End-stage renal failure reduces central clearance and prolongs the elimination half life of remifentanyl

[L'insuffisance rénale terminale réduit la clairance centrale et prolonge la demi-vie d'élimination du rémifentanyl]

Ashraf A. Dahaba MD MSc,* Karl Oettl PhD,† Fedor von Klobucar MD,* Gilbert Reibnegger PhD,†
Werner F. List MD*

Purpose: To evaluate the pharmacokinetics of remifentanyl in 13 end-stage renal failure patients compared to matched control patients with normal renal function.

Methods: Remifentanyl was infused for 20 min at a rate of $0.1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Serial arterial blood samples (3 mL) were drawn at the start of infusion (zero), five, ten, 15, 20, 22.5, 25, 27.5, 30, 35, 40, 45, 50, 55 and 60 min. Blood samples were immediately preserved with citric acid and chilled on ice. High performance liquid chromatography-tandem mass spectrometry concentration assay was performed using GI 95779B internal standard.

Results: A two-compartment pharmacokinetic model provided an adequate fit for individual patient data. There was no difference in the mean $\pm$ SD distribution half life ($t_{1/2\alpha}$) between the renal failure group (1.65 ± 0.7 min) and the control group (1.58 ± 0.54 min). There was a significant difference in the central clearance (Cl_c) and elimination half life ($t_{1/2\beta}$) between the renal failure group ($28 \pm 7 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and 18.86 ± 2.06 min, respectively) and the control group ($46.3 \pm 13.8 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and 16.35 ± 2.99 min, respectively). Remifentanyl blood concentrations were significantly higher in the renal failure group than in the control group.

Conclusion: We have demonstrated a significant reduction in the Cl_c and a prolongation of $t_{1/2\beta}$ of remifentanyl in end-stage renal failure patients. While statistically significant, these variations in the pharmacokinetics of remifentanyl were clinically modest and may be explained by a reduced volume of distribution in the period following hemodialysis.

Méthode : Le rémifentanyl a été perfusé pendant 20 min à $0,1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Une série d'échantillons de sang artériel (3 mL) a été prélevée au début de la perfusion (zéro), puis à cinq, dix, 15, 20, 22,5, 25, 27,5, 30, 35, 40, 45, 50, 55 et 60 min. Le sang a été préservé avec de l'acide citrique et conservé sur de la glace. Une analyse des concentrations par chromatographie liquide haute performance et spectrométrie de masse en tandem a été réalisée en utilisant un étalon interne GI 95779B.

Résultats : Un modèle pharmacocinétique à deux compartiments a fourni un ajustement adéquat des données de chaque patient. Il n'y a pas eu de différence de demi-vie de distribution moyenne $\pm$ l'écart type ($t_{1/2\alpha}$) entre les patients atteints d'insuffisance rénale ($1,65 \pm 0,7$ min) et les patients témoins ($1,58 \pm 0,54$ min). Il y a eu une différence significative de clairance centrale (Cl_c) et de demi-vie d'élimination ($t_{1/2\beta}$) entre le groupe d'insuffisance rénale ($28 \pm 7 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ et $18,86 \pm 2,06$ min, respectivement) et le groupe témoin ($46,3 \pm 13,8 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ et $16,35 \pm 2,99$ min, respectivement). Les concentrations sanguines de rémifentanyl ont été significativement plus élevées chez les patients atteints d'insuffisance rénale.

Conclusion : Nous avons démontré une réduction significative de la Cl_c et une prolongation de $t_{1/2\beta}$ du rémifentanyl chez des patients atteints d'insuffisance rénale terminale. Quoique statistiquement significatives, ces variations de la pharmacocinétique du rémifentanyl sont cliniquement faibles et peuvent s'expliquer par la réduction du volume de distribution qui suit l'hémodialyse.

Objectif : Évaluer la pharmacocinétique du rémifentanyl chez 13 patients présentant une insuffisance rénale terminale, comparés à des témoins appariés dont la fonction rénale est normale.

From the Departments of Anaesthesiology and Intensive Care Medicine,* and Medical Chemistry and Pregl Laboratory,† Karl-Franzens University, Graz, Austria.

Address correspondence to: Dr. Ashraf Dahaba, Department of Anaesthesiology and Intensive Care Medicine, Karl-Franzens University, Auenbruggerplatz 29, A-8036, Graz, Austria. Phone: ++ 43-316-385-2829; Fax: ++ 43-316-385-3267; E-mail: Ashraf.Dahaba@kfunigraz.ac.at

Accepted for publication November 13, 2001.

Revision accepted January 18, 2002.

PATIENTS with end-stage renal failure require anesthesia for various surgical procedures from vascular access for hemodialysis to kidney transplantation. An opioid, which is independent of renal metabolism, would be valuable in such a case. Remifentanyl hydrochloride is a potent ultra-short-acting μ receptor agonist. Its methyl propionic acid ester side chain makes it highly susceptible to rapid hydrolysis by nonspecific naturally present plasma and tissue esterases.¹

End-stage renal failure patients manifest fluid volume depletion following recent hemodialysis.² However, their impaired compensatory responses,³ the associated biochemical and physiological disturbances such as renin-angiotensin disorders,⁴ in addition to the long-term antihypertensive therapies result in a reduced ability to regulate fluid volume status, and hence might modify the distribution, elimination and clearance of remifentanyl. The purpose of this study was to evaluate the pharmacokinetics of remifentanyl in 13 end-stage renal failure patients compared to matched control patients with normal renal function.

Patients and methods

Study design

A prospective controlled clinical consecutive study was conducted in conformity with the guidelines of the "consolidated standards of reporting trials (CONSORT)-statement".⁵ We considered remifentanyl elimination half life ($t_{1/2}$) as the primary clinical variable upon which *a priori* power analysis for t test was performed. Based upon previously reported data,⁶ an assumed $t_{1/2}$ of nine minutes revealed that a group size of 13 would be required to detect a two-minute difference between the two groups with > 0.8 power. After approval of our Institutional Ethics Committee, all patients who agreed to participate in the study gave a written informed consent. We excluded potential participants with a known hypersensitivity to opioids or with 20% deviation from ideal body weight. None of the female participants were pregnant or breast feeding. Recruitment was three to four patients per week in the period from May 7 2001 until June 28 2001.

Thirteen end-stage renal failure patients, undergoing the creation of end-to-side arterio-venous fistulas or insertion of a prosthetic arterio-venous graft were included in the study. Each end-stage renal failure patient was matched for gender, age and body weight with an ASA I-II patient with normal renal function who was undergoing an elective surgical procedure expected to last 1–1.5 hr. All patients had preoperative measurements of creatinine clearance, serum creati-

nine, urea, hemoglobin and potassium concentrations. Patients in the renal failure group had undergone hemodialysis within 24 hr prior to surgery and were receiving human recombinant erythropoietin therapy.

Anesthesia protocol

Patients were premedicated with 5–10 mg midazolam orally one hour before the operation. Anesthesia was induced with 2–3 mg·kg⁻¹ propofol until the eyelash reflex was obtunded. Remifentanyl was infused for 20 min,⁶ at a clinically relevant rate of 0.1 μ g·kg⁻¹·min⁻¹. Following termination of the remifentanyl infusion, analgesia was maintained with 50–100 μ g fentanyl supplements. The trachea was intubated following 0.6 mg·kg⁻¹ rocuronium administration. Anesthesia was maintained with 60% nitrous oxide in oxygen and 0.1–0.15 mg·kg⁻¹·min⁻¹ propofol infusion. Ringer's lactate solution was infused in the control patients, and potassium-free Ringer's acetate was infused in the renal failure patients to replace fluid loss.

Blood sample acquisition, handling and processing

Serial arterial blood samples (3 mL) were drawn at the start of infusion (zero), five, ten, 15, 20, 22.5, 25, 27.5, 30, 35, 40, 45, 50, 55 and 60 min. Blood samples were immediately preserved by the addition of 50 μ L of 50% citric acid then chilled on ice.

Remifentanyl concentration assay

After all samples were collected, a modified Selinger *et al.*⁷ method was used for the extraction. The samples were denatured by the addition of 1 mL of 1 mol·L⁻¹ phosphate buffer (pH 7.4) and 5 mL n-butyl chloride to 1 mL of blood. One hundred μ L (50 μ g·L⁻¹ in acetonitrile) of the internal standard GI 95779B (GlaxoSmithKline, Middlesex, UK) were added. The tubes were then roto-mixed for ten minutes, centrifuged at 1800 g at 4°C for another ten minutes. The organic layer was transferred into a conical tube and the solvent evaporated under nitrogen at 37°C. The residue was dissolved in 150 μ L of acetonitrile.

Blood samples were analyzed in duplicate. Fifty μ L of the samples were injected into a high performance liquid chromatograph (Spectronex, Vienna, Austria). Separation was conducted using a 200 $\times$ 3 mm column filled with cyanopropyl silica (prontosil 120-3-CN particles) and 10 mM ammonium acetate with 1% acetic acid in 30% acetonitrile as solvent. The system was coupled with an ion trap mass spectrometer (Finnigan, San Jose, USA) equipped with an atmospheric pressure chemical ionisation ion source in the tandem mass spectrometer mode. The mother ions for remifentanyl (377.2 m/z⁻¹) and the internal standard

TABLE I Patient demographics and preoperative blood investigations

	Control group	Renal failure group	P value
Male/female	7/6	7/6	
Age (yr)	58.2 ± 11.5	60.5 ± 7.7	0.632
Weight (kg)	69 ± 18.4	72.8 ± 12.8	0.515
Cr (μmol·L ⁻¹)	93.9 ± 11.2	494.1 ± 99.3	0.001
Cl _{cr} (mL·min ⁻¹ ·1.73 m ⁻²)	75.1 ± 9	9.5 ± 3.9	0.011
Urea (mmol·L ⁻¹)	5.8 ± 2.3	16.1 ± 4.4	0.014
Hb (g·dL ⁻¹)	15.1 ± 0.8	10.4 ± 0.9	0.0001
K ⁺ (mmol·L ⁻¹)	4 ± 0.1	4.4 ± 0.9	0.534

Mean ± SD; *n* = 13; Cr = creatinine; Cl_{cr} = creatinine clearance; Hb = hemoglobin; K⁺ = potassium.

(391.2 m z⁻¹) were isolated and fragmented with collision energy of 15%. For quantification, the ratio of peak areas remifentanil/internal standard were taken from the chromatogram of the almost exclusive remifentanil daughter ion (344.9 m z⁻¹) and that of the internal standard (358.9 m z⁻¹). The internal standard levels were used to rectify any variations in recovery and stability among samples. Two sets of calibration curves for quantification were constructed using blank blood spiked with remifentanil (0.5, 1, 2, 5 and 10 μg·L⁻¹) and internal standard (50 μg·L⁻¹) with a lower quantification limit of 0.1 μg·L⁻¹.

Pharmacokinetic analysis

The pharmacokinetic analysis was performed using the SCIENTIST® program (MicroMath Scientific Software Inc., Salt Lake City, Utah, USA). Data analysis involved fitting the remifentanil blood concentration time profile of individual patients to non-compartmental as well as multi-compartmental pharmacokinetic models.

Moment analysis

A classic non-parametric moment analysis was applied to calculate the model independent pharmacokinetic parameters. The area under the concentration *vs* time curve (AUC) was calculated by the linear trapezoidal method. Mean residence time (MRT) is equivalent to a time constant for a single compartment model and indicates the time taken for 63.2% of a remifentanil dose to leave the body (Appendix).

Non-linear mixed effects model compartmental analysis

The parametric non-linear mixed effects model compartmental goodness of fit analysis for individual patients was performed. The model comprised central

TABLE II Pharmacokinetic variables

	Control group	Renal failure group	P value
Moment analysis			
AUC (μg·min ⁻¹ ·L ⁻¹)	46.2 ± 11.9	75.9 ± 21.4	0.009
MRT (min)	11.6 ± 5.01	11.92 ± 3.18	0.895
Vd _{ss} (mL·kg ⁻¹)	566.4 ± 116.3	358 ± 57.7	0.002
Cl (mL·kg ⁻¹ ·min ⁻¹)	48.7 ± 14.6	29.9 ± 7.8	0.017
Non-linear mixed effects model compartmental analysis			
<i>Micro rate constants (min⁻¹)</i>			
K ₁₀	0.32 ± 0.17	0.29 ± 0.14	0.697
K ₁₂	0.15 ± 0.05	0.19 ± 0.11	0.357
K ₂₁	0.07 ± 0.02	0.07 ± 0.02	0.884
<i>Apparent volumes of distribution (mL·kg⁻¹)</i>			
V ₁	176.5 ± 33.4	118.3 ± 27.1	0.006
V ₂	392.3 ± 99.2	291.5 ± 59.1	0.045
Vd _{ss}	568.9 ± 118	410 ± 83.6	0.019
<i>Central clearance (mL·kg⁻¹·min⁻¹)</i>			
Cl _c	46.3 ± 13.8	28 ± 7	0.014
<i>Fractional coefficients (μg·L⁻¹)</i>			
A	14.48 ± 9.29	19.55 ± 8.49	0.307
B	0.79 ± 0.37	1.35 ± 0.36	0.019
<i>Hybrid rate constants (min⁻¹)</i>			
α	0.49 ± 0.19	0.5 ± 0.25	0.927
β	0.04 ± 0.01	0.03 ± 0.01	0.643
<i>Half lives (min)</i>			
t _{1/2} α	1.58 ± 0.54	1.65 ± 0.7	0.856
t _{1/2} β	16.35 ± 2.99	18.86 ± 2.06	0.045

Mean ± SD; *n* = 13; AUC = blood remifentanil concentration *vs* time area under the curve; MRT = mean residence time; Vd_{ss} = apparent volume of distribution at steady state; Cl = clearance; K₁₀ = elimination rate constant; K₁₂, K₂₁ = inter-compartment rate constants; V₁ = central volume of distribution; V₂ = peripheral volume of distribution; Cl_c = central clearance; α, β = hybrid rate constants; t_{1/2} α = distribution half life; t_{1/2} β = elimination half life.

and peripheral compartments with exit and input into the central compartment, and elimination only from the central compartment. Alpha and β indicate the hybrid rate constants, since each comprises elements of distribution as well as elimination (Appendix).

Statistical analysis

As our data displayed a normal distribution, the *t* test for difference between means was used for data analysis. Repeated measures analysis of variance (ANOVA) was used for remifentanil blood concentrations group comparison. Data were expressed as mean ± SD. *P* < 0.05 was considered statistically significant.

Results

The two groups were comparable with respect to body weight at the day of surgery and age. Blood investigations in the renal failure group were typical of patients undergoing regular hemodialysis (Table I).

FIGURE Remifentanyl blood concentrations *vs* time decay curve. Mean $\pm$ SD; $n = 13$. Remifentanyl blood concentrations were significantly higher in the renal failure group than in the control group (repeated measures ANOVA, $P < 0.05$).

In the blood concentration *vs* time decay curve, remifentanyl concentrations were significantly higher in the renal failure group compared to the control group (Figure).

Moment analysis

There was no difference in the MRT between the two groups. The AUC was higher, while the volume of distribution at steady state ($V_{d_{ss}}$) and clearance (Cl) were reduced in the renal failure group compared to the control group (Table II).

Non-linear mixed effects model compartmental analysis

There was no difference in the exit, inter-compartment rate constants or distribution half life ($t_{1/2\alpha}$) between the two groups. The volumes of distribution and central clearance (Cl_c) were reduced, while $t_{1/2\beta}$ was prolonged, in the renal failure group compared to the control group (Table II).

Discussion

Moment analysis

Our results of a classic moment analysis in patients with normal renal function (Cl of $3.3 \text{ L}\cdot\text{min}^{-1}$, MRT

of 11.6 min, and a $V_{d_{ss}}$ of 37.6 L) are in accordance with previous model-independent studies. Remifentanyl Cl of $2.9 \text{ L}\cdot\text{min}^{-1}$, MRT of 10.9 min, and a $V_{d_{ss}}$ of 31.8 L were reported in two studies.^{6,8} Three $\text{L}\cdot\text{min}^{-1}$ Cl, eight minutes MRT and 24.1 L $V_{d_{ss}}$ were reported in a third study.⁹

Non-linear mixed effects model compartmental analysis

In our study, compartmental statistical analysis of the goodness of fit demonstrated that a two-compartment model provided an adequate fit for individual patient data. This is consistent with a central compartment comprising blood and rapidly perfused tissues through which remifentanyl distributes rapidly and a peripheral compartment comprising adipose and other, less perfused, tissues through which remifentanyl distributes more slowly.

Our study revealed that remifentanyl blood concentration *vs* time decay was bi-exponential as blood concentrations leveled out at the lower quantification limit of the assay ($0.1 \mu\text{g}\cdot\text{L}^{-1}$) near the end of the 60 min sampling period. This implies that distribution to a much smaller third compartment, below the lower sensitivity limit of our assay could still be present.

Since our study was designed to evaluate remifentanil pharmacokinetics in clinically relevant infusion rates, this did not allow us to demonstrate if a tri-exponential decay to a smaller third compartment would exist with much higher infusion rates. The elimination characteristics of remifentanil were previously described by bi-exponential,¹⁰ or tri-exponential,^{6,8,9} rates of decline, reflecting elimination from two or three compartments respectively. A two-compartment model was reported to describe remifentanil kinetics accurately for the first postinfusion hour.⁶ The distribution of remifentanil into a third compartment, with much higher doses, was quite limited and accounted for less than 5% of the total exposure.⁶

The results of the present study in patients with normal renal function (Cl_c of $3.2 \text{ L}\cdot\text{min}^{-1}$, $t_{1/2\alpha}$ of 1.6 min, and a Vd_{ss} of 38.1 L) were comparable to previous multi-compartment analysis studies, in which remifentanil Cl_c of $2.8\text{--}2.9 \text{ L}\cdot\text{min}^{-1}$, $t_{1/2\alpha}$ of 0.9 min, and a Vd_{ss} of $21.8\text{--}32.8 \text{ L}$ were reported.^{6,9}

End-stage renal failure

Using a one-compartment model for data analysis, Hoke *et al.*¹¹ reported no significant difference between remifentanil pharmacokinetics in healthy volunteers and those with renal disease. This is in contrast to our results, which clearly demonstrate that remifentanil exhibited a bi-exponential decay in patients of both groups. Data analysis based only on a one-compartment model would not be adequate in such a case.

Our results show a significant alteration in remifentanil pharmacokinetics in end-stage renal failure. This cannot be explained only by degradation, since remifentanil metabolism is esterase based which, probably, makes its degradation independent of renal function. However, the role of the kidney cannot be totally excluded since the elimination of the principal metabolite of remifentanil GI 90291, which possesses $1/300\text{--}1/1000$ the potency of the parent compound,⁸ has been reported to be markedly reduced in renal failure.¹¹

A possible explanation is that end-stage renal failure patients manifest fluid volume depletion following recent dialysis.² In addition, the numerous biochemical and physiological disturbances associated with end-stage renal failure result in a reduced ability to regulate fluid volume status.⁴ This was evidenced by the reduced volumes of distribution in renal failure patients. Since dosing of remifentanil was based on the patients' body weight on the day of surgery, this would result in a higher remifentanil blood concentration in the hypovolemic end-stage renal failure patients when compared to the matched-for-weight control patients. This would consequently reduce Cl_c and prolong $t_{1/2\beta}$.

In our study, the Vd_{ss} in the renal failure group ($358 \pm 57.7 \text{ mL}\cdot\text{kg}^{-1}$) was significantly lower than that of the control group ($566.4 \pm 116.3 \text{ mL}\cdot\text{kg}^{-1}$). Conversely, Hoke *et al.*¹¹ reported a higher volume of distribution in volunteers with renal failure ($229 \text{ mL}\cdot\text{kg}^{-1}$) compared to healthy volunteers ($191 \text{ mL}\cdot\text{kg}^{-1}$), which they attributed to the patients becoming hypervolemic between hemodialysis treatments. However, this did not result in a significant difference in the pharmacokinetic parameters reported. One of the differences between their study and ours may be that remifentanil was infused on the day before their study patients' next scheduled hemodialysis. This was not the case in our study where patients, by study design, underwent hemodialysis on the day prior to surgery. We believe this is more in line with common anesthesia practice in patients with end-stage renal failure undergoing elective surgery. Thus, volume status of these patients may have differed between the two studies, explaining (in part at least) the different results. Another difference is the smaller number of patients in Hoke *et al.*'s study¹¹ ($n = 8$) compared to ours ($n = 13$, the number required to detect a significant difference between the two groups with > 0.8 power). In addition, the infusion rates used in the Hoke *et al.*¹¹ trial ($0.025\text{--}0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) were lower than the clinically relevant doses that would be used during general anesthesia for end-stage renal failure patients.

It should be noted that an alteration of remifentanil pharmacokinetics in end-stage renal failure does not necessarily reflect a clinically significant prolongation of therapeutic effect. The pharmacodynamic recovery parameters, following a clinically relevant remifentanil infusion, as we have shown in a previous study,¹² were not significantly prolonged in end-stage renal failure patients compared to patients with normal renal function.

In conclusion, we have demonstrated a significant reduction in the Cl_c and a prolongation of $t_{1/2\beta}$ of remifentanil in end-stage renal failure patients. While statistically significant, these variations in the pharmacokinetics of remifentanil were clinically modest and may be explained by a reduced volume of distribution in the period following hemodialysis.

Acknowledgement

The authors would like to thank Elisabeth Koppe, Department of Medical Chemistry and Pregl Laboratory, Karl Franzens University, for her meticulous work in remifentanil processing and concentration assays. Her great efforts were indeed a valuable contribution to the study.

APPENDIX Pharmacokinetic variables and calculations*Moment analysis*

AUC = area under the concentration vs time curve

Cl = clearance

Cl = dose /AUC

MRT = mean residence time

$V_{d_{ss}}$ = apparent volume of distribution at steady state

$V_{d_{ss}}$ = Cl $\times$ MRT

Non-linear mixed effects model compartmental analysis

K_{10} = central compartment elimination rate constant

K_{12} = central to peripheral compartment rate constant

K_{21} = peripheral to central compartment rate constant

V_1 = central volume of distribution

V_2 = peripheral volume of distribution

Cl_c = central clearance

$Cl_c = K_{10} \times V_1$

A = concentration intercept at time zero of the distribution phase

α = distribution rate constant

$t_{1/2\alpha}$ = distribution half life

B = concentration intercept at time zero of the elimination phase

β = elimination rate constant

$t_{1/2\beta}$ = elimination half life

References

- 1 Birkle H, Dunbar S, Van Aken H. Remifentanyl: a novel, short-acting, μ -opioid. *Anesth Analg* 1996; 83: 646–51.
- 2 Henderson LW. Symptomatic hypotension during hemodialysis. *Kidney Int* 1980; 17: 571–6.
- 3 Lazarus JM, Hampers CL, Lowrie EG, Merrill JP. Baroreceptor activity in normotensive and hypertensive uremic patients. *Circulation* 1973; 47: 1015–21.
- 4 Bailey JL, Mitch WE. Pathophysiology of uremia. In: Brenner BM (Ed.) *The Kidney*, 6th ed. Philadelphia: WB Saunders Company, 2000: 2059–78.
- 5 Moher D, Schulz KF, Altman DG, for the CONSORT group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; 357: 1191–4.
- 6 Egan TD, Lemmens HJM, Fiset P, et al. The pharmacokinetics of the new short-acting opioid remifentanyl (GI87084B) in healthy adult male volunteers. *Anesthesiology* 1993; 79: 881–92.
- 7 Selinger K, Lanzo C, Sekut A. Determination of remifentanyl in human and dog blood by HPLC with UV detection. *J Pharm Biomed Anal* 1994; 12: 243–8.
- 8 Westmoreland CL, Hoke JF, Sebel PS, Hug CC Jr, Muir KT. Pharmacokinetics of remifentanyl (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 1993; 79: 893–903.
- 9 Egan TD, Minto CE, Hermann DJ, Barr J, Muir KT, Shafer SL. Remifentanyl versus alfentanil. Comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. *Anesthesiology* 1996; 84: 821–33.
- 10 Glass PSA, Hardman D, Kamiyama Y, et al. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanyl (GI87084B). *Anesth Analg* 1993; 77: 1031–40.
- 11 Hoke JF, Shlugman D, Dershwitz M, et al. Pharmacokinetics and pharmacodynamics of remifentanyl in persons with renal failure compared with healthy volunteers. *Anesthesiology* 1997; 87: 533–41.
- 12 Dababa AA, von Klobucar F, Rehak PH, List WF. Total intravenous anesthesia with remifentanyl, propofol and cisatracurium in end-stage renal failure. *Can J Anesth* 1999; 46: 696–700.