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

C.R. Cambic, M.J. Avram, D.K. Gupta, C.A. Wong

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1 **IJOA 13-00002**

2 ORIGINAL ARTICLE

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

5 C. R. Cambic, M. J. Avram, D. K. Gupta, C. A. Wong

6 *Department of Anesthesiology, Northwestern University Feinberg School of Medicine,*

7 *Chicago, IL, USA*

8

9 Short Title: Ritonavir and plasma fentanyl concentration

10

11 Correspondence to: C.R. Cambic, Department of Anesthesiology, Northwestern University

12 Feinberg School of Medicine, 251 E. Huron, F5-704, Chicago, IL 60611, USA

13 E-mail address: [c-cambic@md.northwestern.edu](mailto:c-cambic@md.northwestern.edu)

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**15 ABSTRACT**

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

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

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

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

39  
40 **Keywords:** Analgesia obstetric, Analgesic techniques extradural, Pharmacokinetics fentanyl,  
41 Ritonavir

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**43 Introduction**

44 The use of highly active antiretroviral therapy (HAART) in patients with human  
45 immunodeficiency virus (HIV) during pregnancy has been shown to lower the vertical  
46 transmission rate to 1-2% secondary to a decrease in maternal viral load or post-exposure  
47 prophylaxis in neonates.<sup>1</sup> Ritonavir is used as a component of HAART because it is a potent  
48 inhibitor of cytochrome P450 (CYP) 3A enzymes. Ritonavir-induced inhibition of CYP3A

49 enzymes decreases the elimination clearance of other protease inhibitors, resulting in  
50 improved clinical efficacy of HAART with lower doses and less frequent dosing.<sup>2</sup> Although  
51 ritonavir-induced CYP3A inhibition is advantageous in HIV therapy, it may be detrimental  
52 when administering other drugs, such as fentanyl and other synthetic opioids, which are  
53 metabolized by CYP3A4.<sup>3,4</sup> Because ritonavir decreases fentanyl clearance in human  
54 volunteers by 67%, it is recommended that intravenous fentanyl doses be reduced during  
55 continuous infusions or repeated bolus administration.<sup>5</sup>

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

68

## 69 **Methods**

70 There are no published pharmacokinetic models of the absorption and systemic disposition of  
71 epidural fentanyl. The most detailed pharmacokinetic description of drug absorption from the  
72 epidural space is that of the biphasic absorption of both levobupivacaine and ropivacaine.<sup>6</sup>  
73 Biphasic fentanyl absorption parameters were estimated by modeling the plasma fentanyl  
74 concentration versus time relationship observed in the first 20 min after epidural  
75 administration of fentanyl 80 µg in pregnant patients in the first stage of labor using the  
76 SAAM II software system (SAAM Institute, University of Washington, Seattle, WA, USA)  
77 implemented on a Windows-based (Microsoft, Redmond, WA, USA) computer.<sup>7</sup> Drug  
78 absorption was described using two parallel tanks-in-series delay elements to characterize the  
79 non-instantaneous appearance of the drug in the central compartment of a three-compartment  
80 pharmacokinetic model of systemic drug disposition, which includes plasma, after epidural  
81 administration (Fig. 1).<sup>8,9</sup> The systemic disposition of fentanyl was described using the  
82 average parameters of the three-compartment pharmacokinetic model of Scott and Stanski.<sup>10</sup>

83 Therefore, there were only three parameters (two delay times and the distribution of  
84 absorption between the two delays) that were adjusted to fit the model predictions to the  
85 reported data. The validity of the resulting absorption-disposition model was assessed by  
86 comparing the predicted plasma fentanyl concentrations after epidural fentanyl bolus and  
87 infusion dosing with those reported by others (Fig. 2a and 2b).<sup>11</sup> The predictions of the  
88 present model are consistent with the results of a previous attempt to describe the systemic  
89 pharmacokinetics of epidurally-administered fentanyl (3 µg/kg) in immature pigs in as much  
90 as the central venous plasma fentanyl concentration from 2 min until 240 min after its  
91 administration were below the lower limit of quantitation of their gas chromatography-mass  
92 spectrometry assay of 0.05 ng/mL.<sup>12</sup>

93 Since the model fitted these data well,<sup>7</sup> it was used to simulate plasma fentanyl  
94 concentrations that are produced over 24 h by six sample PCEA regimens, Groups A–F  
95 (Table 1), in a patient with normal CYP3A4 activity (normal simulations). The effect of  
96 chronic ritonavir therapy was modeled by reducing the fentanyl elimination clearance by 67%  
97 (ritonavir simulations).<sup>5</sup> The simulated data were then analyzed to determine if plasma  
98 fentanyl concentrations that produce a 50% decrease in minute ventilation ( $EC_{50, MV}$  6.1  
99 ng/mL, 95% CI 4.9–7.2) were achieved.<sup>13</sup>

100

## 101 Results

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

114

## 115 Discussion

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

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

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

146 Pharmacokinetic simulations such as these serve a vital role not only in the  
147 development of novel pharmacologic agents, but also in safety monitoring during phase III  
148 and phase IV trials of newly-marketed drugs.<sup>16-18</sup> Although no case reports exist describing  
149 the occurrence of fentanyl-induced respiratory depression in laboring women on ritonavir

150 receiving epidural fentanyl, the potential exists. Consequently, conducting these simulations  
151 allows investigators to determine if a safety issue exists, thereby warranting further  
152 evaluation. Given the promising results from our simulations, combined with the difficulties  
153 with conducting a clinical trial in our patient population, we felt that proceeding with a  
154 clinical trial was not warranted. In addition, since the absorption-disposition model developed  
155 for these simulations predicted plasma drug concentration that are consistent with data  
156 obtained in other animal and clinical studies of epidural fentanyl administration, it appears to  
157 predict plasma fentanyl concentrations after epidural administration with reasonable accuracy.

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

169 Several limitations exist regarding the application of these simulations to the clinical  
170 setting. While the present simulations suggest the use of prolonged epidural fentanyl infusions  
171 will be safe in patients taking ritonavir chronically, it is important to remember that they are  
172 based on a pharmacokinetic model developed from the combination of observations from  
173 pregnant patients (i.e. systemic absorption of epidural fentanyl during the first stage of labor)<sup>7</sup>  
174 and non-pregnant patients (i.e. the systemic disposition of fentanyl).<sup>10</sup> It is unclear how the  
175 systemic disposition of fentanyl is affected by the cardiovascular changes associated with  
176 pregnancy and labor. Another limitation is that the plasma fentanyl concentrations associated  
177 with ventilatory depression were based on data from healthy male volunteers.<sup>13</sup> It is unknown  
178 if pregnancy and/or labor affect the pharmacodynamics of opioids, especially the  
179 concentration-effect relationship for ventilatory depression.

180 A further limitation may be the external validity of the results. The simulations were  
181 based on PCEA infusion regimens commonly used at our institution; other institutions may  
182 use different opioids, different fentanyl concentrations, or different infusion and bolus  
183 regimens, which may affect plasma opioid concentrations. The dose-response relationship for

184 fentanyl combined with a local anesthetic for the maintenance of epidural analgesia has not  
185 been well studied. A review of the literature on the use of the PCEA technique with a  
186 continuous background infusion for labor analgesia found the majority of studies using  
187 fentanyl did so in concentrations ranging from 2 to 3  $\mu\text{g}/\text{mL}$ , with continuous infusion rates of  
188 3 to 6 mL/h and boluses of 3 to 5 mL with a 20-min lockout interval.<sup>19</sup> Because commonly  
189 used fentanyl PCEA dosing regimens are similar to our middle-dose group (Group C), these  
190 dosing regimens (or even continuous epidural infusions without PCEA boluses) are unlikely  
191 to produce plasma fentanyl concentrations associated with ventilatory depression. Finally,  
192 these results only apply to the pregnant population and not to the non-pregnant surgical  
193 population, whose postoperative analgesic needs are different.

194 It should be noted that ritonavir is given in combination with other antiretroviral  
195 medications, which are known to have various effects on CYP activity. For example,  
196 efavirenz, a non-nucleoside reverse transcriptase inhibitor, has been shown to induce multiple  
197 enzymes, including CYP2B6 and CYP3A4/5, thereby altering the pharmacokinetics of  
198 methadone.<sup>20,21</sup> In addition, several different CYP3A4 genotypes exist, which may affect the  
199 expression and metabolic activity of this enzyme.<sup>22</sup> The effect of co-administered  
200 antiretroviral medications and the interpersonal variability of CYP3A4 gene expression and  
201 metabolic activity were not taken into account in the development of this simulation, and may  
202 result in differences in observed findings in clinical subjects.

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

212

### 213 **Disclosure**

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

216

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- 277
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- 279

**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  $D_S$ )<sup>8,9</sup> 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).<sup>6</sup> Systemic disposition of fentanyl was described with the average parameters of the three-compartment pharmacokinetic model.<sup>10</sup> 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  $\mu\text{g}$  demonstrates the model accuracy.<sup>7</sup>

$V_C$ : 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.

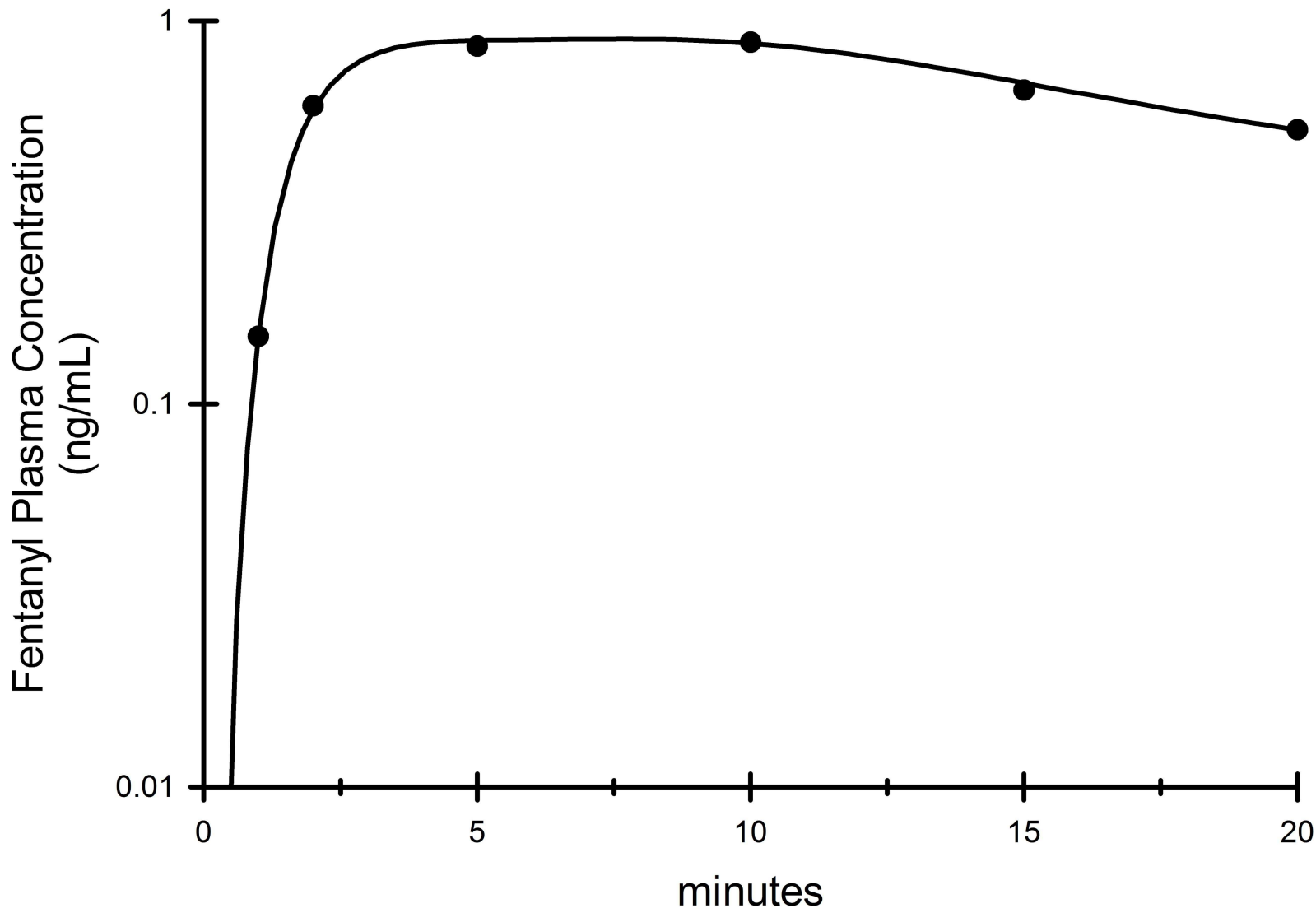
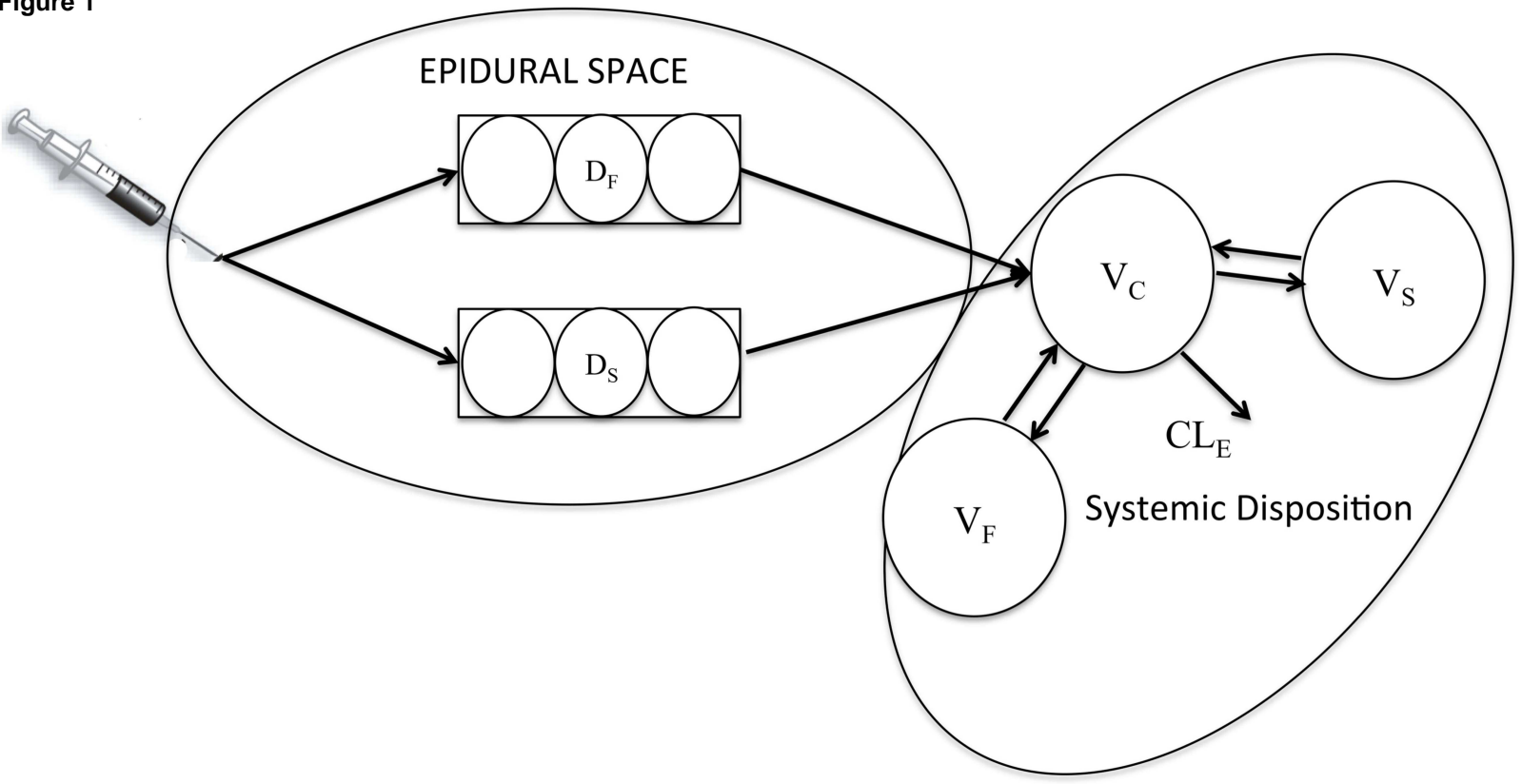
**Fig. 2a and 2b:** Comparison of predicted plasma fentanyl concentrations (solid line) versus previously published mean ( $\pm$  SD) plasma fentanyl concentrations reported (dots) after epidural fentanyl bolus administration (Fig. 2a) and during continuous infusion (Fig. 2b).<sup>11</sup> Both figures 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).<sup>13</sup> Although the 100- $\mu\text{g}$  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.

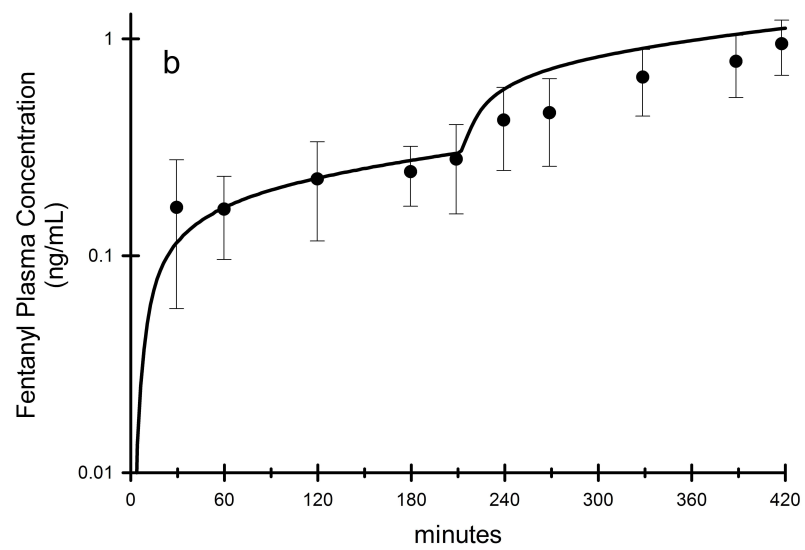
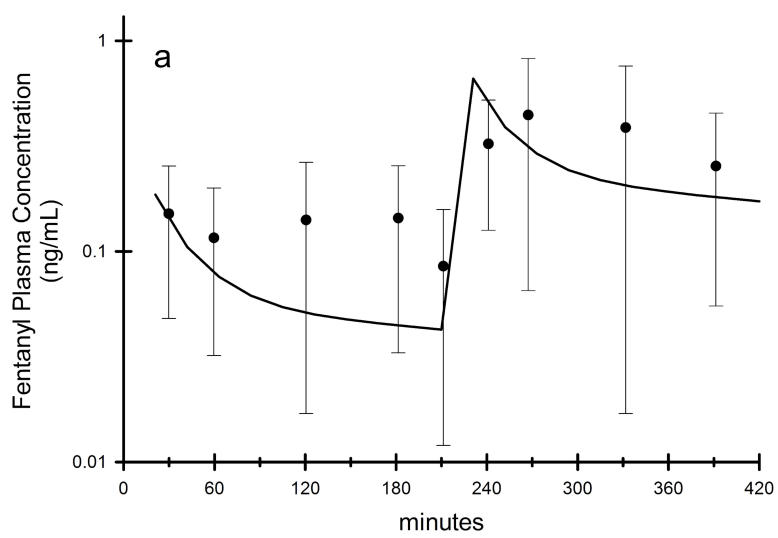
314 **Fig. 4:** The plasma fentanyl concentration profile for ritonavir simulations in group F  
315 representing the time needed to reach concentrations associated with a 50% decrease in  
316 minute ventilation (6.1 ng/mL). Even with high-dose fentanyl, plasma concentrations do not  
317 reach clinically significant concentrations until approximately 72 h after infusion initiation.

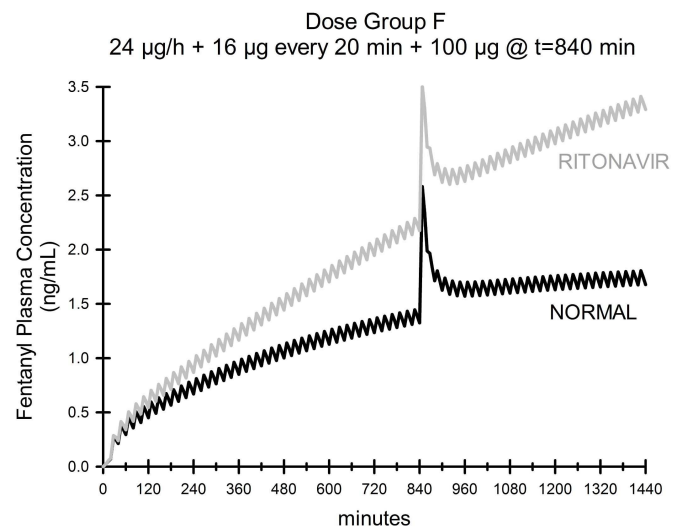
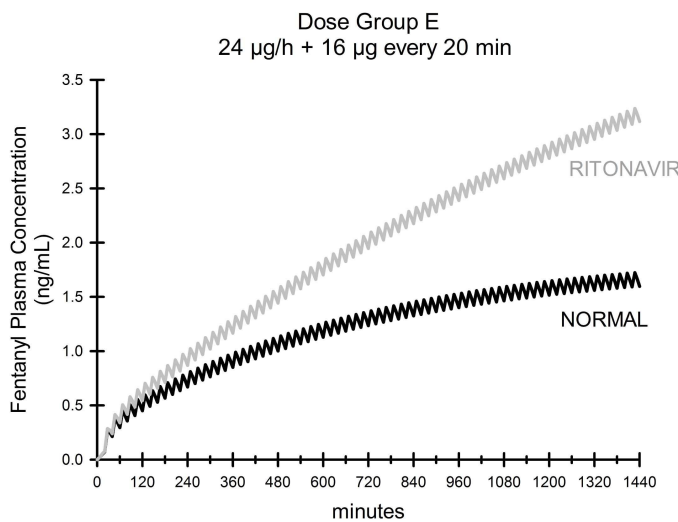
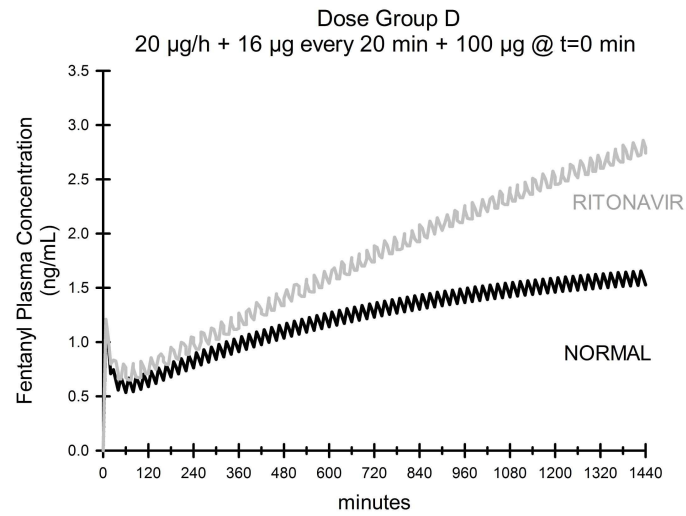
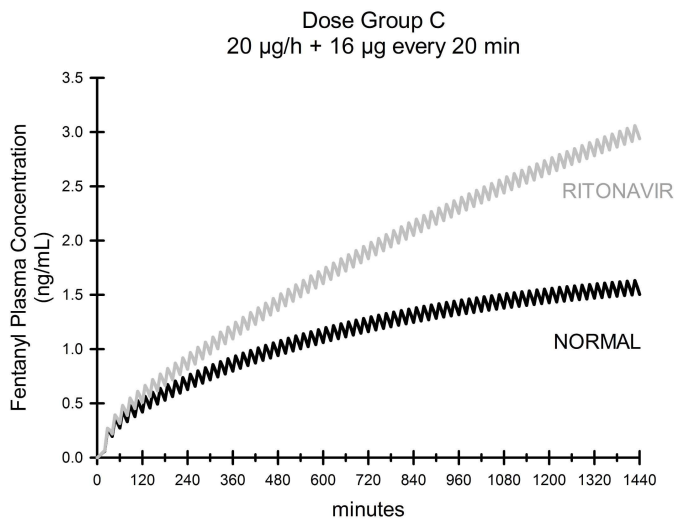
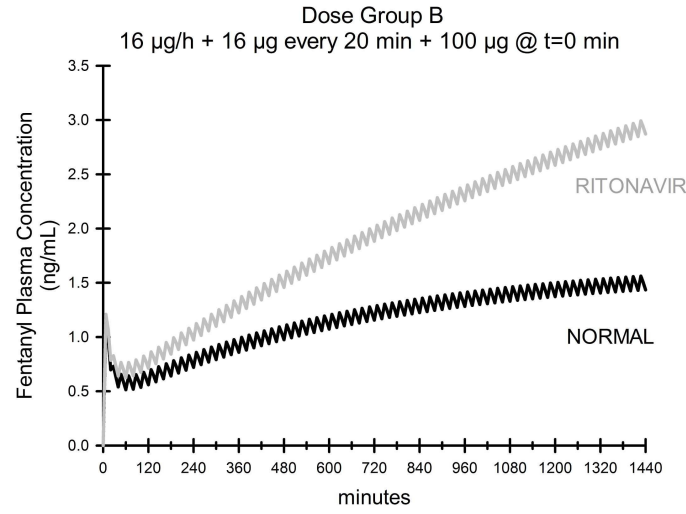
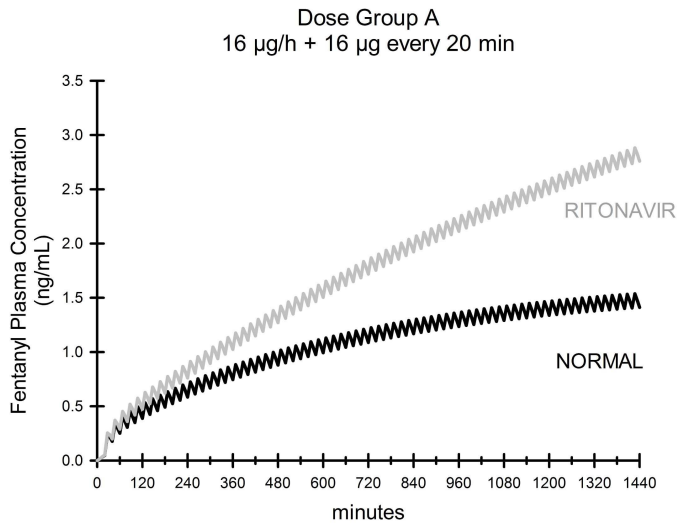
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Figure 1



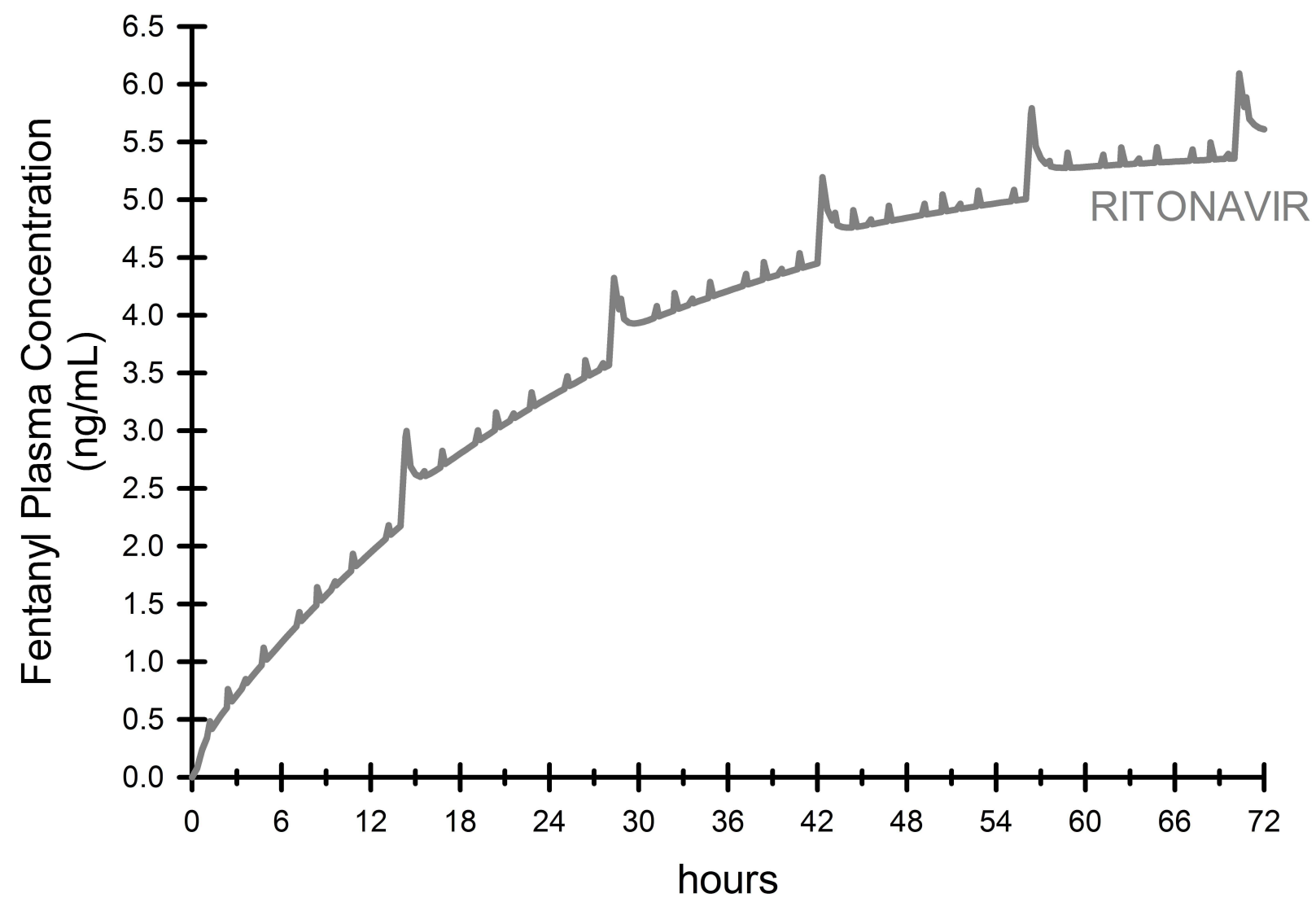
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Dose Group F

24  $\mu\text{g}/\text{h}$  + 16  $\mu\text{g}$  every 20 min + 100  $\mu\text{g}$  every 840 min

**Table 1 Patient-controlled epidural analgesia dose groups**

|   | Fentanyl infusion rate | 16 µg fentanyl bolus interval | 100 µg fentanyl bolus |
|---|------------------------|-------------------------------|-----------------------|
| A | 16 µg/h                | 20 min                        | None                  |
| B | 16 µg/h                | 20 min                        | at t = 0 min          |
| C | 20 µg/h                | 20 min                        | None                  |
| D | 20 µg/h                | 20 min                        | at t = 0 min          |
| E | 24 µg/h                | 20 min                        | None                  |
| F | 24 µg/h                | 20 min                        | at t = 840 min        |

**Table 2 Summary of simulation results**

|   | Control                                      |                                 | Ritonavir                                    |                                 |
|---|--|---------------------------------|--|---------------------------------|
|   | Maximum plasma fentanyl conc at 24 h (ng/mL) | Plasma fentanyl AUC (ng/min/mL) | Maximum plasma fentanyl conc at 24 h (ng/mL) | Plasma fentanyl AUC (ng/min/mL) |
| A | 1.5  | 1516                            | 2.9  | 2448                            |
| B | 1.6  | 1654                            | 3.0  | 2714                            |
| C | 1.6  | 1612                            | 3.1  | 2604                            |
| D | 1.7  | 1750                            | 3.2  | 2878                            |
| E | 1.7  | 1709                            | 3.2  | 2759                            |
| F | 1.8  | 1809                            | 3.4  | 2908                            |

AUC: area under curve