl concentrations that produce a 50% decrease in minute ventilation (EC₅₀, MV 6.1 ng/mL, 95% CI 4.9–7.2) were achieved.

**Results**

Simulated plasma fentanyl concentrations in the ritonavir group were consistently higher than those in the control group for all six PCEA regimens (Fig. 3). The maximum plasma fentanyl concentrations for Groups A-E were 1.8 ng/mL and 3.4 ng/mL for the normal and ritonavir simulations, respectively (Table 2). A 100-µg fentanyl epidural bolus at 840 min (Group F) resulted in a rapid increase in plasma fentanyl concentrations, with a maximum change of 1.3 ng/mL. However, approximately 120 min after the fentanyl bolus, both the treatment and control group plasma concentration profiles were within 10% of those predicted in the non-bolus simulations (Group E). During the simulated 24-h infusion the epidural analgesic regimens in both the normal and ritonavir simulations resulted in maximum plasma fentanyl concentrations that were approximately half of the plasma concentration that causes a 50% decrease in minute ventilation. Finally, when simulating the highest fentanyl dosing regimen, (Group F), plasma fentanyl concentrations reached 6.1 ng/mL at 72 h (Fig. 4).

**Discussion**
The results of these simulations demonstrate that ritonavir-induced CYP3A4 inhibition of fentanyl metabolism does not produce plasma fentanyl concentrations associated with a 50% decrease in minute ventilation, even when a high-dose fentanyl PCEA dosing regimen is used. Therefore, in the absence of concomitant disease processes (e.g., obstructive sleep apnea) or medications known to potentiate ventilatory depression (e.g., magnesium sulfate), a fentanyl-based PCEA regimen for labor analgesia is unlikely to increase the risk of respiratory depression in parturients receiving ritonavir. A combined spinal-epidural technique would also be predicted to be safe since the systemic absorption of intrathecally administered fentanyl has been shown to be negligible compared to epidural administration.\textsuperscript{14}

These simulations represent the ‘worst case scenario’ in fentanyl PCEA administration because it is extremely unusual for laboring patients to self-administer PCEA doses every 20 min. However, even if the most aggressive dosing regimen were used, plasma fentanyl concentrations would not reach 6.1 ng/mL until more than 70 h after initiation of the fentanyl infusion. This time is unlikely to be reached in contemporary obstetric practice, as recent labor progression data suggest 95% of nulliparous women deliver within 24 h of onset of spontaneous labor.\textsuperscript{15} These simulations also predict that the administration of a single 100-µg epidural fentanyl bolus, either when initiating epidural analgesia or 14 h later, would produce plasma fentanyl concentrations that are well below the EC\textsubscript{50,MV} of 6.1 ng/mL. These fentanyl boluses were incorporated into the simulation as they are commonly administered at the initiation of epidural labor analgesia or immediately before the onset of the second stage of labor (arbitrarily chosen at time = 840 min) to decrease the amount of local anesthetic needed to achieve effective analgesia.

We performed pharmacokinetic simulations rather than conduct a clinical study because the low rate of HIV among parturients at our institution would have made such a study difficult. In addition, the frequent blood sampling required for such a prospective study would make patient recruitment problematic. Finally, laboring patients with and without concomitant ritonavir use participating in a prospective pharmacokinetic study would have other sources of inter-individual variability, such as different PCEA use by each patient. This variability would require more complex modeling strategies to characterize the data and complicate data interpretation.

Pharmacokinetic simulations such as these serve a vital role not only in the development of novel pharmacologic agents, but also in safety monitoring during phase III and phase IV trials of newly-marketed drugs.\textsuperscript{16-18} Although no case reports exist describing the occurrence of fentanyl-induced respiratory depression in laboring women on ritonavir
receiving epidural fentanyl, the potential exists. Consequently, conducting these simulations allows investigators to determine if a safety issue exists, thereby warranting further evaluation. Given the promising results from our simulations, combined with the difficulties with conducting a clinical trial in our patient population, we felt that proceeding with a clinical trial was not warranted. In addition, since the absorption-disposition model developed for these simulations predicted plasma drug concentration that are consistent with data obtained in other animal and clinical studies of epidural fentanyl administration, it appears to predict plasma fentanyl concentrations after epidural administration with reasonable accuracy.

While the present simulations predict even with maximal dosing of epidural fentanyl over 24 h, ritonavir-induced CYP3A4 inhibition is unlikely to produce plasma fentanyl concentrations associated with decrease in minute ventilation, it should be noted that because this model was based on average data and average pharmacokinetic parameters, these simulations reflect the central tendency and do not include potential outliers. Several clinical factors such as obstructive sleep apnea, pharmacogenetic subgroups, and the presence of other factors altering CYP activity, may be present in certain patients that may affect fentanyl metabolism and the risk of respiratory depression. Since adverse events tend to occur in patients who do not lie within the norm, our results may not fully encompass the risk of respiratory depression in all patients. A clinical trial may be warranted in such vulnerable patient populations.

Several limitations exist regarding the application of these simulations to the clinical setting. While the present simulations suggest the use of prolonged epidural fentanyl infusions will be safe in patients taking ritonavir chronically, it is important to remember that they are based on a pharmacokinetic model developed from the combination of observations from pregnant patients (i.e. systemic absorption of epidural fentanyl during the first stage of labor) and non-pregnant patients (i.e. the systemic disposition of fentanyl). It is unclear how the systemic disposition of fentanyl is affected by the cardiovascular changes associated with pregnancy and labor. Another limitation is that the plasma fentanyl concentrations associated with ventilatory depression were based on data from healthy male volunteers. It is unknown if pregnancy and/or labor affect the pharmacodynamics of opioids, especially the concentration-effect relationship for ventilatory depression.

A further limitation may be the external validity of the results. The simulations were based on PCEA infusion regimens commonly used at our institution; other institutions may use different opioids, different fentanyl concentrations, or different infusion and bolus regimens, which may affect plasma opioid concentrations. The dose-response relationship for
Fentanyl combined with a local anesthetic for the maintenance of epidural analgesia has not been well studied. A review of the literature on the use of the PCEA technique with a continuous background infusion for labor analgesia found the majority of studies using fentanyl did so in concentrations ranging from 2 to 3 µg/mL, with continuous infusion rates of 3 to 6 mL/h and boluses of 3 to 5 mL with a 20-min lockout interval. Because commonly used fentanyl PCEA dosing regimens are similar to our middle-dose group (Group C), these dosing regimens (or even continuous epidural infusions without PCEA boluses) are unlikely to produce plasma fentanyl concentrations associated with ventilatory depression. Finally, these results only apply to the pregnant population and not to the non-pregnant surgical population, whose postoperative analgesic needs are different.

It should be noted that ritonavir is given in combination with other antiretroviral medications, which are known to have various effects on CYP activity. For example, efavirenz, a non-nucleoside reverse transcriptase inhibitor, has been shown to induce multiple enzymes, including CYP2B6 and CYP3A4/5, thereby altering the pharmacokinetics of methadone. In addition, several different CYP3A4 genotypes exist, which may affect the expression and metabolic activity of this enzyme. The effect of co-administered antiretroviral medications and the interpersonal variability of CYP3A4 gene expression and metabolic activity were not taken into account in the development of this simulation, and may result in differences in observed findings in clinical subjects.

Using a pharmacokinetic model of epidural fentanyl absorption and systemic disposition, we performed simulations to assess whether ritonavir-induced CYP3A4 inhibition might result in plasma fentanyl concentrations associated with ventilatory depression during labor analgesia with PCEA fentanyl. Based on these results, it appears that such an interaction is unlikely to be clinically significant, even if a high-dose fentanyl regimen is used. Although the results of these simulations suggest a low likelihood of an adverse clinical event in patients receiving both ritonavir and epidural fentanyl, caregivers should be aware of the combined effects of ritonavir and other patient factors not included in the models used to perform the simulations of this study, which may increase the risk for respiratory depression.

Disclosure

The work was supported by the Northwestern University Feinberg School of Medicine Department of Anesthesiology.

References


Figure legends

**Fig. 1:** The compartmental pharmacokinetic model describing fentanyl absorption from the epidural space and systemic disposition of fentanyl. Drug absorption was described using parallel fast and slow tanks-in-series delay elements ($D_F$ and $D_S$)\textsuperscript{8,9} to characterize the non-instantaneous appearance of drug in the central compartment ($V_C$) of a three-compartment pharmacokinetic model of systemic drug disposition, which includes plasma, after epidural administration (syringe).\textsuperscript{6} Systemic disposition of fentanyl was described with the average parameters of the three-compartment pharmacokinetic model.\textsuperscript{10} Predicted plasma concentrations after fitting the model to the data from plasma fentanyl concentration versus time data observed in the first 20 min after epidural administration of fentanyl 80 µg demonstrates the model accuracy.\textsuperscript{7}

$V_C$: central compartment; $V_F$: rapidly (fast) equilibrating peripheral compartment; $V_S$: slowly equilibrating peripheral compartment; $CL_E$: elimination clearance; $CL_F$: intercompartmental clearance to the rapidly equilibrating peripheral compartment; $CL_S$: intercompartmental clearance to the slowly equilibrating peripheral compartment.

**Fig. 2a and 2b:** Comparison of predicted plasma fentanyl concentrations (solid line) versus previously published mean (± SD) plasma fentanyl concentrations reported (dots) after epidural fentanyl bolus administration (Fig. 2a) and during continuous infusion (Fig. 2b).\textsuperscript{11} Both figures demonstrate that predicted plasma fentanyl concentrations are within one standard deviation of the reported means. (Data reproduced with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Ginosar Y, Riley ET, Angst MS. The site of action of epidural fentanyl in humans: the difference between infusion and bolus administration, Anesth Analg 2003;97:1428-38.)

**Fig. 3:** Plasma fentanyl concentration profiles for control (black line) and ritonavir (grey line) simulations that are produced by dose groups A-F (Table 1). These simulations demonstrate that inhibition of CYP3A4-mediated fentanyl elimination clearance results in a rapid increase in plasma fentanyl concentrations compared to normal CYP3A4 activity simulations. At 24 h, neither the ritonavir nor normal simulations produce a fentanyl concentration high enough to produce a 50% decrease in minute ventilation (6.1 ng/mL).\textsuperscript{13} Although the 100-µg fentanyl epidural bolus at 840 min (simulating the start of the second stage of labor) rapidly increased the plasma fentanyl concentrations by 1.3 ng/mL (Group F vs. Group E), this transient increase did not result in concentrations near the fentanyl concentration producing a 50% decrease in minute ventilation. Furthermore, the effects of this bolus on the systemic fentanyl plasma concentration dissipated within 120 min of administration.
Fig. 4: The plasma fentanyl concentration profile for ritonavir simulations in group F representing the time needed to reach concentrations associated with a 50% decrease in minute ventilation (6.1 ng/mL). Even with high-dose fentanyl, plasma concentrations do not reach clinically significant concentrations until approximately 72 h after infusion initiation.
Dose Group F
24 μg/h + 16 μg every 20 min + 100 μg every 840 min
<table>
<thead>
<tr>
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<th>100 µg fentanyl bolus</th>
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<tr>
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<td>20 min</td>
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</tr>
<tr>
<td>B</td>
<td>16 µg/h</td>
<td>20 min</td>
<td>at t = 0 min</td>
</tr>
<tr>
<td>C</td>
<td>20 µg/h</td>
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<td>None</td>
</tr>
<tr>
<td>D</td>
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</tr>
<tr>
<td>E</td>
<td>24 µg/h</td>
<td>20 min</td>
<td>None</td>
</tr>
<tr>
<td>F</td>
<td>24 µg/h</td>
<td>20 min</td>
<td>at t = 840 min</td>
</tr>
<tr>
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<td>Ritonavir</td>
<td>Ritonavir</td>
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<td>------</td>
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</tr>
<tr>
<td></td>
<td>Maximum plasma fentanyl conc at 24 h (ng/mL)</td>
<td>Plasma fentanyl AUC (ng/min/mL)</td>
<td>Maximum plasma fentanyl conc at 24 h (ng/mL)</td>
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<tr>
<td>A</td>
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<td>1516</td>
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AUC: area under curve