Rifampin reduces the analgesic effect of transdermal fentanyl

TO THE EDITOR: Fentanyl, a synthetic opioid commonly used in anesthesia, is predominantly metabolized by CYP3A4.[1] Although fentanyl toxicity caused by coadministration of CYP3A4 inhibitors (eg, itraconazole) has been reported,[2] little is known about CYP3A4 inducers. The following case illustrates an interaction between transdermally administered fentanyl and rifampin resulting in the loss of the analgesic effect of fentanyl.

Case Report. A 61-year-old man with recurrence of parotid gland adenocarcinoma was admitted to our hospital for relief of severe pain in the left shoulder and chest due to lung metastasis. He had previously been treated for pain with slow-release morphine 40 mg/day; however, severe nausea and vomiting developed. Thus, transdermal fentanyl patch (1.67 mg every 3 days) was started for pain relief (day 1). Serum concentrations were measured by HPLC, and the ratio of serum fentanyl concentration to dose (C/D ratio) was used to assess the disposition kinetics.

Serum concentrations of fentanyl at 48 and 72 hours after day 1 treatment were 0.90 ng/mL (C/D ratio 0.54) and 0.77 ng/mL (0.46), respectively (Figure 1). The reported minimal effective concentration of fentanyl for pain relief ranged from 0.2 to 1.2 ng/mL.[3] On day 5, the fentanyl dose was increased by 2.5 mg every 3 days due to insufficient pain control. On day 7, oral rifampin 300 mg/day, isoniazid 300 mg/day, and ethambutol 750 mg/day were started for treatment of pulmonary tuberculosis. The following day, severe pain developed.

Fentanyl serum concentrations 48 and 72 hours after treatment on day 8 were 0.53 and 0.21 ng/mL, respectively, and the corresponding C/D ratios were 0.21 and 0.08, respectively. Even after a dose titration up to 7.5 mg every 3 days and coadministration of loxoprofen 180 mg/day, the patient still complained of moderate pain. The fentanyl serum concentration 72 hours after treatment on day 19 (7.5 mg every 3 days) was 0.69 ng/mL. He had also received other drugs, including oral pyridoxine 30 mg/day, haloperidol 0.75 mg/day, and prochlorperazine maleate 15 mg/day for at least one month.

Discussion. Based on the Naranjo probability scale, the interaction of rifampin with fentanyl in this case was probable.[4] There is no report describing pharmacokinetic and pharmacodynamic interactions between fentanyl and the concomitant drugs described here except for respiratory depression induced by haloperidol. Similar to alfentanil,[5] concomitant use of rifampin, a potent inducer of CYP3A4, was associated with reduced serum concentration and pharmacologic efficacy of fentanyl.

It is interesting to note that this interaction occurred even when fentanyl was administered transdermally. With the introduction of rifampin, the C/D ratio decreased to 20–50% of the baseline value, indicating that enhanced

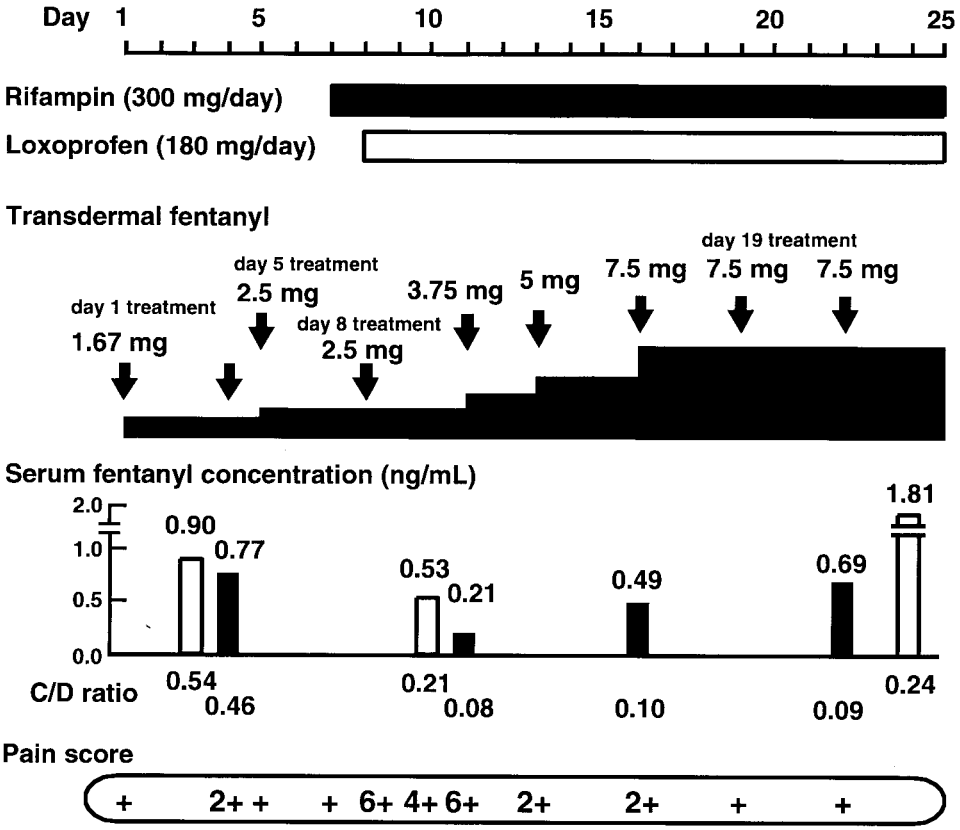

Figure 1. Fentanyl concentration profile. Pain score was assessed using the verbal descriptive scale (0 = pain free to 10 = severe). C/D ratio = serum fentanyl concentration to dose ratio. White and black columns indicate serum concentrations at 48 and 72 hours, respectively, after the patch was placed on the patient.

clearance had occurred. As shown in this case, when rifampin and fentanyl are used concomitantly, the analgesic effect of fentanyl may be considerably reduced. Thus, an increase in fentanyl dosage needs to be considered.

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Comment: death of twins after intravenous varicella zoster immunoglobulin

TO THE EDITOR: We wish to comment on the report about the death of 2 newborns associated with the use of varicella zoster immunoglobulin (VZIG; Varitect CP, Biotest Pharma GmbH, Dreieich, Germany).[1] The case was reported to the Biotest Department of Drug Safety in April 2003 and has been investigated with great diligence. According to the requirements of German drug law, we have also informed our supervising governmental authority, the Paul-Ehrlich-Institut. The result of our investigation is as follows:

1. In our production and quality control records, we found no indication of any technical failure of the lot used in India (lot 155011). No adverse drug reactions have been reported for this lot by other hospitals.
2. Varitect CP was diluted in 10 mL of distilled water. However, Varitect CP is a ready-for-use solution and must not be diluted; this is mentioned in the instructions for use.
3. Along with Varitect CP, the infants also received intramuscular vitamin K, intravenous ranitidine in 1 mL of distilled water, and intravenous acyclovir in 10 mL of distilled water.
4. The total volume of distilled water administered to the babies via the diluted drugs was >20 mL. The total blood volume of a newborn weighing around 2000 g is approximately 160–180 mL.
5. Our research department investigated the effect of such dilution to whole blood. If undiluted Varitect CP is mixed with whole blood, no hemolysis occurs. However, if it is mixed with distilled water, hemolysis is induced.

In view of these facts, we came to the conclusion that the death of the 2 babies was a result of hemolysis caused by the administration of >20 mL of distilled water with various drugs. The total blood volume was diluted by >10%. In our opinion, the death of the 2 infants was caused by inappropriate actions of the physician and is not suspected to be an adverse drug reaction.

Because Bhambhani et al.'s letter does not report the full information about the case (eg, total volume of distilled water infused), we chose to present the assessment of Varitect CP's marketing authorization holder.

Both authors are employees of Biotest AG, the parent company of Biotest Pharma GmbH, the marketing authorization holder of Varitect CP.

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AUTHORS' REPLY: We read the comments of Pabst and Dehnicke, on behalf of the manufacturers of Varitect CP (Biotest), with interest. We would like to reiterate that acute transfusion–related lung injury (TRALI) is not an indicator that the pharmaceutical manufacturer was deficient in good manufacturing practices. TRALI is a reaction between transfused antileukocyte antibodies and recipient granulocytes. The twins may have had the same genetic make-up and similar granulocyte antigens, causing both to react adversely. The manufacturer cannot be held responsible for this reaction. We wholeheartedly agree with Pabst and Dehnicke that technical failures in the manufacturing process are not to blame.

TRALI is a diagnosis arrived after exclusion of other possibilities. The Naranjo score is an attempt to estimate the probability that the adverse reaction was caused by a drug. The twins we reported on died catastrophically with pulmonary hemorrhage within 5 minutes of each other, and within 15 minutes of receiving Varitect CP. Pabst and Dehnicke suggest 4 alternate possibilities, which need to be examined.

They suggest that vitamin K received by the babies 12 hours earlier, acyclovir received 8 hours earlier, or ranitidine received 5 hours earlier

Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.–ED.

could have been culprits. Given the chronology of events, this seems unlikely. The Naranjo score for each of these is below 1 and so the association is doubtful.

The fourth suggestion is that the water used to dilute the drugs may have caused the deaths. Their letter says that 20 mL of water was used (10 mL with Varitect CP and 10 mL with acyclovir), and that experiments performed at Biotest found that this can induce hemolysis. There are notable inaccuracies here.

First, hemolysis is not the same thing as pulmonary hemorrhage. The twins in our original report died of pulmonary hemorrhage, not hemolysis and anemia. Secondly, 10 mL of water for injection with acyclovir had been given 8 hours previously. This would have been sufficient time for it to equilibrate within the body before Varitect CP was given.

Finally, regarding the dilution of acyclovir, this was diluted as per the manufacturer's instructions and administered to the babies slowly over 30 minutes. In a letter dated June 4, 2003 (forwarded to us for reply), Biotest suggested that the babies might have died because of the use of undiluted acyclovir. We wrote to reassure them about the dilution of acyclovir. Now they write that dilution, rather than the use of undiluted acyclovir, contributed to the deaths. This change in stance shows a lack of conviction and a desire to place blame anywhere but on Varitect CP.

Ultimately, TRALI still appears a strong candidate for the cause of the twins' death from pulmonary hemorrhage. The experiment by Biotest underlines this. Although it is not caused by defects in the manufacturing process, TRALI is more likely to occur with an intravenous preparation than with the standard intramuscular preparation.

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Comment: supratherapeutic response to ezetimibe administered with cyclosporine

TO THE EDITOR: I read with interest the article by Koshman et al.[1] I agree, as mentioned in the article, that this particular patient appears to have had a "supratherapeutic" response to ezetimibe. However, I suspect that this response may not be due—or at least, not entirely—to the interaction with cyclosporine. As pointed out in the article, an interaction between ezetimibe and cyclosporine deemed to be clinically significant has been reported. However, the data concerning lipid alterations were not reported. A premarketing dose-ranging study of ezetimibe that included 243 subjects who received doses between 0.25 and 40 mg/day demonstrated a flattened dose–response curve.[2,3] Mean low-density lipoprotein cholesterol (LDL-C) was reduced by 9.9%, 12.6%, 16.4%, 18.7%, and 20.0% in the patients randomized to receive ezetimibe 0.25, 1, 5, 10, 20, and 40 mg, respectively, after 8 weeks of treatment.

Similarly, 190 patients were administered a structural analog (active metabolite) of ezetimibe (SCH 48461) with doses ranging from 1 to 400 mg.[4] Mean LDL-C reduction ranged from 0.6% to 15.5%. These data suggest that if cyclosporine had increased serum total ezetimibe or ezetimibe glucuronide within the range of the doses studied above, the LDL-C response in Koshman et al.'s[1] case would not be due to the drug–drug interaction.

An alternative hypothesis is that this patient is a hyper-absorber of cholesterol and, therefore, falls on the extreme end of the Gaussian curve for LDL-C responses to an inhibitor of cholesterol absorption.[5] These types of patients tend to have a lower rate of cholesterol synthesis and fall on the opposite end of the Gaussian curve for LDL-C responses to statins. In this case,[1] the patient's baseline LDL-C was 156 mg/dL when he was started on atorvastatin 10 mg/day. The dosage was gradually titrated to 60 mg/day, which resulted in an LDL-C level of 103 mg/dL. This represents an LDL-C change of only 34%, which was considerably less than expected based on the manufacturer's prescribing information (50% for 40 mg and 60% for 80 mg).[6] Thus, this patient had a less-than-expected response to statin therapy.

Ziajka et al.[7] demonstrated that the initial response to a statin predicted the subsequent response to the addition of ezetimibe ($r = 0.77$; $p < 0.001$). In this retrospective analysis, the patient's actual response was compared with predicted response (manufacturer's prescribing information) for the agent and dose used. The additional decrease in LDL-C after the addition of ezetimibe ranged from 6% to 60%. Patients who responded poorly to a statin had the largest reduction in LDL-C when ezetimibe was added. We have found similar results in a prospective, randomized study of ezetimibe and simvastatin that was designed to confirm data presented at the 2005 Annual Meeting of the American College of Clinical Pharmacy.[8] Patients in our study will be phenotyped for absorption efficiency in an effort to aid in a more suitable drug selection. This case provides a good opportunity to educate clinicians on the importance of variability in cholesterol absorption and synthesis on the observed response to lipid-lowering agents.

Dr. Ito has served as a consultant and speaker for Kos Pharmaceuticals, Merck & Co., Merck/Schering-Plough Pharmaceuticals, and AstraZeneca and has received research grants from Kos Pharmaceuticals and Merck & Co.

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AUTHORS' REPLY: We appreciate Dr. Ito's insightful comments. We agree that inter-individual variability in response to lipid-lowering therapy is complex and may be attributed to a host of intrinsic or genetically determined factors, as well as to familiar extrinsic factors such as diet and medication adherence.

While Ito suggested that our patient was hyporesponsive to atorvastatin, we provide more complete data to refute this claim. With a gradual upward dosage titration, the patient achieved a 42% low-density lipoprotein cholesterol (LDL-C) reduction 14 months after transplantation (Table 1). In a systematic review of randomized controlled trials, mean LDL-C reductions of 49% (95% CI 44% to 53%) with atorvastatin 40 mg/day and 55% (95% CI 48% to 61%) with atorvastatin 80 mg/day have been demonstrated.[1] Our patient demonstrated an LDL-C reduction consistent with these observations, which is notable considering the negative impact on lipids expected from immunosuppressant medications. Cyclosporine-containing regimens may increase LDL-C levels by up to 57%.[2] Additionally, heart transplant patients treated with prednisone have LDL-C values approximately 22% higher after 12 months than patients receiving a steroid-free regimen.[3] Consequently, the true baseline LDL-C level for this patient after transplantation was likely significantly higher; therefore, his LDL-C response to atorvastatin was probably >42%.

We also agree that LDL-C reductions achieved with ezetimibe were remarkably consistent across the range of doses evaluated in the preclinical studies, and would add that results have also been concordant across multiple patient sub-groups. However, ezetimibe produces a wide range of LDL-C reduction that varies between individuals. Given that our patient had a "normal" statin response, we doubt that he was a hyper-absorber of cholesterol. Perhaps Ito's study will help identify patients with a genetic phenotype who are more efficient cholesterol absorbers and expected to be ezetimibe hyper-responders; however, this hypothesis remains speculative.

Recently, a study evaluating the possible genetic basis for the wide range of inter-individual variation in LDL-C response to ezetimibe demonstrated that a common variant in the drug's molecular target in the brush border of the intestinal wall (Nieman-Pick C1 Like 1 protein [NPC1L1]) was significantly associated with a hyper-response.[4] These investigators demonstrated that this genetic variation, defined by a 3-site single nucleotide polymorphism, produced a unique NPC1L1 haplotype in 1 of 8 subjects. Twelve weeks of treatment with ezetimibe 10 mg/day produced a 35.2% reduction in LDL-C in the subjects with this variant NPC1L1 haplotype, compared with a 23.6% LDL-C reduction in those with the most common NPC1L1 haplotype ($p = 0.02$). We can neither confirm nor refute whether this genetic variation was involved in our patient, but it is plausible.

We hope that Ito's comments and our reply have provided further insight into the complexity and interrelationship of the genetic and extrinsic factors which might account for inter-individual variability in responses seen with ezetimibe. On the basis of current evidence and knowledge about this drug, we maintain that ezetimibe should be initiated at a lower than recommended dose (≤5 mg/day) and titrated upward with careful and consistent monitoring in patients concomitantly receiving cyclosporine.

Table 1. LDL-C Response to Atorvastatin Dosage Titration

Timeline	Atorvastatin Dosage (mg/day)	LDL-C (mg/dL)	Incremental LDL-C Reduction (%)	LDL-C Reduction from Baseline (%)
Pretreatment (baseline)		156		
~6 wk post-treatment	10	118	24.4	24.4
~7 mo post-treatment	20	111	5.9	28.9
~8.5 mo post-treatment	40	99	10.8	36.5
~14 mo post-treatment	60	90	9.1	42.3

LDL-C = low-density lipoprotein cholesterol.

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Comment: pathophysiology of mifepristone-induced septic shock due to *Clostridium sordellii*

TO THE EDITOR: We were very interested in the article written by Dr. Miech about pathophysiology of mifepristone-induced septic shock.[1] Several recent deadly cases in

North America (California, in particular) have not been clearly elucidated as to their cause and require further study to understand the connection between the use of mifepristone and misoprostol for early abortion, and the alarming rate of severe bacterial infection leading to death. All the cases occurred through the vaginal application of misoprostol. The most recent recommendation by the Food and Drug Administration (FDA) underscores the particular attention that must be paid to the use of these drugs prior to their widespread, generalized use in developing countries, where the rate of bacterial infection is very high. In Africa, the high frequency of genital infections, along with poor medical care, may result in a significant number of deaths if the use and application of mifepristone and misoprostol are not reexamined. This is especially true in light of the increased use in Africa of spermicide, which enhances genital bacteria carriage.[2]

A recent fatal case (in California) was that of my (Pr. Sicard) 34-year-old daughter, the mother of 2 children. Five days after taking mifepristone and misoprostol, which was taken vaginally 24 hours after the mifepristone, she died in just a few hours from an infection and septic shock. The day before her death, she experienced bleeding, severe abdominal pain, and dizziness; 2 days before, she presented all the signs of an adrenal insufficiency (ie, hypotension, extreme fatigue).

Three issues seem important: (1) The fatal consequence of the inhibition of adrenal reaction during an acute genital infection linked to the death of the embryo, if *Clostridium* is present. (2) The lack of specificity of symptoms 2 or 3 days after taking mifepristone and misoprostol. Abdominal pain and bleeding are common with this drug combination. Lack of awareness of the severity of the situation at this moment is dangerous. (3) Combining mifepristone with misoprostol through vaginal application is extremely common in Anglo-Saxon countries, and specifically indicated in North America. Vaginal application is prohibited in France, where misoprostol can be prescribed only in oral form, and it is contraindicated in case of infection. There are no reported cases of such life-threatening bacterial infections in France.

Lastly, would it be useful to systematically give an antibiotic one day prior, during, and after the absorption of mifepristone, to eradicate *Clostridium*, and give dexamethasone in case of suspicion of the beginning of septic shock?

The alarming rate of deaths in healthy, young women in North America must be carefully examined prior to the generalized use of these drugs in developing countries. Issues that remain unaddressed are (1) the relationship between the vaginal application of misoprostol relative to the cause of severe bacterial infection, leading to death; (2) the effect of spermicide or other intra-uterine device as a carriage for bacteria, increasing the likelihood of severe infection following the use of mifepristone and misoprostol; and (3) whether the FDA's recommendation for mifepristone and misoprostol must be further modified as it relates to the use of prophylactic antibiotics, to ensure against the risk of severe, lethal infection.

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Correction: identification of inappropriate drug prescribing by computerized, retrospective DUR screening in Korea

The correct spelling of the first author's name in this article (2005; 39:1918-23) is Jong Hun Yeom.

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Correction: aralast: a new α_1-protease inhibitor for treatment of α-antitrypsin deficiency

In the recent article about Aralast in α-antitrypsin deficiency (2005;39: 1861-9), the following change should be made to Table 2: the starting material for Aralast should be changed from "IV-1 paste" to "not available."

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Letters are subject to review prior to acceptance. They should address areas related to pharmacy practice, research, or education, or articles recently published. Corrections of previously published material also are accepted. Letters are limited to no more than five authors. In cases where adverse drug effects are described, the Naranjo ADR probability scale should be used to determine the likelihood that the adverse effect was drug-related (Clin Pharmacol Ther 1981;30:239-45). Text: limit 500 words. References: limit 5. Art: limit 1 table or figure.