Pharmacokinetics and Pharmacodynamics of Remifentanil in Volunteer Subjects with Severe Liver Disease

Mark Dershwitz, M.D., Ph.D., J. Frank Hoke, Ph.D.,† Carl E. Rosow, M.D., Ph.D.,‡ Piotr Michalowski, M.D., Ph.D.,§ Patricia M. Connors, R.N., B.S.N.,¶ Keith T. Muir, Ph.D.,# Jules L. Dienstag, M.D.*

Background: Remifentanil, a new μ-opioid agonist with an extremely short duration of action, is metabolized by circulating and tissue esterases; therefore, its clearance should be relatively unaffected by changes in hepatic or renal function. This study was designed to determine whether severe hepatic disease affects the pharmacokinetics or pharmacodynamics of remifentanil.

Methods: Ten volunteers with chronic, stable, severe hepatic disease and awaiting liver transplantation and ten matched controls were enrolled. Each subject was given a 4-h infusion of remifentanil. The first five pairs received 0.0125 μg·kg⁻¹·min⁻¹ for 1 h followed by 0.025 μg·kg⁻¹·min⁻¹ for 3 h; the second five pairs received double these infusion rates. During and after the infusion, arterial blood was obtained for pharmacokinetic analyses, and the ventilatory response to a hypercapnic challenge was assessed. Simultaneous pharmacokinetic and pharmacodynamic analyses were performed. The pharmacokinetics were described using an one-compartment intravenous infusion model, and ventilatory depression was modeled using the inhibitory Fmax model. The pharmacokinetics of the metabolite GR90291 were determined using noncompartmental methods.

Results: There were no differences in any of the pharmacokinetic parameters for remifentanil or GR90291 between the two groups. The subjects with liver disease were more sensitive to the ventilatory depressant effects of remifentanil. The EC50 values (the remifentanil concentrations determined from simultaneous pharmacokinetic/pharmacodynamic analyses to depress carbon dioxide-stimulated minute ventilation by 50%) in the control and hepatic disease groups were 2.52 ng/ml (95% confidence interval 2.07–2.97 ng/ml) and 1.56 ng/ml (95% confidence interval 1.37–1.76 mg/ml), respectively.

Conclusions: The pharmacokinetics of remifentanil and GR90291 are unchanged in persons with severe, chronic liver disease. Such patients may be more sensitive to the ventilatory depressant effects of remifentanil, and a finding of uncertain clinical significance, considering the extremely short duration of action of the drug. (Key words: Analgesics, opioids: GR90291; remifentanil. Anesthetics, intravenous: remifentanil. Liver disease. Pharmacokinetics. Pharmacodynamics.)

REMIFENTANIL is a new, selective μ-opioid agonist with an extremely short duration of action. It contains a methyl-ester linkage, which renders it susceptible to metabolism by circulating and tissue esterases, a metabolic pathway analogous to that which occurs with esmolol. The resulting carboxylic acid metabolite, GR90291, has approximately 1/4,600 the potency of remifentanil as a μ-opioid agonist in anesthetized dogs. In humans, GR90291 is eliminated primarily via renal excretion with a terminal half-life of approximately 1.5–2 h.

In experimental pain studies in human volunteers, remifentanil was found to be approximately 20–30 times more potent than fentanyl and 30–50 times more potent than remifentanil for the abolition of discomfort. On discontinuation of remifentanil, 0.025 to 2 μg·kg⁻¹·h⁻¹, the mean times to emergence were 9 min for the first and 6 min for the second volunteers. The mean times to emergence times of remifentanil.

Fentanyl, sufentanil, and oxymorphone are all metabolized by the liver. Sufentanil and remifentanil are susceptible to hepatic metabolism, and sufentanil can be given as single dose. Sufentanil is substantially bound to plasma proteins. Sufentanil and remifentanil are metabolized by hepatic microsomal enzymes, and these drugs are metabolized by a single enzyme, cytochrome P450 3A4. Fentanyl is metabolized by a cytochrome P450 2D6 isoenzyme.

We predicted that remifentanil would be an effective anesthetic. We predicted that remifentanil would be an effective anesthetic.

Methods

This was an open-label, single-blind, randomized study of remifentanil in patients with cirrhosis. Patients were randomized to receive remifentanil or placebo. The primary outcome was the percentage of patients who required a rescue medication for pain. The primary outcome was the percentage of patients who required a rescue medication for pain. The primary outcome was the percentage of patients who required a rescue medication for pain.

Anesthesiology, V 84, No 4, Apr 1996
times more potent than alfentanil. In the initial study of remifentanil as part of balanced anesthesia, the ED$_{50}$ for the abolition of all responses to surgical stimuli was 0.52 µg·kg$^{-1}$·min$^{-1}$ in the presence of 67% N$_2$O. After discontinuation of remifentanil infusions ranging from 0.025 to 2 µg·kg$^{-1}$·min$^{-1}$ and lasting from 1.0 to 6.8 h, the mean times to spontaneous ventilation, responsiveness, and extubation ranged from 2.5 to 7.0 min. Emergence times were not related to the infusion rate of remifentanil.

Fentanyl, sufentanil, and alfentanil undergo extensive hepatic metabolism. When fentanyl and sufentanil are given as single doses, the kinetics are unchanged in patients with cirrhosis. Both opioids, however, are substantially bound to plasma proteins, and patients with liver disease of even moderate severity often have decreased blood concentrations of such proteins, thereby altering the unbound fraction of drug available for metabolism. In contrast, alfentanil has reduced clearance, and recovery may be prolonged when alfentanil is administered by infusion to patients with impaired hepatic function. Esmolol has been studied in patients with cirrhosis, and its pharmacokinetics were not altered by the presence of hepatic impairment. We predicted that the pharmacokinetics of remifentanil would be unchanged in persons with impaired hepatic function. The purpose of this study was to examine this hypothesis in patients with severe liver disease and very little hepatic reserve. We also determined whether such persons have altered sensitivity to the opioid agonist effects of remifentanil.

Methods

This was an open-label, parallel design study of ten volunteer subjects with hepatic disease awaiting liver transplantation and ten matched controls with normal liver function. Each control subject was matched for gender, race, age (±7 yr) and weight (±15%) with his or her counterpart with hepatic disease. The study was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital, and each volunteer gave written, informed consent.

Each subject with liver disease had a history of chronic, stable hepatic disease (hepatitis B, hepatitis C, or primary biliary cirrhosis), and all were recruited from the list of patients awaiting liver transplantation. The primary determinant of the magnitude of hepatic impairment for inclusion in the study was hypoalbuminemia (≤3.2 g/dl). Most subjects with liver disease also had a prolonged prothrombin time and clinical features indicative of cirrhosis. All had evidence of portal hypertension, but none had encephalopathy or elevated blood ammonia concentrations at the time of their participation. Subjects were excluded if they had a history of anesthesia or opioid use within 8 weeks of the study, current or recent history of ethanol or other substance abuse, or current use of psychotropic medications.

The pharmacodynamic indicator of µ-opioid effect used was a decreased ventilatory response to a hypercarbic challenge. When each subject came for the screening visit, within 14 days of his or her participation in the study, two measurements of ventilatory drive were made to determine whether the subject could tolerate the hypercarbic challenge. At that time, each also had a neurologic examination to exclude encephalopathy, and blood tests of hepatic function were performed.

On the day of the study, each subject had the neurologic evaluation repeated. Intravenous and radial arterial catheters were inserted, and electrocardiogram and pulse oximetry were monitored continuously. Two baseline determinations of ventilatory drive were made, an infusion of remifentanil was begun, and during the 4-h infusion, six additional determinations of ventilatory drive were made. After stopping the infusion, ventilatory drive was measured until it had returned to baseline. Immediately after each ventilatory drive measurement, an arterial blood sample was obtained for determination of remifentanil and GR90291 concentrations, and the subject performed two psychomotor tests using pen and paper and completed several visual analog scales.

For safety reasons, very low doses of remifentanil were used in the first five pairs of subjects: The initial infusion rate of remifentanil was 0.0125 µg·kg$^{-1}$·min$^{-1}$, and it was maintained for 1 h. The infusion rate was then doubled and continued for an additional 3 h (low-dose group). In the second five pairs of subjects, the initial and final remifentanil infusion rates were doubled to 0.025 and 0.05 µg·kg$^{-1}$·min$^{-1}$, respectively (high-dose group). The largest dose was chosen on the basis of prior studies in volunteers. This dose was less than the lowest dose at which significant oxyhemoglobin desaturation occurred in a dose-escalation study in normal volunteers breathing room air (0.075 µg·kg$^{-1}$·min$^{-1}$).

For determination of ventilatory drive, the subjects were fitted with an airtight mask equipped with a tur-
bine to measure expired volume (Interface Associates VMM-2) and a side port for measurement of carbon dioxide by infrared spectroscopy (Datex PB253). Two one-way valves were used to maintain an open system in which the subject breathed a defined gas mixture (7.5% CO₂, 50% O₂, balance nitrogen) and exhaled into the environment. For each determination of ventilatory drive, the subject breathed room air for 5 min, baseline minute ventilation was recorded, and then he or she breathed the carbon dioxide mixture for 5 min. Minute ventilation measured during the last min of each 5-min period was used in all calculations.

The analog outputs from the ventilation monitor and the capnometer were fed simultaneously to a paper chart recorder and an analog-to-digital converter board installed in a PC-class computer. Using software previously described in detail, we obtained breath-by-breath analysis of minute ventilation.

To prevent blood esterases from metabolizing remifentanil in blood once it had been drawn, we processed arterial blood samples immediately by mixing with acetonitrile to inactivate esterase activity. Remifentanil was extracted by the addition of methylene chloride. The organic and aqueous phases were separated and stored at −70°C. Determination of remifentanil and GR90291 concentrations was by high-resolution gas chromatographic mass spectrometry. The detection limits of remifentanil and GR90291 in blood were 0.1 ng/ml and 1 ng/ml, respectively.

To study whether opioid-induced encephalopathy had occurred, the subjects were evaluated after each determination of ventilatory drive by the use of two psychomotor tests, the Trieger dot and Halstead trail-making tests, and several visual analog scores, as previously described. The Trieger dot test was scored as the number of dots missed, and the Halstead trail-making test was scored as the number of lines correctly connected. The visual analog scale was scored as a value from 0 to 100. Each subject was admitted to the hospital for the night following the study, and serial blood samples for the analysis of remifentanil and GR90291 were collected for 20 h after the end of the remifentanil infusion.

The pharmacokinetic/pharmacodynamic relationship of remifentanil was evaluated using nonlinear regression analysis (PCNONLIN version 4.2). A model was developed whereby the pharmacokinetics and pharmacodynamics were fit simultaneously. In addition, independent analyses of the pharmacokinetics were performed for each subject. The pharmacokinetics were described using a one-compartment intravenous infusion model, and the pharmacodynamics (minute ventilation) were modeled using the inhibitory E max model:

\[
MV = E_0 - \frac{E_{\text{max}} \cdot C}{E_{\text{so}}} + C
\]

where \(E_0\) is baseline minute ventilation, \(C\) is the remifentanil blood concentration, \(E_{\text{so}}\) is the concentration at which 50% of the maximum response occurs, and \(\gamma\) is a dimensionless parameter describing the shape of the sigmoid curve. At very high blood remifentanil concentrations (\(C >> E_{\text{so}}\)), the equation above simplifies to:

\[
MV = E_0 - E_{\text{max}}
\]

Because the maximum response to remifentanil would be apnea (minute ventilation 0), \(E_{\text{max}}\) was fixed to equal \(E_0\).

### Table 1. Models and Parameters

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>(E_0, k_{10}, E_{\gamma}, E_{\text{so}}, \gamma)</td>
</tr>
<tr>
<td>Reduced model with (\gamma = 1)</td>
<td>(E_0, k_{10}, E_{\gamma}, E_{\text{so}})</td>
</tr>
<tr>
<td>Reduced model with fixed (E_0)</td>
<td>(k_{10}, E_{\gamma}, E_{\text{so}})</td>
</tr>
<tr>
<td>Simple model with (\gamma = 1) and fixed (E_0)</td>
<td>(k_{10}, E_{\gamma}, E_{\text{so}})</td>
</tr>
</tbody>
</table>

### Table 2. Subject Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender (M/F)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>[Albumin] (mg/dl)</th>
<th>PT Prolongation (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose, liver disease</td>
<td>4/1</td>
<td>43.2 ± 3.6 (37–55)</td>
<td>80.8 ± 10.4 (60–114)</td>
<td>2.7 ± 0.2 (2.3–3.2)</td>
<td>1.7 ± 0.5 (0.5–2.9)</td>
</tr>
<tr>
<td>Low-dose, control</td>
<td>4/1</td>
<td>38.4 ± 3.4 (31–49)</td>
<td>81.8 ± 7.7 (66–107)</td>
<td>4.1 ± 0.2 (3.8–4.5)</td>
<td>-0.1 ± 0.3 (-0.9–0.6)</td>
</tr>
<tr>
<td>High-dose, liver disease</td>
<td>4/1</td>
<td>49.2 ± 3.7 (41–60)</td>
<td>81.8 ± 7.6 (64–102)</td>
<td>3.0 ± 0.2 (2.5–3.6)</td>
<td>1.7 ± 0.6 (0.2–2.8)</td>
</tr>
<tr>
<td>High-dose, control</td>
<td>4/1</td>
<td>50.4 ± 5.0 (41–64)</td>
<td>82.2 ± 7.5 (71–105)</td>
<td>3.8 ± 0.1 (3.5–4.0)</td>
<td>-0.5 ± 0.2 (-0.9–0.1)</td>
</tr>
</tbody>
</table>

Values are demographics for the subjects with liver disease and their matched controls. Values are means ± SEM (with range in parentheses). The values for serum albumin and prothrombin time were those recorded on the day of the study.

Anesthesiology, V 84, No 4, Apr 1996
PHARMACOKINETICS AND PHARMACODYNAMICS OF REMIFENTANIL

Fig. 1. Pharmacokinetic and pharmacodynamic data for subject 12. Closed circles represent the remifentanil concentrations, and closed squares represent the minute ventilation values. The solid line is the model of the blood concentration data, and the dashed line is the model of the minute ventilation data. During the first hour of the infusion at 0.025 μg·kg⁻¹·min⁻¹, the concentration of remifentanil reached a plateau and the infusion rate was doubled and maintained for an additional 3 h. At the initial infusion rate, minute ventilation was depressed 51%, increasing to 48% depression at the final infusion rate.

The modeling procedure was assessed using ¼ or ¼² weighting or no weighting, as appropriate, where Y is the predicted value for concentration or minute ventilation. Four pharmacodynamic models were assessed as shown in table 1. Using the weighted sums of squares, the Akaike information criterion was calculated to determine which of the models provided the best fit.

The pharmacokinetic parameters of GR90291 were determined using noncompartmental methods. The terminal rate constant was obtained using an algorithm contained within PCNONLIN and confirmed by visual inspection.

The pharmacokinetic parameters for remifentanil and GR90291 were log-transformed before statistical analysis. The following pharmacokinetic parameters for remifentanil were analyzed: volume of distribution (Vd), clearance (Cl), elimination rate constant (kno), and half-life (t1/2). For GR90291, the area under the concentration versus time curve (AUC), maximum blood concentration (Cmax), and half-life (t1/2) were determined. The pharmacodynamic parameters were analyzed without transformation. One-way analysis of variance was used to compare the dose groups and subject groups. Two-way analysis of variance was used to assess a dose x subject group interaction. A P value less than 0.05 was considered significant. Based on the data, the sample size of ten subjects per group (control vs. liver disease) would provide 80% power to detect a 26% difference in clearance, and five subjects per group (low-dose vs. high-dose) would provide 80% power to detect a 39% difference in clearance.

Results

The demographics of the subjects are listed in table 2. Ten subjects with chronic liver disease were enrolled in the study, eight with hepatitis C, one with hepatitis B, and one with primary biliary cirrhosis. Two of the ten were women. On the day of the study, the serum albumin level for subject 12 exceeded the inclusion criterion. Because he had had multiple serum albumin determinations in the recent past with values less than 3 mg/dl and because he had biopsy-proven cirrhosis, he underwent the experimental protocol. Serial albumin determinations in the days and weeks after the study were less than 3 mg/dl, so his data were included in the analyses. Several subjects had evidence of mild or moderate ascites, but none had difficulty completing the ventilatory measurements.

The simultaneous pharmacokinetic and pharmacodynamic results for a representative subject are shown in figure 1. As the blood remifentanil concentrations increased, minute ventilation decreased. The solid line depicts the predicted blood concentrations, and the dashed line depicts the minute ventilation values based on the model described in methods.

Table 3. Summary Pharmacokinetic Parameters for Remifentanil

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Low-dose Hepatic Disease</th>
<th>High-dose Hepatic Disease</th>
<th>Low-dose Healthy Subjects</th>
<th>High-dose Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (ml·min⁻¹·kg⁻¹)</td>
<td>39.1 (33.2–46.0)</td>
<td>33.3 (23.0–48.3)</td>
<td>31.5 (23.8–41.6)</td>
<td>33.0 (28.5–38.1)</td>
</tr>
<tr>
<td>t1/2 (min)</td>
<td>4.7 (3.7–5.9)</td>
<td>5.7 (4.0–8.1)</td>
<td>4.6 (2.8–7.4)</td>
<td>4.3 (4.1–4.5)</td>
</tr>
</tbody>
</table>

Each value is the geometric mean. The 95% confidence intervals are in parentheses.

Anesthesiology, V 84, No 4, Apr 1996

Anesthesiology, V 84, No 4, Apr 1996
Figure 2 shows the remifentanil concentration versus time data for all subjects. The pharmacokinetic parameters for remifentanil are summarized in Table 3. There were no significant differences in Cl, V, or t1/2 between any of the groups. In addition, independent analysis of the pharmacokinetic parameters provided results consistent with those obtained from the simultaneous pharmacokinetic-pharmacodynamic modeling.

The concentration versus time data for GR90291 in the subjects are shown in Figure 3, and the pharmacokinetic parameters are summarized in Table 4. There were no significant differences in any of the pharmacokinetic parameters when the healthy subjects and the subjects with hepatic disease were compared within dosage groups. Subjects who received the higher dose of remifentanil had measurable concentrations of GR90291 for a longer period. There were significant differences noted between the low- and high-dose.

Fig. 2. The remifentanil blood concentration versus time data for the subjects with liver disease (A) and the control subjects (B). Each dashed line represents the data from one subject, and the heavy lines are the mean values. In all groups, a stable plateau was reached during the first hour, and another plateau was achieved during the next 3 h of the infusion. After termination of the infusion, the concentrations declined rapidly. There were no differences between the subjects with liver disease or the control subjects in the low- or high-dose groups.

Fig. 3. The GR90291 blood concentration versus time data for the subjects with liver disease (A) and the control subjects (B). Each dashed line represents the data from one subject, and the heavy lines are the mean values. In all groups, the concentrations of GR90291 continued to increase during the 4 h infusion of remifentanil. After termination of the remifentanil infusion, the concentrations of GR90291 gradually declined. The apparently higher concentrations of GR90291 in the subjects with liver disease compared with the control subjects in the high-dose group were not statistically different.
Table 4. Summary Pharmacokinetic Parameters for GR90291

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Low-dose Hepatic Disease</th>
<th>High-dose Hepatic Disease*</th>
<th>Low-dose Healthy Subjects</th>
<th>High-dose Healthy Subjects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng·min⁻¹·ml⁻¹)</td>
<td>805 (620–1,047)</td>
<td>1,301 (740–2,288)</td>
<td>767 (536–1,098)</td>
<td>966 (743–1,308)</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>3.7 (3.0–4.5)</td>
<td>5.1 (3.3–7.9)</td>
<td>3.9 (3.0–5.1)</td>
<td>4.2 (3.0–6.0)</td>
</tr>
<tr>
<td>t₁/₂ (min)</td>
<td>71 (60–83)</td>
<td>115 (71–188)</td>
<td>69 (45–107)</td>
<td>112 (68–183)</td>
</tr>
</tbody>
</table>

Each value is the geometric mean. The 95% confidence intervals are in parentheses.
* Normalized to low-dose (i.e., AUC and Cmax were divided by two for comparison in this table).

Table 5. Summary AUC Ratio and EC₅₀ Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low-dose Hepatic Disease</th>
<th>High-dose Hepatic Disease</th>
<th>Low-dose Healthy Subjects</th>
<th>High-dose Healthy Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₉₀/AUC₉₅₀/AUCremovetanil</td>
<td>6.2 ± 1.4</td>
<td>4.5 ± 1.9</td>
<td>4.8 ± 1.4</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>EC₅₀ (ng/ml)</td>
<td>1.5 ± 0.5</td>
<td>*</td>
<td>*</td>
<td>1.5 ± 0.5</td>
</tr>
</tbody>
</table>

Each value is the arithmetic mean ± standard deviation of the values determined for the individuals in the group.
* EC₅₀ values in the low-dose groups are not estimated because most of the subjects did not manifest a 50% reduction in ventilation.
† Significantly different from the high-dose hepatic disease group (P < 0.0276).

Anesthesiology, V 84, No 4, Apr 1996
ther or both tests, but there were no differences between groups in performance after remifentanil. Remifentanil produced dose-dependent sedation as measured by visual analog scale; however, there were no differences between the control group and the group with liver disease.

Discussion

The pharmacokinetics of remifentanil were not altered in subjects with severe hepatic disease awaiting liver transplantation. Hepatic function in the subjects was severely compromised; although none had encephalopathy, all had evidence of portal hypertension on physical examination. All had hypoalbuminemia, and most had a prolongation in prothrombin time. As shown in figure 2, there was no evidence of accumulation of remifentanil in these subjects after a 4-h infusion.

There were also no differences in the disposition of GR90291 between the control subjects and the subjects with liver disease. The ratio of AUC for GR90291 to remifentanil ranged from 3.1 to 6.2, providing an estimate of the ratio of the blood concentrations at steady state. Profound analgesia during surgery under anesthesia with nitrous oxide and remifentanil is achieved with blood concentrations of remifentanil ranging from 10 to 35 ng/ml.4 If we assume that 6 times as much metabolite might be present, steady-state blood concentrations of GR90291 as high as 210 ng/ml may occur during surgery. Because GR90291 is about 1/4.600th as potent in dogs as remifentanil as a μ-opioid agonist,4 the blood concentration of GR90291 under such circumstances would be approximately equivalent to 0.05 ng/ml remifentanil, a concentration that does not produce detectable ventilatory depression, assuming a similar potency ratio in humans. The potency of GR90291 in humans is unknown.

Subjects who received the larger dose of remifentanil had detectable concentrations of GR90291 for a longer period, and therefore the estimate of AUC and $t_{1/2}$ is more accurate in the high-dose groups. This explains the differences in AUC and $t_{1/2}$ between the low- and high-dose groups. The ratio of AUC for GR90291 to remifentanil is less for both control subjects and subjects with liver disease in the high-dose groups; thus, the actual contribution of GR90291 to overall μ-opioid effect is likely to be less than the worst-case scenario assumed in the preceding paragraph.

The EC$_{50}$ values were less in the subjects with hepatic disease, suggesting that they may be more sensitive to the ventilatory depressant effects of remifentanil. When remifentanil is used in such patients, the dose necessary to provide analgesia may be less than in a patient without liver disease. Because the drug is cleared so rapidly, regardless of the presence of liver disease, a twofold difference in dose is unlikely to produce any change in duration. The mechanism of the altered EC$_{50}$ in the patients with liver disease is unknown. We do not know the nature of remifentanil metabolism.

As is possible to interact the EC$_{50}$ of remifentanil with the concentration of albumin. For example, because of the nature of remifentanil metabolism and the concentration of albumin, the concentration of remifentanil is higher in patients with liver disease.
natively, the central nervous system may be more sensitive to the depressant effects of the drug.

For completeness, we must raise the possibility that the difference in sensitivity to remifentanil is due to unusually high values for EC_{50} in the control subjects in this study. In two prior studies of normal volunteers, the EC_{50} values in normal volunteers were similar to those obtained in our subjects with liver disease and less than in our control subjects. Figure 4 shows that the high-dose control subjects did not experience a greater response than the low-dose controls, so it is possible that individuals in the former group were relatively resistant to the ventilatory depressant effects of remifentanil. It is not surprising to observe this level of individual variability in the response to opioids.†

Our data allow us to conclude that remifentanil may be an appropriate opioid to use in patients with severe hepatic failure. Severe hepatic impairment does not alter the pharmacokinetics of remifentanil. Recovery from the effects of remifentanil is rapid, even when large doses are given, because of three factors: rapid disappearance from the circulation, rapid equilibration between blood and "effect" sites, and the relative inactivity of the metabolite. Furthermore, recovery is similar in normal individuals and in patients with severe liver disease. The apparent difference in sensitivity to the ventilatory depressant effect of remifentanil in subjects with hepatic disease, if real, is small and unlikely to cause meaningful changes in the safety of the drug in the recovery period.

References