Anesthesiology
1999; 91:681–5

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.[1] The protease inhibitors saquinavir, ritonavir, indinavir, and nelfinavir greatly reduce the viral load and increase CD4+ counts, especially if combined with reverse transcriptase inhibitors.[2]

Most of the protease inhibitors are also inhibitors of the cytochrome P450 (CYP) 3A4 enzyme, important for the metabolism of several drugs,[3] 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.[4,5]

Fentanyl is a synthetic opioid analgesic widely used as intravenous boli, as continuous infusions, and, in recent years, also by transdermal route.[6] It is metabolized mainly by CYP3A4, although some studies have suggested that also other CYPs may play a minor role.[7–9] Because fentanyl has an extraction ratio from 0.8–1.0,[10] its rate of hepatic elimination should be more dependent on liver blood flow than on changes in its intrinsic clearance.[11,12] In our earlier study, the azole antimycotic itraconazole, a potent inhibitor of CYP3A4, did not affect the elimination of fentanyl.[11] Although ritonavir may be an even more potent inhibitor of CYP3A4 than is itraconazole,[5,13] 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,[14–16] 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

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Received from the Departments of Anesthesia and Clinical Pharmacology, University of Helsinki, Finland. Submitted for publication February 1, 1999. Accepted for publication April 30, 1999. Supported in part by the Janssen Research Foundation, Beerse, Belgium, and the Helsinki University Central Hospital Research Fund.

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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.[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 12 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 μg/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°C until analysis of ritonavir and fentanyl concentrations. Fentanyl concentrations were determined by a specific radioimmunoassay method,[17] and those of ritonavir by a high-performance liquid chromatography.[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 μg/ml, and the coefficient of variation was 3.8, 2.5, and 2.9% at 0.608, 4.72, and 11.16 μg/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 (AUC_{0-18}) was calculated by use of the trapezoidal rule, and the $AUC_{0-\infty}$ 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.[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 ± SD. All the data were analyzed with the statistical program Systat for Windows, version 6.0 (Systat, Evanston, IL).

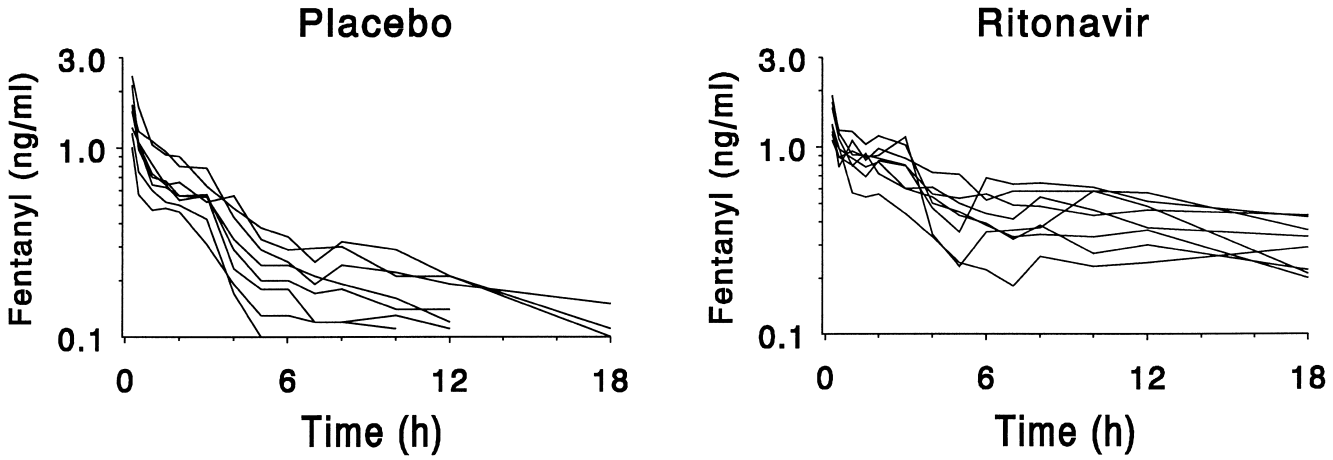

Fig. 1. Plasma concentrations of fentanyl after an intravenous dose of 5 μg/kg fentanyl following pretreatment with oral placebo (*left*) or ritonavir (*right*) in 11 healthy volunteers. Drug-administration regimen as in table 1.

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 $AUC_{0-\infty}$ 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

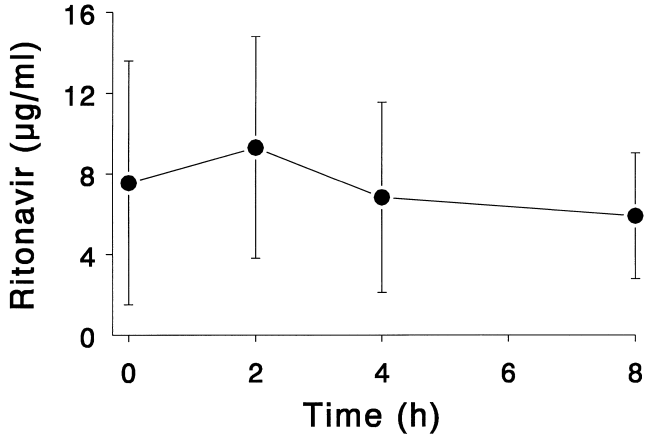

Fig. 2. Plasma concentrations of ritonavir (mean ± SD) on the second day of the study in 11 healthy volunteers. On the first day ritonavir 200 mg was given orally three times, and on the second day the ritonavir dose was increased to 300 mg three times. Time 0 h refers to the time of fentanyl injection 2 h after the afternoon dose of ritonavir.

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

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

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 hours after fentanyl injection; $AUC_{0-\infty}$ = area under fentanyl plasma concentration–time curve extrapolated to infinity.

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

potent inhibitor of CYP3A4, itraconazole, had no effect on the pharmacokinetics of fentanyl in our previous study,[11] although in the present study ritonavir decreased the clearance of fentanyl considerably. By use of the "well-stirred" model of hepatic elimination,[12] we can estimate that up to a 90% inhibition of intrinsic fentanyl clearance would be required to cause the 67% decrease observed in total clearance of fentanyl. Ritonavir is, however, one of the most potent inhibitors of CYP3A4, with a K_i value of 0.019 μM.[5] Our plasma concentrations of ritonavir ranged from 1.2 to 22.2 μg/ml (1.6 to 30.7 μM), being at least 100-fold above the K_i of ritonavir. Because itraconazole has a K_i of 0.27 μM,[13] which is at the level achieved during itraconazole treatment at 200 mg once daily,[11] it is plausible that this reduction in fentanyl elimination during concomitant ritonavir may have been caused entirely by inhibition of CYP3A4 function. Unfortunately, no data are available on the effect of HIV protease inhibitors on liver blood flow, so we have no conclusive evidence as to the exact mechanism of interaction between ritonavir and fentanyl.

Secondary peaks of plasma fentanyl concentrations appeared in six subjects between 5 and 9 h after fentanyl administration. 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.[20,21] In addition to the liver, CYP3A4 is expressed also in the gut wall.[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 glucuronyltransferase,[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.[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.[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.[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.

The authors thank Kerttu Mårtensson and Jouko Laitila for skillful determination of ritonavir plasma concentrations, and the Janssen Research Foundation for bioanalysis of fentanyl plasma concentrations.

References

1. Barry M, Gibbons S, Back D, Mulcahy F: Protease inhibitors in patients with HIV disease. Clin Pharmacokinet 1997; 32:194–209

2. Barry M, Mulcahy F, Back DJ: Antiretroviral therapy for patients with HIV disease. Br J Clin Pharmacol 1998; 45:221–8

3. von Moltke LL, Greenblatt DJ, Grassi JM, Granda BW, Xiang Duan S, Fogelman SM, Daily JP, Harmatz JS, Shader RI: Protease inhibitors as inhibitors of human cytochromes P450: High risk associated with ritonavir. J Clin Pharmacol 1998; 38:106–11

4. Kumar GN, Rodrigues AD, Buko AM, Denissen JF: Cytochrome P450-mediated metabolism of the HIV-1 protease inhibitor ritonavir (ABT-538) in human liver microsomes. J Pharmacol Exp Ther 1996; 277:423–31

5. Eagling VA, Back DJ, Barry MG: Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. Br J Clin Pharmacol 1997; 44:190–4

6. Clotz MA, Nahata MC: Clinical uses of fentanyl, sufentanil and alfentanil. Clin Pharm 1991; 10:581–93

7. Tateishi T, Krivoruk Y, Ueng Y-F, Wood AJJ, Guengerich FP, Wood M: Identification of human liver cytochrome P-450 3A4 as the enzyme responsible for fentanyl and sufentanil N-dealkylation. Anesth Analg 1996; 82:167–72

8. Guitton J, Buronfosse T, Desage M, Lepape A, Brazier JL, Beaune P: Possible involvement of multiple cytochrome P450S in fentanyl and sufentanil metabolism as opposed to alfentanil. Biochem Pharmacol 1997; 53:1613–9

9. Labroo RB, Paine MF, Thummel KE, Kharasch ED: Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: Implications for interindividual variability in disposition, efficacy, and drug interactions. Drug Metab Dispos 1997; 25:1072–80

10. Bailey PL. Stanley TH: Intravenous opioid anesthetics, Anesthesia. Edited by Miller RD. New York, Churchill Livingstone, 1994, pp 353–7

11. Palkama VJ, Olkkola KT, Neuvonen PJ: The CYP3A4 inhibitor itraconazole has no effect on the pharmacokinetics of iv fentanyl. Br J Anaesth 1998; 81:598–600

12. Rowland M, Tozer TN: Elimination, Clinical Pharmacokinetics: Concepts and Applications, 3rd Ed. Edited by Rowland M, Tozer TN. Baltimore, Williams and Wilkins, 1995, pp 156–183

13. Back DJ, Tjia JF: Comparative effects of the antimycotic drugs ketoconazole, fluconazole, itraconazole and terbinafine on the metabolism of cyclosporin by human liver microsomes. Br J Clin Pharmacol 1991; 32:624–6

14. Breitbart W, Rosenfeld BD, Passik SD, McDonald MV, Thaler H, Portenoy RK: The undertreatment of pain in ambulatory AIDS patients. Pain 1996; 65:243–9

15. Lebovits AH, Smith G, Maignan M, Lefkowitz M: Pain in hospitalized patients with AIDS: Analgesic and psychotropic medications. Clin J Pain 1994;10:156–61

16. Wesselmann U: Schmerzsyndrome bei AIDS. Anaesthesist 1996; 45:1004–14

17. Woestenborghs R, Stanski D, Scott J, Heykants J: Assay of methods for fentanyl in serum: Gas-liquid chromatography versus radioimmunoassay. ANESTHESIOLOGY 1987; 67:85–90

18. Marsh KC, Eiden E, McDonald E: Determination of ritonavir, a new HIV protease inhibitor, in biological samples using reversed-phase high-performance liquid chromatography. J Chromatogr B 1997; 704: 307–13

19. Gibaldi M, Perrier D: Pharmacokinetics, 2nd ed. New York, Marcel Dekker, 1982, pp 409–17

20. Stoeckel H, Hengstmann JH, Schüttler J: Pharmacokinetics of fentanyl as a possible explanation for recurrence of respiratory depression. Br J Anaesth 1979; 51:741–4

21. McClain DA, Hug CC: Intravenous fentanyl kinetics. Clin Pharmacol Ther 1980; 28:106–14

22. Lown KS, Kolars JC, Thummel KE, Barnett JL. Kunze KL, Wrighton SA, Watkins PB: Interpatient heterogeneity in expression of CYP3A4 and CYP3A5 in small bowel. Drug Metab Dispos 1994; 6:947–55

23. Handal KA, Schauben JL, Salamone FR: Naloxone. Ann Emerg Med 1983; 12:438–45

24. Lea AP, Faulds D: Ritonavir. Drugs 1996; 52:541–6

25. Jeal W, Benfield P. Transdermal fentanyl: A review of its pharmacological properties and therapeutic efficacy in pain control. Drugs 1997; 53:109–38