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Pharmacokinetics and Pharmacodynamics of Remifentanil in Persons with Renal Failure Compared with Healthy Volunteers

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Background: **Remifentanil is an opioid analgesic for use in anesthesia. An ester linkage renders it susceptible to rapid metabolism by blood and tissue esterases. Thus it was hypothesized that remifentanil elimination would be independent of renal function. Because its principal metabolite (GR90291) is eliminated renally, it would depend on renal function. This study was designed to evaluate the pharmacokinetics and pharmacodynamics of remifentanil and its metabolite in persons with and without renal failure.**

Methods: **Two groups of volunteers received two-stage infusions of remifentanil: low dose with 0.0125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h; and high dose with 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h. Blood samples were collected for analysis of remifentanil and GR90291 concentrations. The pharmacokinetics of remifentanil were fit using a one-compartment pharmacokinetic model. Remifentanil's effect was determined intermittently using minute ventilation during a hypercapnic (7.5% CO_2) challenge.**

Results: **Fifteen patients with renal failure and eight control participants were enrolled. The clearance and volume of distribution of remifentanil were not different between those with renal failure and the controls. Patients with renal failure showed a marked reduction in the elimination of GR90291; the half-life of the metabolite increased from 1.5 h in the controls to more than 26 h in patients with renal failure. The steady-state concentration of GR90291 is likely to be more than 25 times higher in persons with renal failure. There were no obvious differences in opioid effects on minute ventilation in the controls and in patients with renal failure.**

Conclusions: **The pharmacokinetics and pharmacodynamics of remifentanil were not altered in patients with renal disease, but the elimination of its principal metabolite, GR90291, was markedly reduced. Based on simulations, the concentration of GR90291 at the end of a 12-h remifentanil infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is not likely to produce significant opioid effects. (Key words: Analgesics, opioids: GR90291; remifentanil. Anesthetics, intravenous: remifentanil. Kidney disease. Pharmacodynamics. Pharmacokinetics.)**

REMIFENTANIL is an esterase-metabolized opioid developed for use as an adjunct in general anesthesia. The principal metabolite of remifentanil, GR90291, possesses about 1/4,600th the potency of remifentanil as determined from electroencephalographic spectral edge and delta wave activity in anesthetized dogs.[1] Unlike remifentanil, GR90291 is eliminated primarily by

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the kidneys. Because remifentanil is metabolized in peripheral tissues to a compound with much lower potency as an opioid, there may be advantages to using remifentanil in patients with severe renal or hepatic disease. Esmolol is a compound that undergoes similar rapid hydrolysis by blood and tissue esterases.[2] The pharmacokinetics of esmolol were not altered when administered to persons with renal failure; however, its principal metabolite, which is renally eliminated, exhibited slower elimination in these persons with renal failure.[3]

The pharmacokinetics of the other fentanyl derivatives have been compared in control subjects and in persons with renal failure.[4–6] None of these studies simultaneously assessed the pharmacodynamic characteristics of the drug in the patients with renal failure. Although pharmacokinetic changes may be evident in patients with renal failure, the changes may or may not warrant a change in dose. It is also possible that the disease process itself may alter the sensitivity of these patients to opioid effects. Thus we investigated pharmacokinetic and pharmacodynamic characteristics of remifentanil in persons with renal failure compared with matched volunteers with normal renal function.

Materials and Methods

Study Design

This study was conducted as an open-label, balanced, parallel design with two treatment groups (persons with renal failure and control volunteers with normal renal function) and two infusion regimens of remifentanil. The study was approved by the Institutional Review Board for Clinical Investigations at Duke University Medical Center and the Subcommittee on Human Studies of the Massachusetts General Hospital.

The infusion regimen of remifentanil was selected based on safety and to provide sufficient data to permit the kinetic analysis of remifentanil. The largest dose of remifentanil used in this study was less than the smallest dose at which significant oxyhemoglobin desaturation occurred in a dose-escalation study in healthy volunteers breathing room air (0.075 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The doses were not anticipated to result in clinically significant respiratory depression or in prolonged opioid effects. Each person received a reduced infusion rate of remifentanil for the first hour followed by a twofold increase in infusion rate for the remaining 3 h of the protocol.

There were two dosing regimens of remifentanil: low dose with 0.0125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h; and high dose with 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h. There were three groups of participants: patients with renal failure given the low dose, patients with renal failure given the high dose, and control participants given the high dose.

Before drug infusion, each participant was assessed for eligibility using clinical laboratory tests, electrocardiograph, and physical examination. Blood pressure, heart rate, peripheral oxyhemoglobin saturation, end-tidal carbon dioxide, respiratory rate, and the electrocardiogram were measured during and after the remifentanil infusion. Renal function of each participant was determined using the method of Cockcroft and Gault[7] for estimating creatinine clearance. Persons with a creatinine clearance ≤ 30 ml $\cdot$ min$^{-1} \cdot 1.73$ m^{-2} were classified as having renal failure. For those persons requiring hemodialysis (14 of 15), the remifentanil infusion was administered on the day before hemodialysis therapy. All participants with renal failure were required to have stable renal function with no significant change in renal function status within 2 months before the study period. Each person with renal failure given the high dose was matched for sex, race, age ($\pm$ 7 yr), and weight ($\pm$ 15%) with a control participant with normal renal function.

Remifentanil Pharmacokinetics and Pharmacodynamics

Arterial blood samples (5 ml) were collected for analysis of remifentanil at baseline, 2, 5, 10, 15, 30, 60, 75, 90, 120, 150, 180, 210, and 230 min during the infusion, and at 2, 5, 10, 15, 30, 60, 90, 120, 240, and 360 min after the infusion. An additional venous sample was drawn 1,200 min after stopping the infusion. Blood samples were immediately processed to minimize degradation of remifentanil by circulating esterases. Acetonitrile was added as a protein denaturant, followed by liquid–liquid extraction with methylene chloride and separation of aqueous and organic phases. Determination of remifentanil[8] and GR90291[9] was by high-resolution gas chromatographic mass spectrometry. The detection limit was 0.1 ng/ml for remifentanil and 1 ng/ml for GR90291.

The pharmacokinetic parameters for remifentanil were determined using nonlinear least squares regression analysis (PCNONLIN, version 4.2, SCI Software, Lexington, KY). Single- and multiple-exponential mod-

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els for remifentanil pharmacokinetics were evaluated. The modeling procedure was conducted using 1/Y or $1/Y^2$ weighting, or no weighting, as appropriate, where Y is the predicted concentration. The choice of model was determined using visual inspection of fitted profiles, residual plots, and the F-test.[10]

Using procedures previously described,[11] ## opioid effect was assessed (in the 17 persons given the high-dose remifentanil infusion regimen) intermittently using minute ventilation after a hypercapnic challenge. The participants were either maintained at a constant end-tidal carbon dioxide concentration of 7.5% (12 persons at Duke University) or at a constant inspired carbon dioxide concentration of 7.5% (5 persons at Massachusetts General Hospital) for 4 min before minute ventilation was measured during a 1-min period.

GR90291 Pharmacokinetics

The pharmacokinetics of GR90291 were determined using noncompartmental methods. The parameters estimated were area under the concentration *versus* time curve (AUC), maximum concentration, and terminal half-life ($t_{1/2}$). The ratio of the AUC for GR90291 and remifentanil was calculated to determine the concentration ratio that would occur for GR90291 to remifentanil at steady-state.[12] Blood samples obtained after the beginning of dialysis were not used in the determination of AUC.

Hemodialysis

Arterial, venous, and dialysate samples were collected from patients undergoing hemodialysis on the day after remifentanil infusion. These samples were used to estimate extraction of GR90291 by the dialyzer. If dialysis began before the last scheduled venous blood sample (1,200 min after the end of the remifentanil infusion), this sample was obtained before beginning dialysis.

Statistical Methods

The primary statistical analysis of the pharmacokinetic parameters for remifentanil was performed after log-transformation. Analysis of variance (SAS version 6.07; SAS, Cary, NC) was used to assess the effect of renal failure on the pharmacokinetics of remifentanil compared with controls. P values < 0.05 were considered significant. Based on the data obtained in this study, the sample size of 10 persons per group (high dose) provided greater than 80% power to detect a 32% difference in total clearance, which was the primary pharmacokinetic variable used to assess differences between the patients with renal failure and the controls.

Results

Twenty-three persons (18 at Duke University Medical Center and 5 at Massachusetts General Hospital), 14 men and 9 women, were recruited. Fifteen had renal failure (average creatinine clearance approximately 9 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), and eight had normal renal function (average creatinine clearance approximately 88 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$). Of the 15 persons with renal failure, 14 were receiving hemodialysis therapy.

The adverse events were similar for the persons with renal failure and the controls. These events were generally the result of typical μ-opioid effects and included dyspnea, somnolence, nausea, vomiting, and chills. Some persons with renal failure exhibited an elevation in blood pressure during or after the remifentanil infusion. The timing in relation to the beginning or end of the infusion was not the same among the participants, and the elevation was not high enough to require antihypertensive therapy in any of them.

Remifentanil Pharmacokinetics and Pharmacodynamics

Evaluation of the models for the pharmacokinetics indicated that a single-compartment model provided an adequate fit to the data. The individual and mean concentration-time profiles for the participants are shown in figure 1. Inspection of the high-dose profiles for the persons with renal failure and the controls shows that the individual (except for one control participant) and mean profiles are essentially superimposable. The clearance, volume of distribution, and $t_{1/2}$ of remifentanil were not different in the persons with renal failure compared with the controls, as listed in table 1.

Table 2 summarizes the minute ventilation values as a percentage of baseline for the persons with renal failure and the controls in the high-dose remifentanil group. At both study sites, a similar decrease in minute ventilation was observed at 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$, whereas a larger (although not significant, $P = 0.054$) decrease in minute ventilation was observed at the Duke study site at 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After stopping the remifentanil infusion, minute ventilation increased substantially above baseline values at both study sites.

Glass PSA, Kapila A, Muir KT, Hermann DJ, Shiraishi M: A model to determine the relative potency of mu opioids: alfentanil versus remifentanil [Abstract]. ANESTHESIOLOGY 1993; 79:3A.

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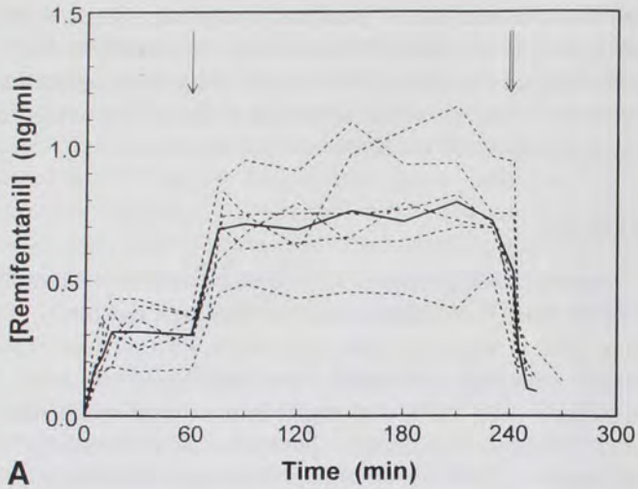

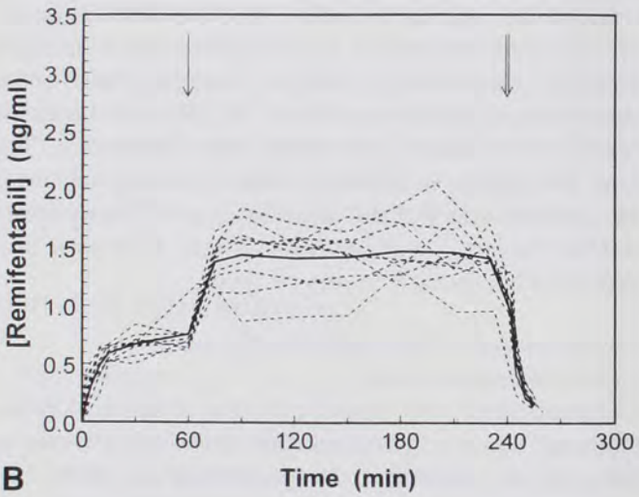

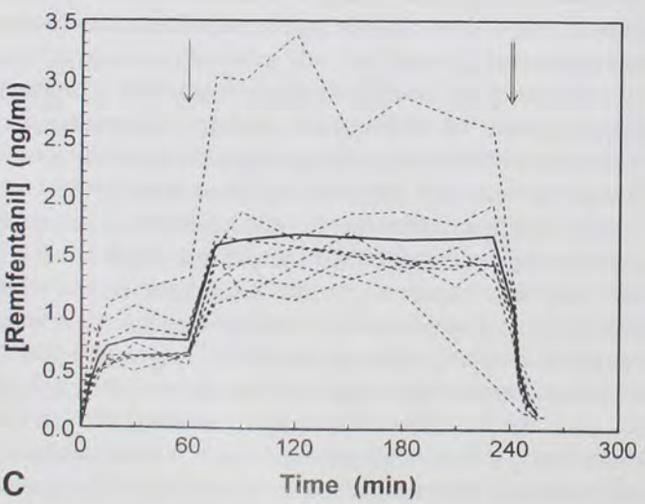

Fig. 1. Individual (dotted lines) and mean (solid line) remifentanil concentration–time profiles. The single arrow indicates the point at which the infusion rate was doubled, and the double arrow indicates the end of the infusion. The Y axes have different scales in the three graphs. (*A*) The patients with renal failure who received the low-dose infusion (0.0125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h). (*B*) The persons with renal failure who received the high-dose infusion (0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h). (*C*) The controls who received the high-dose infusion (0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h).

GR90291 Pharmacokinetics

The individual and mean concentration-time profiles for the principal metabolite of remifentanil, GR90291, are shown in figure 2. The participants with renal failure clearly show a reduction in the elimination of GR90291 compared with controls. A significant increase in AUC, maximum concentration, and $t_{1/2}$ was observed for the persons with renal failure, as listed in table 3. No pharmacokinetic differences were observed between the persons with renal failure who received the low-dose and high-dose infusion regimens.

The ratio of AUC for GR90291 to remifentanil gives an estimate of the ratio of the blood concentrations at steady state.[12] The ratio of AUC for GR90291 to remifentanil was 176 ± 105 in the persons with renal failure given the low-dose infusion, 242 ± 98.5 in the persons with renal failure given the high-dose infusion, and 6.34 ± 1.75 in the controls given the high-dose infusion. Thus, at steady state, the concentration of GR90291 would be approximately 28–38 times higher in persons with renal failure compared with persons with normal renal function.

Hemodialysis

Figure 3 shows the effect of hemodialysis on GR90291 concentrations. All dialysate sample results were below the limit of quantification of the bioanalytical assay because of the large dialysate volume. Using venous and arterial concentrations, the extraction of GR90291 was approximately 35% during dialysis treatments ranging from approximately 3–5 h.

Discussion

Renal failure is thought to prolong the effects of opioids in patients receiving morphine because of accumulation of the active metabolite morphine-6-glucuro-

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Table 1. Summary of Pharmacokinetic Parameters and Statistical Results for Remifentanil

Pharmacokinetic Parameter	Low Dose Subjects with Renal Failure	High Dose Subjects with Renal Failure	High Dose Control Subjects
Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)*	35.1 (25.2–49.0)	35.6 (31.7–40.0)	33.2 (26.5–41.7)
Volume of distribution (ml/kg)*	282 (194–411)	229 (211–249)	191 (151–241)
Half-life (min)*	5.6 (3.3–9.3)	4.5 (3.9–5.1)	4.0 (3.3–4.8)

Values are geometric mean (95% confidence interval).

* No statistically significant differences were noted between subjects with renal failure and control subjects.

nide.[13] Similarly, administration of high or repeated doses of meperidine to patients with reduced renal function can produce seizures resulting from accumulation of normeperidine.[14] The pharmacokinetics of fentanyl, alfentanil, and sufentanil are not altered by the presence of renal failure, although no quantitative study has examined the pharmacokinetics of their metabolites. Because the metabolites are inactive, they are not likely to contribute to the opioid effect, even if they were to accumulate.

Adverse events elicited in this study were the result of typical μ-opioid effects and included dyspnea, somnolence, nausea, vomiting, and chills. None of the adverse events were severe and none of the participants withdrew from the study as a result of an adverse event. Several of the patients with renal failure exhibited an increase in blood pressure before and after termination of the remifentanil infusion. All blood pressure elevations were observed in persons with dialysis fistulae or grafts, which are known to produce a hyperdynamic circulation. Other possible explanations for the increases in blood pressure include catecholamine release induced by the hypercapnic challenge or transient withdrawal from antihypertensive medication.

The relatively low infusion rates used in this study resulted in concentrations of remifentanil that could be adequately characterized using a one-compartment model. Previous pharmacokinetic studies have used two- and three-compartment models for remifentanil.[15–17] These studies were conducted using higher infusion rates of remifentanil, and thus the concentration-time profile could be characterized for longer periods of time. The clearance ($35 ml \cdot min^{-1} \cdot kg^{-1}$) of remifentanil in the patients with renal failure and in control subjects was consistent with estimates obtained in previous pharmacokinetic studies in healthy volunteers and patients. The volume of distribution was slightly lower in the control group compared with the group with renal failure, with mean values of 190 ml/kg in the controls and 230–280 ml/kg in the patients with renal failure. Patients receiving dialysis may become hypervolemic between dialysis treatments, possibly altering the distribution characteristics.

The pharmacokinetics of GR90291 were markedly changed in patients with renal failure, as evidenced by an increase in AUC, maximum concentration, and $t_{1/2}$ compared with control subjects. The AUC and maximum concentration were increased 22–34 and 3–3.5 times, respectively, in the patients with renal failure. In the control subjects, the $t_{1/2}$ of GR90291 was approxi-

Table 2. Summary of Pharmacodynamic Effects of Remifentanil–Minute Ventilation

Study Site	Subject Group	Number of Subjects	0–1 h 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$	1–4 h 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Recovery
Duke	Renal failure	6	55.9 ± 13.1	36.1 ± 9.2	133.2 ± 7.3
	Control	6	59.8 ± 10.7	32.5 ± 10.1	147.4 ± 21.7
MGH	Renal failure	3	59.9 ± 5.1	57.4 ± 12.4	123.4 ± 4.2
	Control	2	61.0 ± 10.4	52.1 ± 6.5	128.8 ± 28.4

Values are percentages of the baseline minute ventilation values and are expressed as arithmetic mean ± SEM. For each subject given the high dose of remifentanil, the minimum value for minute ventilation during the first hour, and the last 3 h, of the infusion was used (*i.e.*, the maximum drug effect for each subject during each of the two infusion rates). During the recovery period, the maximum value for minute ventilation was used. There were no significant differences between the subjects with renal failure and the control subjects within a study site. During the last 3 h of the infusion, the difference in the depression of minute ventilation at the two study sites did not reach significance ($P = 0.054$).

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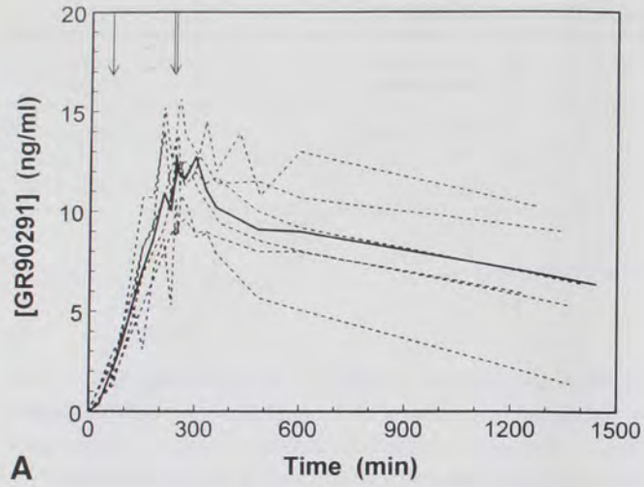

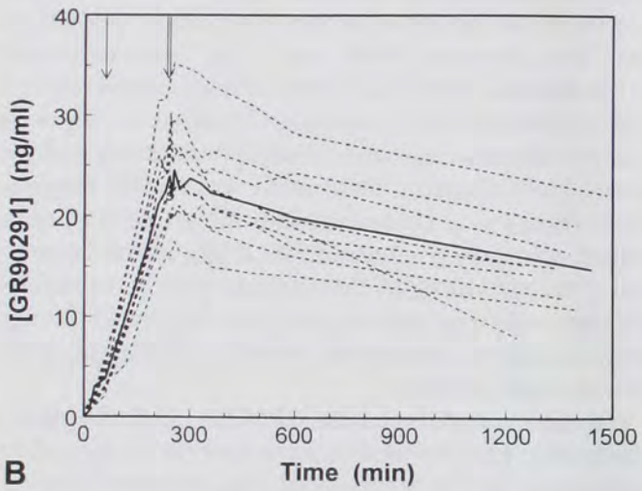

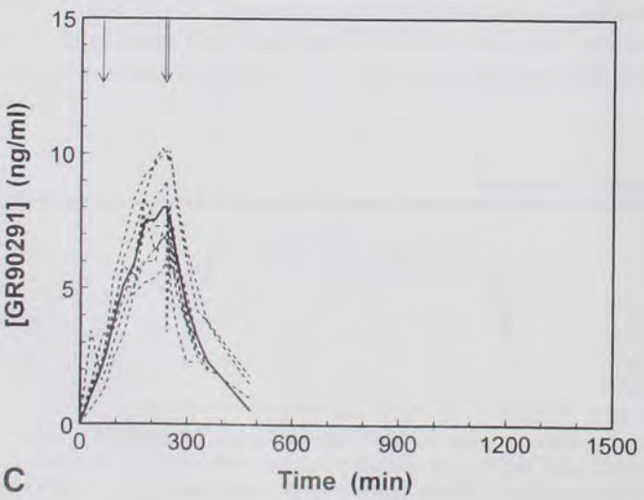

Fig. 2. Individual (dotted lines) and mean (solid line) GR90291 concentration–time profiles. The single arrow indicates the point at which the remifentanil infusion rate was doubled, and the double arrow indicates the end of the infusion. The Y axes have different scales in the three graphs. (*A*) The patients with renal failure who received the low-dose infusion (0.0125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h). (*B*) The patients with renal failure who received the high-dose infusion (0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h). (*C*) The controls who received the high-dose infusion (0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h followed by 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 h).

mately 88 min (1.47 h), which is consistent with values determined in previous studies.[15] The $t_{1/2}$ was increased to 20–30 h in the patients with renal failure, which corresponds to a 15- to 20-fold increase compared with the control subjects. Although the estimated $t_{1/2}$ for GR90291 is essentially equivalent to the duration of blood sampling, the sampling was considered sufficient to determine the $t_{1/2}$ of GR90291 and considered to characterize adequately the effect of renal failure on the elimination of GR90291.

The increase in the AUC of GR90291 in the patients with renal failure is probably due to reduced elimination in these persons. An alteration in the fraction of remifentanil converted to GR90291 is unlikely. Because approximately 98% of an administered dose of remifentanil is metabolized to GR90291 in persons with normal renal function, increasing this fraction to 100% cannot account for the increased AUC we observed in the persons with renal failure.

Determination of the ratio of the AUC for GR90291 to remifentanil provides an estimate of the ratio of blood concentrations at steady state. This ratio is approximately 6 for controls and 175–240 for persons with renal failure. Therefore, at steady-state, the concentration of GR90291 would be approximately 6 times higher than remifentanil in control subjects and as much as 240 times the remifentanil concentration in persons with renal failure. An infusion of remifentanil lasting at least 3 days would be necessary to achieve a steady-state blood concentration of GR90291 in a person with renal failure.

Because of the limited sampling for GR90291 in its terminal phase, the AUC for GR90291 may be less accurately estimated in this study than the AUC for remifentanil. We sampled frequently during the remifentanil infusion and frequently during the disappearance of remifentanil, but we did not sample between 6 and 20 h after the end of the remifentanil infusion. During this

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Table 3. Summary of Pharmacokinetic Parameters and Statistical Results for GR90291

Pharmacokinetic Parameter	Low Dose Subjects with Renal Failure	High Dose Subjects with Renal Failure*	High Dose Control Subjects*
AUC_∞ ($ng \cdot min \cdot ml^{-1}$)	21,541 (11,050–41,991)	32,390 (22,842–45,928)	966.7 (786.1–1,189)
P value	0.169†	<0.001‡	
C_{max} (ng/ml)	14.4 (10.0–20.9)	12.4 (10.5–14.8)	4.2 (3.7–4.7)
P value	0.331†	<0.001‡	
Half-life (min)	1,241 (698–2,206)	1,880 (1,241–2,850)	88.0 (75.2–103)
P value	0.171†	<0.001‡	

Values are geometric mean (95% confidence interval).

* AUC and C_{max} values normalized to the low dose.

† Comparison with high dose subjects with renal failure.

‡ Comparison with high dose control subjects.

time period, the concentrations of GR90291 were decreasing slowly in the patients with renal failure. Thus this portion of the disappearance curve was determined essentially by two points. Considering the enormous difference in the clearance of GR90291 in the persons with renal failure compared with the control subjects, even large errors in the determination of AUC for GR90291 could not substantively alter our conclusions about the contribution of GR90291 to the overall opioid effect in the patients with renal failure.

In the patients with renal failure who received hemodialysis therapy on the day after the remifentanil infusion, a series of blood samples was collected from the arterial and venous sides of the hemodialyzer to determine the extraction of GR90291. The results of the arterial and venous samples indicated that GR90291 is approximately 35% extracted when passing through the dialyzer. This is not to say that 35% of the total amount of GR90291 was removed from the body because some may reside in peripheral tissues.

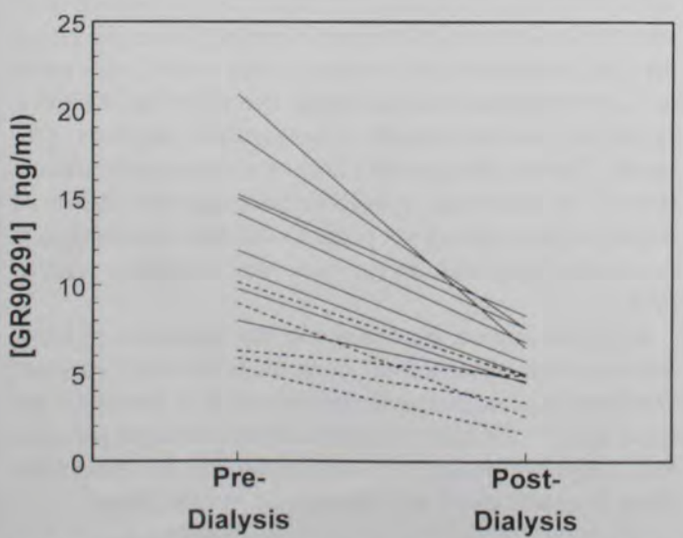

Fig. 3. The decrease in blood concentrations of GR90291 during dialysis. The *dashed lines* represent the persons who received the low-dose infusion of remifentanil; the *solid lines* represent the persons who received the high-dose infusion of remifentanil.

The highest remifentanil infusion rate used in this trial, 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, is lower than the doses now routinely used during general anesthesia with remifentanil and is similar to the remifentanil infusion rates used during monitored anesthesia care to produce analgesia and sedation. To predict the effects of remifentanil and GR90291 after longer infusions at much higher doses in patients with renal failure, we performed infusion simulations using the pharmacokinetic parameters for remifentanil and GR90291 determined in this study.

Using the data for the patients with renal failure receiving the high-dose regimen, the remifentanil and GR90291 concentrations were simultaneously modeled using differential equations (PCNONLIN version 4.2). Although GR90291 may exhibit multicompartmental characteristics, the GR90291 concentration profile observed with the sampling scheme used in this study would not support multicompartmental characteristics. The model used is shown in figure 4 and the following differential equations were used:

$$\frac{dR}{dt} = \frac{K_O}{V_R} - (R \cdot Kt)$$

$$\frac{dM}{dt} = (R \cdot Kf) - (M \cdot Kme)$$

$$= R(Kt - Ke) - (M \cdot Kme)$$

where R and M are the concentrations of remifentanil and GR90291, respectively, K_0 is the remifentanil infu-

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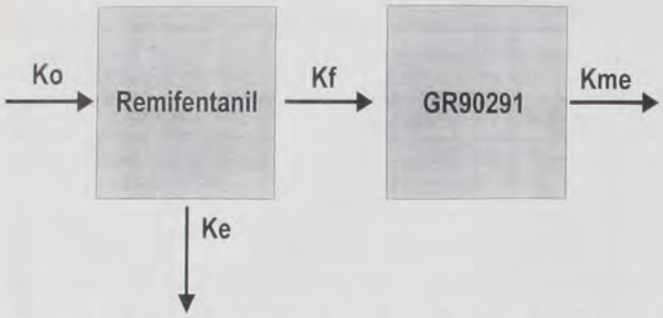

Fig. 4. Pharmacokinetic model for simultaneous analysis of remifentanil and GR90291 in patients with renal failure. See the text for details.

sion rate, V_R is the volume of distribution of remifentanil, Kf is the formation rate of GR90291, Kme is the total elimination rate of GR90291 (*i.e.*, renal and nonrenal), and Kt is the total elimination rate of remifentanil (Kt = Kf + Ke). Because the volume of distribution of GR90291 (V_M) cannot be determined from the data, the rate constant for formation of GR90291 (Kf) is actually a hybrid rate constant representing the ratio of the volume of distribution of remifentanil to GR90291 (V_R/V_M) multiplied by the actual GR90291 formation rate constant. This rate constant also accounts for differences in molecular weight for remifentanil and GR90291. The clearance and volume of distribution of GR90291 cannot be accurately determined from the data without information on the fraction of remifentanil metabolized to GR90291.

A "worst-case" scenario was assumed in which a patient with severe renal failure was given a 12-h remifentanil infusion at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the highest dose recommended for patients having cardiac surgery. After this simulated 12-h infusion, the concentration of GR90291 is predicted to be about 3,000 ng/ml. GR90291 is approximately 4,600 times less potent than remifentanil,[1] thus this predicted concentration of GR90291 would produce an opioid effect approximately equivalent to a remifentanil concentration of 0.65 ng/ml, a concentration achieved at steady-state during an infusion at approximately 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[18] Thus this simulation suggests that after this worst-case scenario, the resulting concentration of GR90291 in a patient with severe renal failure would produce a minimal opioid effect, similar in magnitude to the opioid effect produced by remifentanil at a dose lower than the doses recommended for monitored anesthesia care (0.05–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). At lower infusion rates of remifentanil (*i.e.*, < 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the opioid effect produced by GR90291 in a patient with renal failure is likely to be undetectable.

The sensitivity of the patients with renal failure compared with controls was assessed using the characteristic μ-opioid effects on respiratory function.[19,20] The respiratory stimulant effects of carbon dioxide are suppressed by administration of opioids, and thus minute ventilation during a hypercapnic challenge could be used as a pharmacodynamic indicator of opioid effect. Minute ventilation was previously used as an effective means to assess the relative potency of remifentanil compared with alfentanil ## and to evaluate the sensitivity of persons with hepatic failure compared with control subjects.[11] We had originally intended to model this pharmacodynamic effect and determine the median effective concentration for the persons we studied. Unfortunately, the magnitude of the respiratory effects do not permit an accurate estimate of median effective concentration for some persons. Nevertheless, the effect on ventilation was easily measured and followed a consistent pattern.

Minute ventilation typically showed an initial decline during the first hour of the infusion, and it was followed by a further decline during the remaining 3 h of the increased infusion rate. There was no sign of tolerance to this effect. When the infusion was terminated, the participants showed rapid return of ventilatory responsiveness to the stimulant effects of the carbon dioxide challenge. Shortly after the infusion, minute ventilation determinations exceeded the preinfusion baseline measurements for most of the participants. The explanation for this observation is unclear. It may result from residual cerebrospinal fluid acidosis, the effect of which is uncovered as the opioid concentration declines. The rapid offset of the opioid effect was frequently accompanied by shivering, possibly reflecting the return of the thermoregulatory set point to normal. Shivering may be another explanation for increases in minute ventilation.

As hypothesized, no change in the clearance of remifentanil was observed in persons with renal disease. During a typical surgical procedure in a patient with renal failure, the concentration of the principal metabolite, GR90291, is unlikely to accumulate to concentrations that will elicit any significant opioid effect.

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