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

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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 a 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 1.56 ng/ml (95% confidence interval 1.27–1.76 ng/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, a finding of uncertain clinical significance, considering the extremely short duration of action of the drug. (Key words: Analgesics, opioids. GR90291, remifentanil, Analgesics, intravenous: remifentanil, Liver disease. Pharmacokinetics. Pharmacodynamics.)

REMIFENTANIL is a new, selective μ-opioid agonist with an extremely short duration of action.1–5 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 1/4,000 the potency of remifentanil as a μ-opioid agonist in anesthetized dogs.5 In humans, GR90291 is eliminated primarily via renal excretion with a terminal half-life of approximately 1.5–2 h.5

In experimental pain studies in human volunteers, remifentanil was found to be approximately 20–30 times more potent than fentanyl. The duration of action of remifentanil is suitable for the abolition of pain, 0.52 μg·kg⁻¹·min⁻¹ for the abolition of pain, with a mean time to complete analgesia of 0.025 to 2 μg·kg⁻¹·min⁻¹; h, the mean times of first emergence of analgesia and sufficient for the abolition of pain. The half-life of remifentanil.

Fentanyl, sufentanil, and alfentanil undergo hepatic metabolism and are given in single doses to patients with circulatory failure or severe hepatic or renal impairment. In patients with liver disease, a scenario similar to that of the present study, the time to maximum effect of fentanyl or sufentanil is increased, and the duration of analgesia is prolonged. In patients with cirrhosis or renal impairment, the time to maximum effect of alfentanil is increased and the duration of analgesia is prolonged.

In conclusion, remifentanil may be a useful drug for patients with severe liver disease, as its pharmacokinetics and pharmacodynamics are not altered by cirrhosis. The drug is administered as a continuous intravenous infusion. Its duration of action is brief, and its metabolites are not altered by advanced liver disease.

Methods

This was an open-label, volunteer study of remifentanil tolerance in patients with severe liver disease. The study was conducted at the Massachusetts General Hospital and Harvard Medical School. The study protocol was approved by the institutional review boards of the hospitals. The consent forms were reviewed and approved by the Institutional Review Board of the Massachusetts General Hospital. The study was conducted in accordance with the guidelines of the American Society of Anesthesiologists, October 18, 1994.

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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, recent 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-
Table 1. Models and Parameters

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>( V_0, k_{10}, E_0, EC_{50}, \gamma )</td>
</tr>
<tr>
<td>Reduced model with ( \gamma = 1 )</td>
<td>( V_0, k_{10}, E_0, EC_{50} )</td>
</tr>
<tr>
<td>Reduced model with fixed ( E_0 )</td>
<td>( V_0, k_{10}, EC_{50}, \gamma )</td>
</tr>
<tr>
<td>Simple model with ( \gamma = 1 ) and fixed ( E_0 )</td>
<td>( V_0, k_{10}, EC_{50} )</td>
</tr>
</tbody>
</table>

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.11 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:

\[
MV = E_0 - E_{max} \cdot \frac{C}{EC_{50} + C}
\]

where \( E_0 \) is baseline minute ventilation, \( C \) is the remifentanil blood concentration, \( EC_{50} \) 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 (\( C >> EC_{50} \)), the equation above simplifies to:

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

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

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 (51–40)</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 ± 6.6 (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.

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![Graph showing pharmacokinetic and pharmacodynamic data for remifentanil.](image)

**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 initial hour of the infusion at 0.025 mg·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 \( \chi^2 \) or \( \chi^2 \)-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 (\( V_d \)), clearance (\( C_l \)), elimination rate constant (\( k_{el} \)), and half-life (\( t_{1/2} \)). For GR90291, the area under the concentration versus time curve (AUC), maximum blood concentration (\( C_{max} \)), and half-life (\( t_{1/2} \)) 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*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 multiple serum albumin determinations in the recent past with values less than 5 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 5 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>( C_l ) (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>( V_d ) (ml/kg)</td>
<td>264 (196–356)</td>
<td>272 (162–456)</td>
<td>208 (112–384)</td>
<td>205 (178–235)</td>
</tr>
<tr>
<td>( t_{1/2} ) (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.

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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, Vd, 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 groups for GR90291 hepatic disease.

The ratio of AUC(0-∞) at steady-state was estimated to be from 3.1 to 6.7 between groups, the ratio of the hepatic impairment subjects and the control subjects.

Four models of pharmacokinetics were analyzed. The full model accurately fit because all parameters were included. The high-dose continued to decline in all subjects. The ratios of the other four groups were not included. The differences were not significant.

The minute values are shown in figure 3. The decrease in minute 15 is due to the infusion.
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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>Cₚₜₚ (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 Cₚₜₚ were divided by two for comparison in this table).

groups for GR90291 AUC and t₁/₂ in the subjects with hepatic disease and for t₁/₂ in the control group.

The ratio of AUCs for GR90291 and remifentanil gives an estimate of the ratio of the blood concentrations at steady-state. These ratios are listed in table 5 and range from 3.1 to 6.2. Within both the high- or low-dose groups, the ratio was not different in the control subjects and the subjects with liver disease.

Four models for the simultaneous modeling of the pharmacokinetics and pharmacodynamics were tested. The full model (five parameters) could not be adequately fit because of insufficient information to estimate all parameters simultaneously. One subject in the high-dose control group did not manifest ventilatory depression in response to remifentanil and was not included in the pharmacodynamic analyses. The results indicated that the simple model provided the best overall fit in 15 of the remaining 19 subjects. In three of the other four subjects, although the reduced models provided a better statistical fit than the simple model, there were no differences in the parameter estimates obtained. Thus, in only one subject did the reduced models provide a better statistical fit and different parameter estimates. The simple model was applied to the 19 subjects in whom pharmacodynamic calculations were performed.

The minute ventilation data as a function of time are shown in figure 4. In all four groups, there was a decrease in minute ventilation during the first hour of the infusion. A larger decrease occurred during the subsequent 3 h after the infusion rate had been doubled. Minute ventilation returned rapidly to baseline after termination of the infusion. The subjects with liver disease who were given the higher dose of remifentanil experienced a greater magnitude of ventilatory depression than the corresponding control group.

The values for EC₅₀ are listed in table 5. The EC₅₀ for the subjects with hepatic disease given the higher dose was significantly less than that of the comparable control subjects. Of the subjects given the smaller dose of remifentanil, only two of the ten manifested a 50% (or greater) decrease in minute ventilation. Because EC₅₀ values in these subjects would represent extrapolations, they are not included.

Figure 5 shows the individual minute ventilation measurements as a function of the blood concentration of remifentanil. Fitting the pooled, individual data points to the inhibitory Eᵢₘₐₓ model provides an alternative method for estimating EC₅₀. The EC₅₀ values in the control subjects and the subjects with liver disease 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 ng/ml), respectively. The EC₅₀ values in the two groups were significantly different.

All subjects were able to complete the various psychomotor and visual analog scale measurements at all times. At baseline (i.e., before remifentanil), there were no differences between groups in performance on either the Trieger or the Halstead tests. Most subjects in each group had impaired performance on ei-

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>AUCₚₜₚ/AUCᵢₘₐₓ</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>6.5 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>3.4 ± 2.0†</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).

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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. 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 1/4.6,000th as potent in dogs as remifentanil as a μ-opioid agonist, 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 t½ is more accurate in the high-dose groups. This explains the differences in AUC and t½ 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 EC₅₀ 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 EC₅₀ in the patients with liver disease is unknown. We do not know the nature of this difference.

It is possible that the synthesis of albumin (cofactor, to weakly bind to albumin), thus making the drug less

†† Glaxo Inc. USA.
the nature of remifentanil binding to plasma proteins. It is possible that, because of decreased hepatic synthesis of albumin and other proteins (e.g., $\alpha_1$-acid glycoprotein, to which alfentanil binds more avidly than to albumin), the unbound fraction of remifentanil may be higher in patients with hepatic impairment. Alternatively, 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$\text{50}$ in the control subjects in this study. In two prior studies of normal volunteers, the EC$\text{50}$ 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.\textsuperscript{17}

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.

Fig. 5. The individual minute ventilation determinations as a function of blood remifentanil concentration in the subjects with liver disease (A) and the control subjects (B). Each dashed line represents the data from one subject, and the heavy lines represent the minute ventilation versus remifentanil curve predicted by the model. The subjects with liver disease had an EC$\text{50}$ value of 1.56 ng/ml (95% confidence interval 1.37-1.76 ng/ml). The control subjects had an EC$\text{50}$ value of 2.52 ng/ml (95% confidence interval 2.07-2.97 ng/ml).


References


Remifentanil
Comparative Study in Healthy Adults

Taimage D. Egan, M.D.
Keith T. Muir, Ph.D.

Background: Remifentanil, a rapidly metabolized intravenous analgesic and alfentanil in head-to-head comparison.

Methods: Ten volunteer subjects received an open-label crossover, double-blind study to determine the effect of remifentanil on sedation and analgesia. An end-systolic pressure and aortic pressure were used to determine the drug's effect on myocardial function. The pharmacokinetics were characterized using non-linear mixed-effects modeling and pharmacodynamics. After pharmacodynamic analysis, the spectra were characterized using a non-linear mixed-effects model. The maximum effect was determined.

Results: Pharmacodynamic parameters of steady-state alfentanil were determined.

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