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Non–steady State Analysis of the Pharmacokinetic Interaction between Propofol and Remifentanil

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Background: **The pharmacokinetics of both propofol and remifentanil have been described extensively. Although they are commonly administered together for clinical anesthesia, their pharmacokinetic interaction has not been investigated so far. The purpose of the current investigation was to elucidate the nature and extent of pharmacokinetic interactions between propofol and remifentanil.**

Methods: **Twenty healthy volunteers aged 20–43 yr initially received either propofol or remifentanil alone in a stepwise incremental and decremental fashion *via* a target controlled infusion. Thereafter, the respective second drug was infused to a fixed target concentration in the clinical range (0–4 μg/ml and 0–4 ng/ml for propofol and remifentanil, respectively) and the stepwise incremental pattern repeated. Frequent blood samples were drawn for up to 6 h for propofol and 40 min for remifentanil after the end of administration and assayed for the respective drug concentrations with gas chromatography–mass spectrometry. The time courses of the measured concentrations were fitted to standard compartmental models. Calculations were performed with NONMEM. After having established the individual population models for both drugs and an exploratory analysis for hypothesis generation, pharmacokinetic interaction was identified by including an interaction term into the population model and comparing the value of the objective function in the presence and absence of the respective term.**

Results: **The concentration–time courses of propofol and remifentanil were described best by a three- and two-compartment model, respectively. In the concentration range examined, remifentanil does not alter propofol pharmacokinetics. Coadministration of propofol decreases the central volume of distribution and distributional clearance of remifentanil by 41% and elimination clearance by 15%. This effect was not concentration-dependent in the examined concentration range of propofol.**

Conclusions: **Coadministration of propofol decreases the bolus dose of remifentanil needed to achieve a certain plasma–effect compartment concentration but does not alter the respective maintenance infusion rates and recovery times to a clinically significant degree.**

THE pharmacokinetics of propofol[1–14] and remifentanil[15–22,23] have been extensively investigated. Although propofol and remifentanil are frequently coadministered in clinical practice, very little is known about their pharmacokinetic and pharmacodynamic interaction. The purpose of this investigation was to quantify the extent of pharmacokinetic interaction between propofol and remifentanil in the clinically relevant concentration range.

Methods

Subjects

The study was approved by the Stanford University Institutional Review Board. Written informed consent was obtained from each subject. Ten male and 10 female healthy volunteers (median age, 33.5 yr [range, 20–43 yr]; median weight, 69.3 kg [range, 50–120 kg]) were studied. All volunteers underwent a physical examination, laboratory tests (complete blood cell count, blood chemistries [SMA 20]), and an electrocardiogram.

Study Design

This was a randomized prospective open-label study. After arrival at the operating room, an electrocardiograph, a pulse oximeter, and a noninvasive blood pressure monitor were attached to the volunteer. Thereafter, two intravenous cannulae for drug and fluid administration were placed in a forearm vein on each arm. A 20-gauge plastic cannula was inserted into the radial artery of the nondominant hand for blood sampling. The volunteers received 30 ml magnesium citrate and were supplied with a tight-fitting facemask for the determination of dead space and carbon dioxide responsiveness necessitated by pharmacodynamic aspects of the study and breathed 100% oxygen throughout the drug administration period. Ventilation and end-tidal carbon dioxide pressure were measured and recorded continuously with an anesthesia monitor (Datex, AS3; Helsinki, Finland). Drugs were administered *via* target controlled infusion with a Harvard infusion pump (Harvard Clinical Technology, Inc., South Natick, MA) driven by STANPUMP‖ running on a commercially available laptop computer. The propofol pharmacokinetic parameters were the non–weight-adjusted set reported by Schnider *et al.*[11] The remifentanil pharmacokinetics were the weight-adjusted set reported by Minto *et al.*[23] The administration schedule was optimized for a single drug pharmacodynamic study (respiratory depression) followed by a pharmacodynamic interaction study (central nervous system depression). Throughout the study, the attending anesthesiologist could administer additional drugs as deemed necessary. The main

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‖ Available at no charge from Steven Shafer, M.D., Professor of Anesthesia, Department of Anesthesia, Stanford Medical School, Stanford, California, at http://anesthesia.stanford.edu/pkpd/.

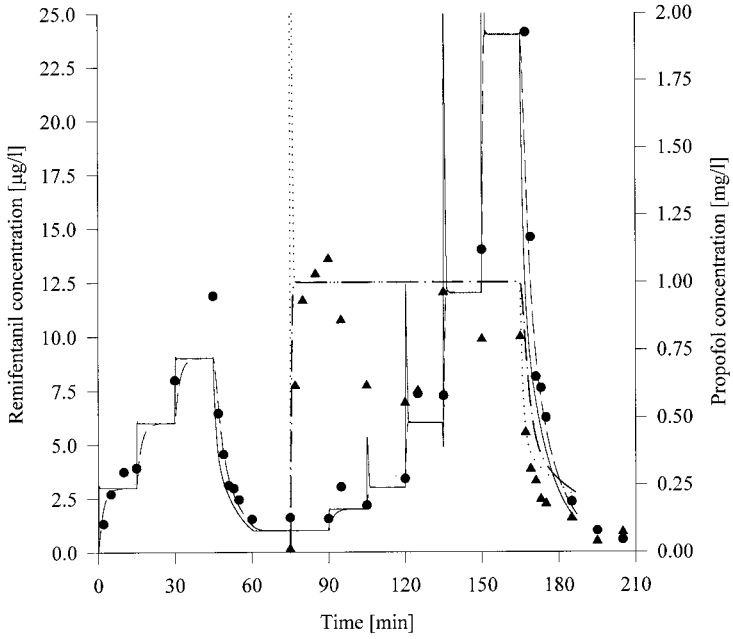

Fig. 1. Target controlled infusion administration schedule in one patient. Initially, either propofol or remifentanil (here remifentanil) was stepped up to characterize its respiratory-depressant potency. Thereafter, the concentrations were allowed to passively decrease to 1 ng/ml for remifentanil (1 μg/ml for propofol), the second drug (here propofol) was started (maintained at a constant concentration), and the first drug stepped up again to characterize the pharmacodynamic interaction with regard to central nervous system depression. (-) Target controlled infusion predicted remifentanil blood concentrations *versus* time; (- - -) corresponding effect compartment concentrations; (...) target controlled infusion–predicted propofol plasma concentrations; (-...-) corresponding effect compartment concentrations; (●) measured remifentanil concentrations; (▲) measured propofol concentrations.

Table 1. Combination of Propofol–Remifentanil

(*A*) Changing propofol (P) Concentrations, Constant Remifentanil (R) Concentrations

Individual	Peak Concentration P only [μg/ml]	Peak Concentration P for P + R [μg/ml]	R Concentration [ng/ml]
3	8	12	0
11	12	12	0
6	12	6	1
7	8	4	2
14	6	3	2
15	9	3	2
12	9	3	3
13	9	2	3
5	9	4	4
18	6	3	4

(B) Changing Remifentanil (R) Concentrations, Constant Propofol (P) Concentrations

Individual	Peak Concentration R only [ng/ml]	Peak Concentration R for R + P [ng/ml]	P Concentration [μg/ml]
1	3	24	0
2	4.5	40	0
16	3	3	1
17	9	24	1
8	3	4	2
20	6	3	2
9	7.5	3	3
19	3	5	3
4	6	1	4
10	9	2	4

(*A*) With the exception of two volunteers (3,11; propofol only), every patient received a step up–down infusion of propofol, followed by a step up–down infusion of propofol in the presence of a constant concentration of remifentanil. The first concentration indicated refers to the highest concentration achieved during the respiratory depression phase (single drug administration), the second concentration indicated refers to the highest concentration achieved during the CNS depression–interaction phase (changing concentrations of the first drug and constant concentrations of the respective second drug). The concentration ranges were determined by pharmacodynamic considerations (see Methods). The remifentanil target for one patient (15) was erroneously set to 2 ng/ml instead of 1 ng/ml. (*B*) With the exception of two volunteers (1,2; remifentanil only), every patient received a step up–down infusion of remifentanil, followed by a step up–down infusion of remifentanil in the presence of a constant concentration of propofol. The first concentration indicated refers to the highest concentration achieved during the respiratory depression phase (single drug administration), the second concentration indicated refers to the highest concentration achieved during the CNS depression–interaction phase (changing concentrations of the first drug and constant concentrations of the respective second drug). The concentration ranges were determined by pharmacodynamic considerations (see text).

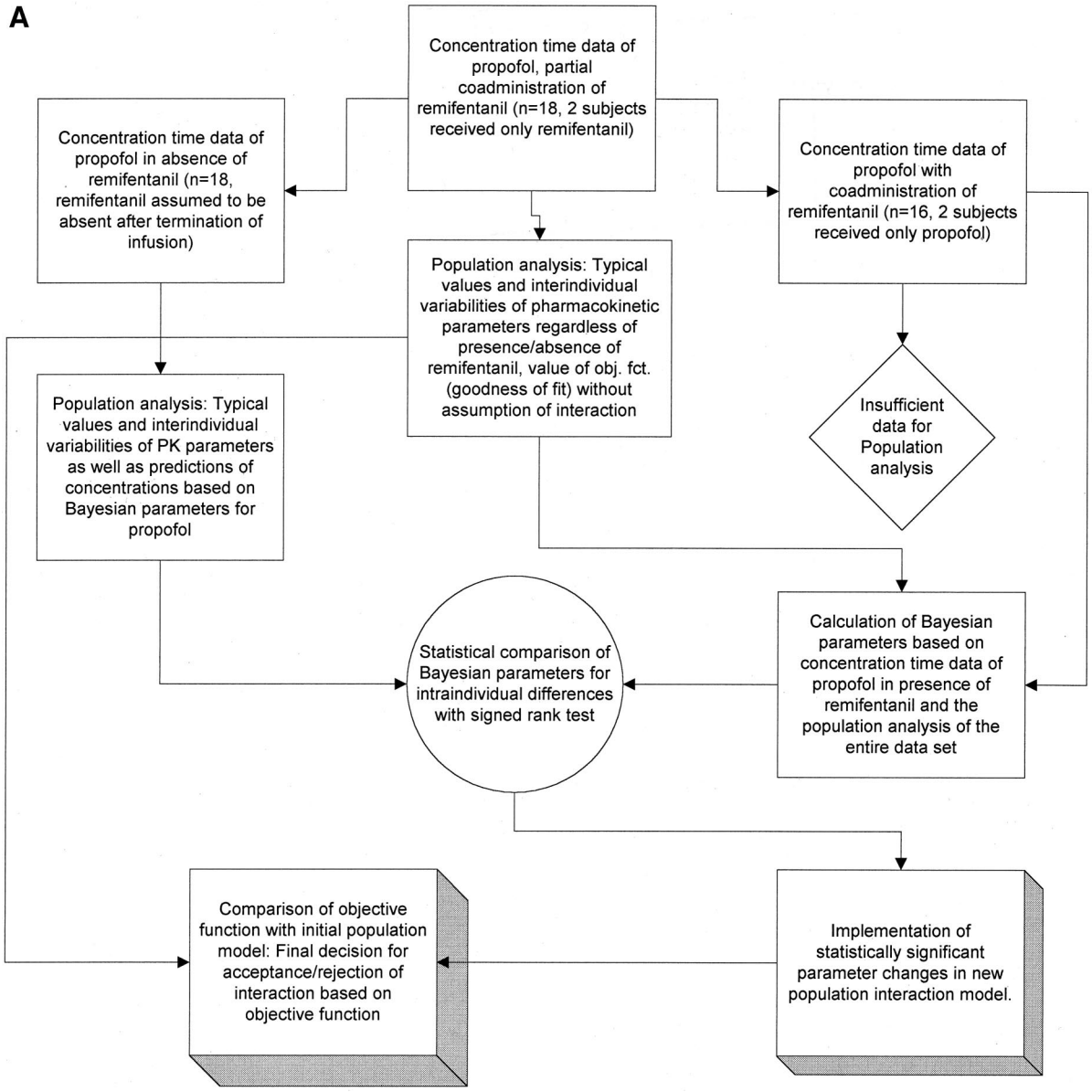

Fig. 2. (*A*) Algorithm used to determine the influence of remifentanil coadministration on the pharmacokinetics of propofol. Eighteen of 20 volunteers received propofol, 16 of 20 volunteers received propofol both in presence and absence of remifentanil. For details see Methods. (*continues*)

expected side effects in the concentration range include nausea (treated with metoclopramid, ondansetron), hypotension (treated with ephedrine, phenylephrine), bradycardia (treated with glycopyrrolate), muscular rigidity (prophylactic treatment with muscle relaxants). Figure 1 displays an example of the administration schedule in one patient.[17] Initially, the volunteers received either propofol or remifentanil (as in fig. 1) alone in a stepwise ascending fashion until their end-tidal carbon dioxide pressure exceeded 65 mmHg or apnea periods of more than 60 s occurred. Thereafter, a target effect compartment concentration of 1 μg/ml for propofol (1 ng/ml for remifentanil) was chosen. As soon as this concentration has been maintained for at least 10 min according to the target controlled infusion predictions, the administration of the respective second drug (propofol in fig. 1) was started. During this phase of the study, end-tidal carbon dioxide pressure was kept constant at 40 mmHg with mask ventilation. The target effect compartment concentration for the second drug was kept constant throughout the pharmacodynamic interaction study. Thereafter, the target effect compartment concentration of the respective first drug (remifentanil in fig. 1) was stepped up again until the volunteer did not respond to laryngoscopy with coughing or movement. Having reached this endpoint, both drug infusions were simultaneously discontinued, allowing propofol and remifentanil concentrations to decrease passively to zero. The number of steps during stepping up and the respective

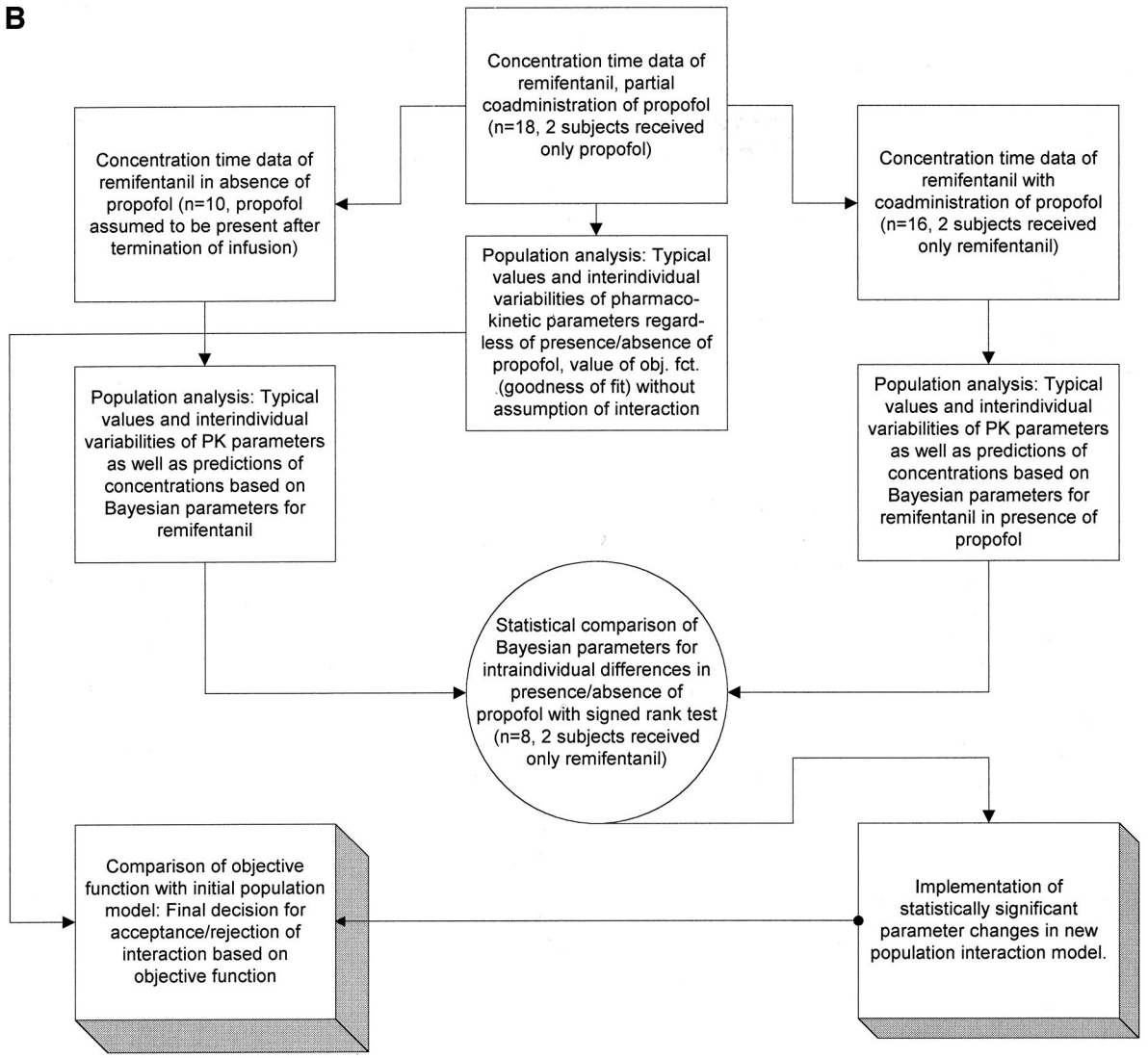

Fig. 2. (*Continued*) (*B*) Algorithm used to determine the influence of propofol coadministration on the pharmacokinetics of remifentanil. Eighteen of 20 volunteers received remifentanil, 8 of 20 volunteers received remifentanil both in presence and absence of propofol. For details see Methods.

(peak) targeted concentrations were therefore determined by the sensitivity of the respective individual to the respiratory and central nervous system–depressant effects of the drugs, whereas the order of administration and the constant target concentration used for the second drug was allocated to each individual prior to the experiment using a randomization list. Table 1 displays the peak target concentrations achieved and the allocated constant target concentrations for the second drug. The constant remifentanil target for one patient was erroneously set to 2 ng/ml instead of 1 ng/ml.

Blood sampling was timed according to pharmacokinetic, pharmacodynamic, and efficiency considerations. A blank sample for both drugs was drawn after insertion of the arterial cannula. Since the study consisted of different phases, the durations of which were not exactly known at the beginning, sampling times were chosen based on the following events: start of the first infusion, step changes of the target concentrations, decrease of the target concentrations at the end of the single drug administration part, start of the second infusion, step changes of the target concentrations during coadministration of both drugs, and simultaneous cessation of both infusions.

Sampling Schedule for the First Drug Administered

Regardless of whether propofol or remifentanil was administered first, blood samples were drawn 2, 5, 10, and 15 min from the start of the infusion. For every further step up, one sample was drawn immediately prior to changing the target concentration. During the passive decrease down to 1 μg/ml for propofol or 1 ng/ml for remifentanil, samples were drawn at 2, 5, 10, 15, 20, and 30 min for propofol and 2, 4, 6, 8, 10, 15, and

30 min for remifentanil, after changing the target concentration. During the second stepping up, either one or two samples were taken alternately at each concentration step, always including a sample immediately prior to stepping up. After cessation of the infusion, samples were taken after the infusion stop at 2, 4, 6, 10, 20, 30, and 40 min and 1, 1.5, 2, 3, 4, and 6 h for propofol, and at 2, 4, 6, 8, 10, 20, 30, and 40 min for remifentanil.

Sampling Schedule for the Second Drug Administered

After the start of the second drug, samples were taken at 2, 5, 10, 15, 20, and 30 min and each further step up of the first drug for propofol, and at 2, 4, 6, and 10 min for remifentanil. The same schedule was followed for subsequent steps of the first drug. After cessation of the infusion (both the infusion of the respective first and second drug were discontinued simultaneously), propofol samples were taken at 2, 4, 6, 10, 20, 30, and 40 min and 1, 1.5, 2, 3, 4, and 6 h, and remifentanil samples were taken at 2, 4, 6, 8, 10, 20, 30, and 40 min after infusion stop.

Citric acid was added to all remifentanil samples immediately after the blood draw. Propofol samples were centrifuged (3,000 rpm, 15 min) to obtain plasma. Both the remifentanil blood samples and the propofol plasma samples were stored at −20°C until assaying.

Analysis of Propofol

Propofol (2,6-diisopropylphenol) and thymol were purchased from Aldrich (Milwaukee, WI). High-quality sodium hydroxide and GC grade methanol were obtained from Fisher Scientific (Pittsburgh, PA). GC grade ethyl acetate and heptane were obtained from Burdick & Jackson (Muskegon, MI). Out-of-date plasma was purchased from the Puget Sound Blood Bank (Seattle, WA). A total of 0.05 ml of 1 M sodium hydroxide solution and 600 μl of a 1:1 mixture of ethyl acetate–heptane containing 150 ng of the internal standard, thymol, were added to 0.2 ml of the plasma sample containing propofol and agitated by a vortex shaker for 30 s. The emulsion was centrifuged for 3 min at 3,000 rpm (1,400*g*) and the upper liquid phase transferred to an autosample vial for analysis. Injections of 2 μl were made in splitless mode with a constant flow of 3 Ψ of the helium carrier gas at 50°C on a J & W 30 m × 0.32 mm DB-5 capillary column with a 0.25-μm film of phenylmethyl silicone. The gas chromatograph (Hewlett-Packard Model 5890 II; Hewlett-Packard, Palo Alto, CA) was equipped with a 5972A mass selective detector operating in the electron impact mode (70 eV) with selected ion monitoring. The detector monitored the 163.1-m/z fragments for propofol and 135.1-m/z fragment for thymol with a dwell time of 100 ms. The data were processed with HP1034C mass spectrometer control software (Hewlett-Packard).

The interday coefficients of variation (bias) were 10.4% (14.0%) for quality control samples containing 0.1 μg/ml propofol and 4.0% (10.1%) for quality-control samples containing 10 μg/ml propofol. The limit of quantitation was 0.1 μg/ml, and the assay was linear from 0.1 to 15 μg/ml propofol.

Analysis of Remifentanil

A total of 2 ml blood containing remifentanil and citric acid was spiked with 5 ng fentanyl in 50 μl acetonitrile (internal standard) and 4 ml acetonitrile as extraction solvent. The mixture was vortexed and equilibrated at 25°C for at least 30 min. A total of 200 μl of 10% zinc sulfate was added, and the tubes were vortexed and centrifuged at 1,650*g* for 15 min. The supernatant was transferred into screw-cap culture tubes containing 2 ml of 0.1 M sodium acetate, pH 6.0. Bond Elut Certify SPEs were placed on a Varian Vac Elut vacuum manifold and preconditioned with 2 ml isopropanol and 2 ml of 0.1 M sodium acetate, pH 6.0. The buffered supernatant (3 ml) was then loaded onto the preconditioned cartridge. The cartridge was rinsed with 1 ml of 1 M acetic acid, dried under vacuum for at least 5 min, rinsed again with 6 ml of isopropanol, and dried under full vacuum for at least 5 min. The extracts were then eluted from the cartridge with 4 ml of freshly prepared methylene chloride–isopropanol–sodium hydroxide (78:20:2 vol:vol:vol, prepared with sonication) by gravity filtration. The eluate was evaporated to dryness under nitrogen using a TurboVap LV evaporator. The residues were redissolved in 50 μl ethyl acetate, briefly vortexed, and loaded into autosampler vials. Samples were analyzed by GC-MSD (Hewlett-Packard Model 5890 II with a 5972A mass selective detector).

Aliquots (5 μl) were injected on a J & W 30 m × 0.32 mm DB-5 capillary column with a 0.25-μm film of phenylmethyl silicone. The MSD was operated in the electron impact mode (70 eV) with selected ion monitoring. The detector monitored the 227.1 m/z fragments for remifentanil and 245.1 m/z fragment for fentanyl with a dwell time of 100 ms. The data were processed with proprietary mass spectrometer control software (HP1034C). The interday coefficients of variation (bias) were 8.5% (5.4%) for quality control samples containing 5 ng/ml remifentanil and 9.3%% (2.4%) for quality control samples containing 20 ng/ml remifentanil. The limit of quantitation was 0.25 ng/ml, and the assay was linear from 0.25 to 30 ng/ml.

Calibration Procedure

Aliquots of the appropriate remifentanil stock solution were pipetted into glass screw-cap culture tubes containing 40 μl of 50% citric acid and 5 ng fentanyl in 50 μl acetonitrile. Blood (2 ml) was added to each tube and vortexed. The final remifentanil concentrations used for calibration curve standards are 0.25, 0.5, 2.5, 5, 15, and 30 ng/ml blood. After the addition of 4 ml acetonitrile, standards were extracted as described above.

Table 2. Additional Drugs Administered during the Study (Cumulative Dose in mg)

Individual	Antiemetics	Antihypotensives	Anticholinergics	Muscle Relaxants
1	MCP (10), OND (8)	—	GLP (0.4)	—
2	MCP (10), OND (4)	—	—	—
3	—	EPD (5)	—	—
4	OND (8)	—	—	—
5	—	EPD (5), PHN (0.35)	—	—
6	—	EPD (10)	—	—
7	—	EPD (5)	—	—
8	—	EPD (10)	—	SUX (20)
9	—	—	—	VEC (2)
10	—	—	—	ROC (10)
11	MCP (10)	—	—	—
12	—	—	—	VEC (2)
13	—	—	—	—
14	—	—	GLP (0.2)	VEC (1)
15	—	—	—	VEC (1)
16	—	—	GLP (0.2)	VEC (2)
17	OND (4)	EPD (5)	—	VEC (4)
18	—	—	—	—
19	MCP (10)	EPD (5)	GLP (0.2)	VEC (1)
20	—	EPD (5)	—	VEC (1)

All volunteers received 30 ml of magnesium citrate prior to drug administration.

MCP = metoclopramide; OND = ondansetron; EPD = ephedrine; PHN = phenylephrine; GLP = glycopyrrolate; SUX = succinylcholine; VEC = vecuronium; ROC = rocuronium.

Pharmacokinetic Analysis

Population Modeling. Initially, the propofol (remifentanil) plasma (blood) concentration data were independently fitted to two- and three-compartment models, which were compared by the Akaike information criterion. Subsets of the data (with–without coadministration) were also fitted to the identical models The models were parameterized in terms of the volumes of distribution ($V_{1,2}$; $V_{1,2,3}$), the elimination clearance (Cl_1) and the intercompartmental (distribution) clearance(s) (Cl_2; Cl_2,Cl_3).

An exponential model was used to describe the interindividual variability in the pharmacokinetic parameters

$$\theta_i = \theta_{TV} \cdot e^{\eta i} \quad (1)$$

where θ_i refers to the individual value of the respective pharmacokinetic parameter, θ_{TV} is the typical value of the parameter, and η_I is a normally distributed random variable with mean zero and diagonal variance–covariance matrix ω.[2] Residual variability was described with a multiplicative error model

$$C_{obs} = C_{exp} \cdot (1 + \varepsilon) \quad (2)$$

where C_{obs} refers to the observed plasma–blood concentration and C_{exp} to the concentration predicted based on dose, time, and the individual pharmacokinetic parameters. ϵ is normally distributed with mean zero and variance σ.[2]

Covariates available were gender, age, and weight. The parameters were plotted against these covariates for visual inspection. Covariates were added one at a time and were kept in the model if they improved the goodness of the fit, judged by the likelihood ratio criterion, with $P < 0.01$. For age and weight, the influence of covariates was expressed as deviation per unit of the covariate from the median value in the study population

$$\theta_i = \theta_{TV} \cdot (1 + \theta_d \cdot (Cov_i - Cov_{median})) \quad (3)$$

where θ_i refers to the value of the respective pharmacokinetic parameter for the individual, θ_{TV} is the population mean of the parameter, θ_d is the deviation from the population mean for one unit of the covariate, Cov_i is the individual value of that covariate, and Cov_{median} is the median value of the covariate in the study population. Note that with this parameterization, the population mean of the parameter equals the value for the median subject.

Model misspecification was examined by plotting the ratio of the measured and the predicted concentrations against observation time on a logarithmic scale. The program system NONMEM version V with the first-order method with conditional estimation was used for all model fits and empirical *post hoc* Bayesian estimation of the individual parameters.

Interaction Analysis

We applied two exploratory approaches to check for propofol–remifentanil interaction and generate hypotheses to be tested in a population model for significance. Initially, we calculated a population model for both drugs irrespective of coadministration of the respective other drug. Based on the Bayesian estimates of both propofol and remifentanil pharmacokinetic parameters from this analysis, we calculated a prediction error (measured concentration/predicted concentration) for each measurement within each individual. These prediction errors were plotted against the corresponding predicted

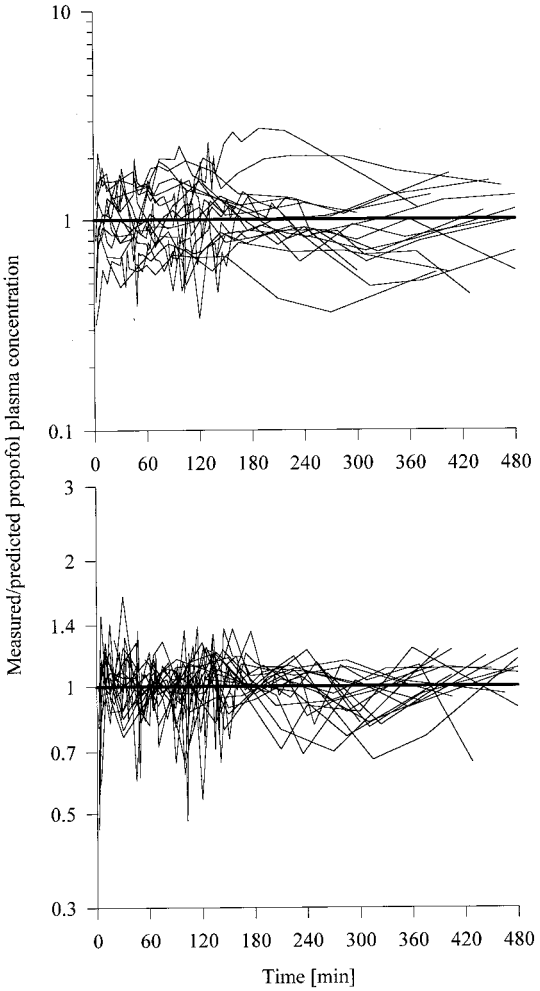

Fig. 3. Goodness-of-fit plots for propofol (all measured concentrations regardless of coadministration of remifentanil). The model used does not include an interaction term on any pharmacokinetic parameter. (*Top*) Predictions based on population means. (*Bottom*) Predictions based on Bayesian estimates.

remifentanil (propofol) concentration. An interaction would reveal itself as a systematic deviation of the prediction errors of the first drug directly related to the concentration of the respective second drug within an individual.

Having determined the population model for all propofol concentration time data regardless of remifentanil coadministration, the data set was split into propofol concentrations measured in the absence and propofol concentrations measured in the presence of remifentanil. To make that dichotomous split, propofol concentrations measured after cessation of both the propofol and remifentanil infusions at the end of the experiment were assumed to be measured in the absence of remifentanil. A three-compartment model could be identified based on the "propofol only" data set, and Bayesian estimation of the individual pharmacokinetic parameters in the absence of remifentanil was performed based on these data. Since the number of propofol concentrations sampled in presence of remifentanil was not sufficient to build a completely independent population model, the individual pharmacokinetic parameters for propofol in presence of remifentanil were calculated based on the typical values and interindividual variabilities from the analysis of the entire data set and the measured propofol concentrations in absence of remifentanil (classic Bayesian–*post hoc* approach to obtain individual parameters from sparse sampling schedules). The difference between the individual pharmacokinetic parameters in the presence and absence of remifentanil was compared with a signed rank test and visualized in appropriate plots. Note that each individual serves as its own control, as in a crossover design. Based on the result of the signed rank test and visual inspection of the plots, hypotheses about the kind of interaction were generated (*e.g.*, remifentanil decreases the central volume of distribution of propofol), which were subsequently tested against the null hypothesis (no influence of remifentanil on the respective pharmacokinetic parameter of propofol) in a population model (likelihood ratio criterion, with $P < 0.01$). If no significant difference of the objective function was found or the 95% confidence interval of the interaction parameter included 0, the interaction hypothesis was rejected. Otherwise, an interaction term (step change of the parameter value in the presence of the interacting drug) was added to the population model and the analysis repeated testing a new hypothesis. In addition, we tested whether the effect was concentration-dependent (linear or nonlinear) in the range observed. The entire procedure is depicted in figure 2A.

After having determined the population model for all remifentanil concentration–time data regardless of propofol coadministration, the data set was split into remifentanil concentrations measured in the absence and remifentanil concentrations measured in the presence of propofol. To make that dichotomous split, remifentanil concentrations measured after cessation of both the propofol and remifentanil infusions at the end of the experiment were assumed to be measured in presence of propofol. Sufficient concentration–time data were available for independent population analyses with a two-compartment model in the presence and absence of propofol, yielding two independently determined pharmacokinetic parameter sets of remifentanil. The further analysis was performed as described above for propofol (exploratory analysis of individual pharmacokinetic parameters in the absence and presence of propofol, subsequent definitive testing in a population model). The analysis procedure for remifentanil is depicted in figure 2B.

Results

General

All volunteers completed the study without major problems. Minor problems that occurred were a moderate decrease of blood pressure, which responded immediately

Table 3. Pharmacokinetic Parameters of Propofol

	Complete Dataset	Propofol Only
	Population Mean (% SE; % CV)	Population Mean (% SE;% CV)
Number of individuals /samples	18/406	18/328
Estimated parameters	—	—
Volume [l]	—	—
Central (V_1)	3.78 (13.4; 58.1)	5.55 (18.4; 53.2)
Rapidly equilibrating (V_2)	31.6 (13.8; 44.8)	30.9 (15.4; 40.4)
Slowly equilibrating (V_3)	209.0 (12.9; 39.2)	209.0 (14.7; 39.0)
Clearance [l/min]	—	—
Systemic (Cl_1)	3.04 (7.0; 25.5)	2.96 (7.3; 21.4)
Rapid distribution (Cl_2)	3.25 (12.8; 31.1)	2.55 (20.7; 23.7)
Slow distribution (Cl_3)	1.09 (10.2; 31.5)	1.0 (12.4; 23.6)
Derived parameters	—	—
Volume of distribution at steady state (Vd_{ss}) [l]	244.4	245.5
Half-lives [min]	—	—
α	0.35	0.57
β	12.2	14.0
γ	183	196

"Complete dataset" refers to all propofol concentrations regardless of coadministration of remifentanil, 'propofol only' refers to propofol concentrations measured in the absence of remifentanil. The interindividual variability of the parameters in the population has been expressed as percent coefficient of variation (CV %), which can be obtained by taking the square root of w^2 and multiplying it by 100. The residual error was 17.8% (16.6%) for all values, values determined in the absence of remifentanil.

to 5–10 mg ephedrine (one volunteer received a cumulative dose of 0.35 mg phenylephrine because of the preference of the attending anesthesiologist), mild bradycardia, which responded immediately to 0.2–0.4 mg glycopyrrolate, and occasional nausea, predominantly when remifentanil was administered alone, which responded to metoclopramide or ondansetron. Table 2 displays the additional drugs administered and their respective cumulative doses during the period of study drug administration (approximately 180 min).

Propofol Pharmacokinetics

The concentration–time course of propofol was well described with a three-compartment model. Figure 3 displays the goodness of fit over the entire time of measurements, and table 3 shows the corresponding pharmacokinetic parameters, including those of an analysis of concentrations in absence of remifentanil only (note the negligible difference). Neither covariate tested (age, weight) reached significance. The model based on all data were used to obtain the prediction errors for the first part of the exploratory interaction analysis.

Remifentanil Pharmacokinetics

The concentration–time course of remifentanil was well described with a two-compartment model. Neither covariate tested (age, weight) reached significance. Figure 4 displays the goodness of fit over the entire time of

Table 4. Pharmacokinetic Parameters of Remifentanil

	Population Mean (% SE; % CV)	Population Mean (% SE;% CV)
Number of individuals/samples	18/272	18/272
Estimated parameters	—	—
Volume [l]	—	—
Central (V_1)	10.50 (12.1; 32.7)	13.50 (6.5; -)
Peripheral (V_2)	8.22 (10.5; 15.5)	8.64 (12.5; 27.4)
Clearance [l/min]	—	—
Systemic (Cl_1)	2.34 (6.8; 27.1)	2.57 (6.5; 25.3)
Distribution (Cl_2)	0.82 (25.6; 47.6)	1.31 (22.8; 7.7)
Propofol scalar on V1 and Cl_2 [$]	—	−0.41 (21.1; 42.1)
Propofol scalar Cl_1 [$]	—	−0.15 (25.5; -)
Derived parameters	—	—
Volume of distribution at steady state (Vd_{ss}) [l]	18.72	22.14
Half-lives [min]	—	—
α	2.1	1.9
β	10.4	8.6
Obj. function	43.0	6.1

The complete dataset was analyzed with a model not accounting for propofol interaction and a model accounting for propofol interaction. The scalars on the respective parameters imply that the presence of propofol decreases the central volume of distribution and distributional clearance of remifentanil by 41%, the elimination clearance by 15%. The interindividual variability of the parameters in the population has been expressed as percent coefficient of variation (CV %), which can be obtained by taking the square root of w^2 and multiplying it by 100. The residual error was 24.2% and 22.6% for the model not accounting and the model accounting for propofol interaction. The difference in the objective function is highly significant ($P < 0.01$).

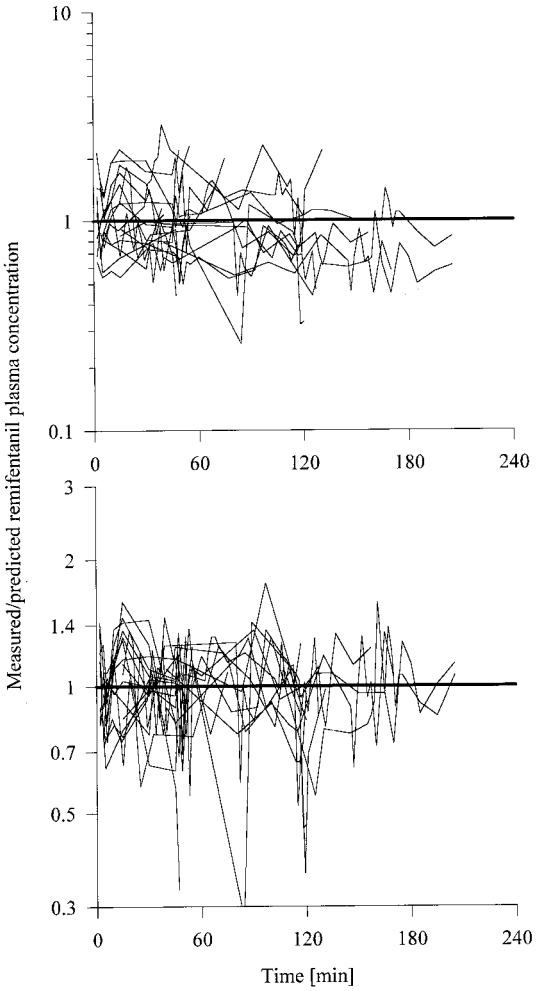

Fig. 4. Goodness-of-fit plots for remifentanil (all measured concentrations regardless of coadministration of propofol). The model used does not include an interaction term on any pharmacokinetic parameter. (*Top*) Predictions based on population means. (*Bottom*) Predictions based on Bayesian estimates.

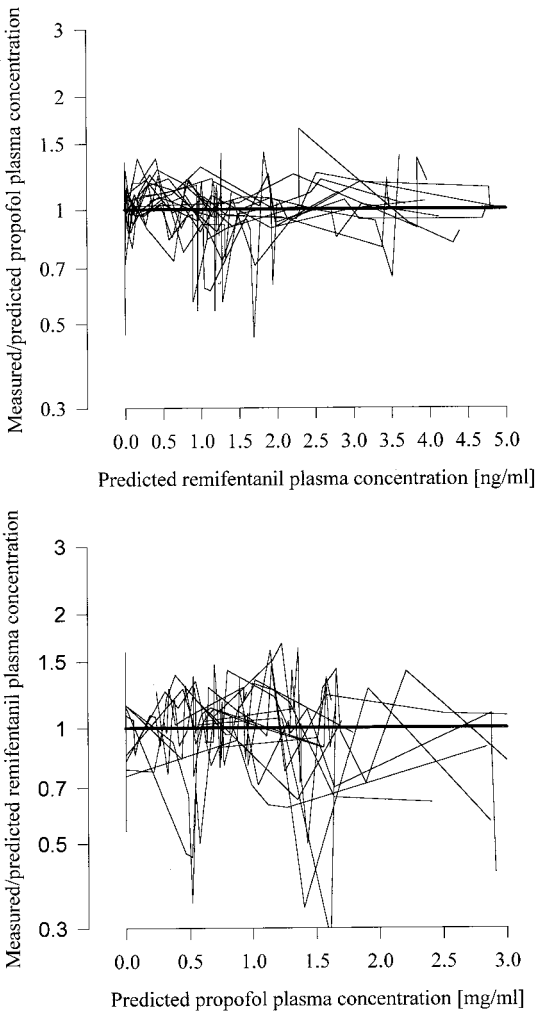

Fig. 5. Exploratory analysis of the effect of remifentanil on propofol pharmacokinetics and *vice versa*, part 1. (*Top*) Prediction errors of propofol *versus* the corresponding predicted remifentanil concentration, both based on Bayesian pharmacokinetic parameters obtained from the population analysis assuming no interaction. (*Bottom*) Prediction errors of remifentanil *versus* the corresponding predicted propofol concentration, both based on Bayesian pharmacokinetic parameters obtained from the population analysis assuming no interaction.

measurements, and the first column of table 4 shows the corresponding pharmacokinetic parameters. This model was used to obtain the prediction errors for the first part of the exploratory interaction analysis.

Interaction Analysis

After having obtained two independent population models of propofol and remifentanil and therefore the possibility to predict the respective concentrations, the prediction error of propofol based on predictions with individual pharmacokinetic parameters (Bayesian predictions) was now plotted against the Bayesian predictions of remifentanil and *vice versa* (fig. 5). For both drugs, the prediction errors were independent of the concentrations of the respective other drug, arguing against a pronounced interaction.

The plots of the Bayesian pharmacokinetic parameters of propofol in the presence and absence of remifentanil and subsequent signed rank tests showed a significant decrease of the central volume of distribution and increase of the fast distribution clearance in presence of remifentanil (fig. 6). However, when these hypotheses were tested in a population model, they could not be confirmed.

The plots of the Bayesian pharmacokinetic parameters of remifentanil in the presence and absence of propofol and subsequent signed rank tests showed a significant decrease of the central volume of distribution and distribution clearance in presence propofol (fig. 7). Since the effect of propofol on elimination clearance missed significance by a very small margin ($P = 0.055$), we included an effect of propofol on the elimination clearance of remifentanil for hypothesis testing in the population model. Implementation of these hypotheses in a population model decreased the objective function by 36.9 points ($P < 0.01$). According to this analysis, propofol

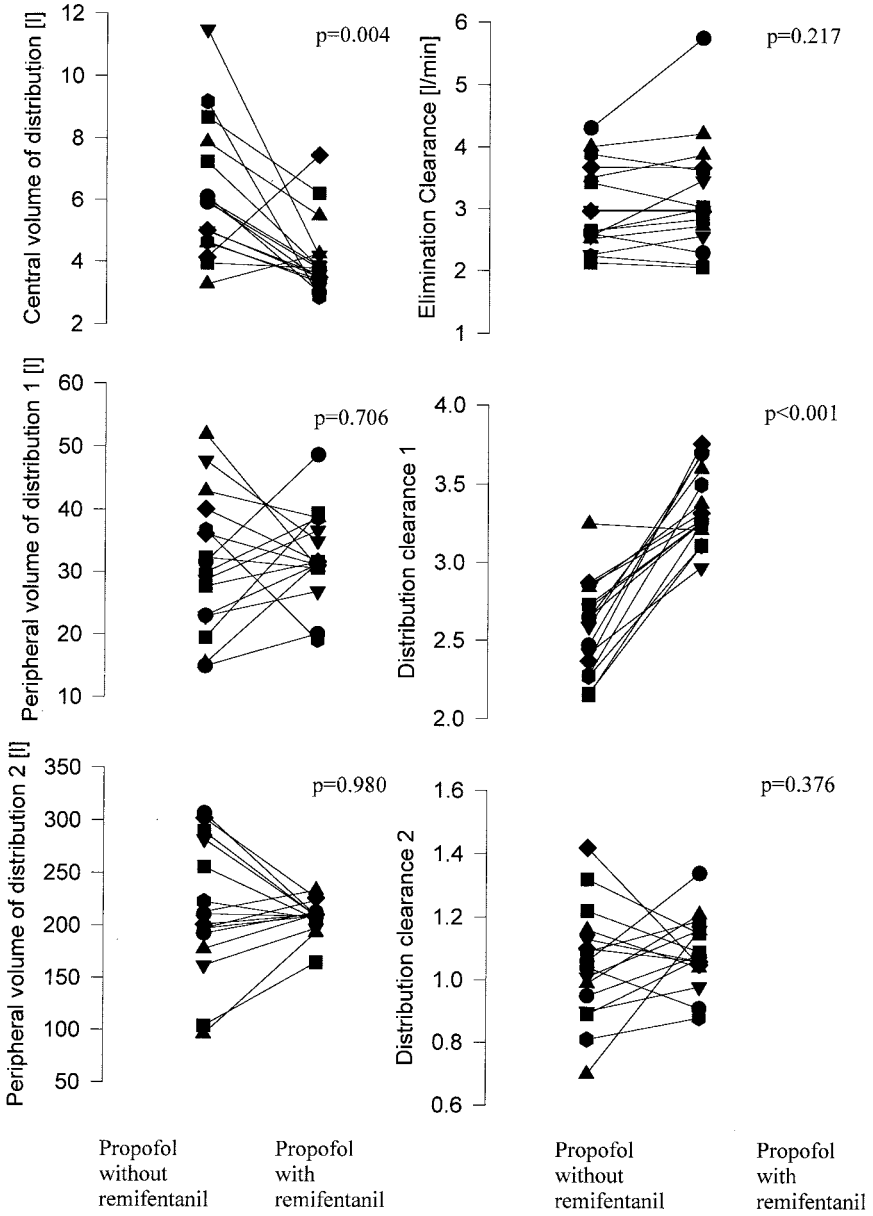

Fig. 6. Exploratory analysis of the effect of remifentanil on the pharmacokinetics of propofol, part 2. Bayesian estimates of propofol pharmacokinetic parameters obtained with and without coadministration of remifentanil. *P* values were obtained with a signed rank test. None of the significant results was confirmed in the final population analysis (see Results).

decreases both the central volume of distribution and distribution clearance of remifentanil by 41% and elimination clearance by 15%. Goodness of fit of the final model is displayed in figure 8, and the pharmacokinetic parameters are shown in the second column of table 4. Introducing a concentration effect of propofol did not lead to further model improvement. A simulation of a standard clinical dosing regimen of remifentanil (1-μg/kg bolus dose, infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 2.5 min, infusion of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ thereafter for the duration of the procedure [here, 60 min]) in the presence and absence of propofol shows that (1) the concentrations after the initial bolus are much higher in presence of propofol, (2) propofol minimally increases the concentrations during the maintenance phase, and (3) the influence of propofol on the recovery times after a remifentanil infusion are negligible (fig. 9).

Discussion

We examined the effect of remifentanil on the pharmacokinetics of propofol and *vice versa* in a single study session. The most important findings of the study are that (1) the pharmacokinetics of propofol are not changed by remifentanil; (2) the central volume of distribution, distribution clearance, and elimination clearance of remifentanil are decreased in the presence of propofol; and (3) the effect of propofol on the concentration–time course of remifentanil is only clinically relevant when bolus doses are administered as determined by simulation (pseudo–steady state concentrations and recovery are barely affected).

The statement that the pharmacokinetics of propofol are not changed by remifentanil has to be supplemented by a qualifier. Testing for covariate effects by comparing

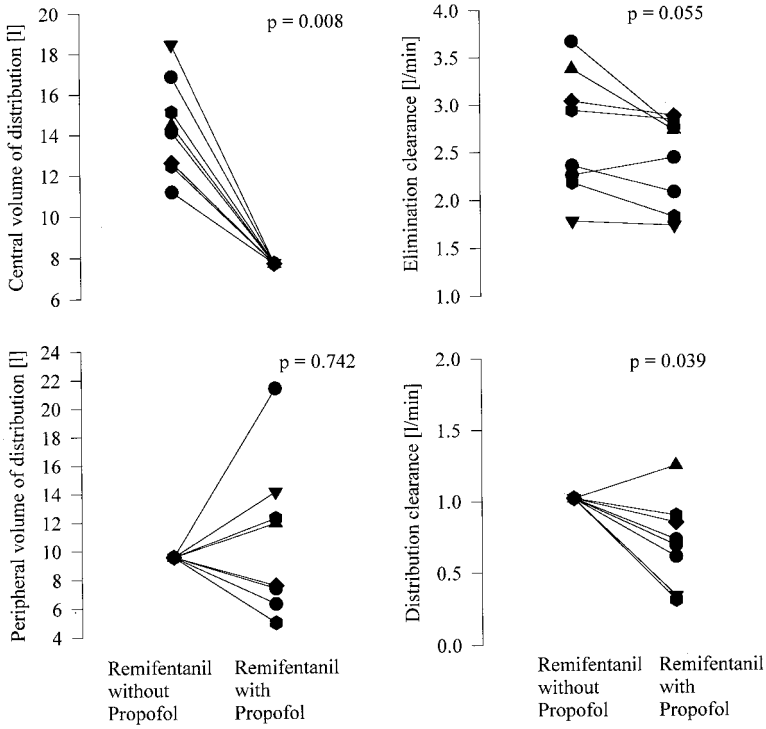

Fig. 7. Exploratory analysis of the effect of propofol on the pharmacokinetics of remifentanil, part 2. Bayesian estimates of remifentanil pharmacokinetic parameters obtained with and without coadministration of propofol. *P* values were obtained with a signed rank test. Propofol decreases the central volume of distribution and the clearances of remifentanil, which was confirmed in the final population analysis (table 4).

different models cannot prove a negative. The estimation of the size of the possibly missed difference can only be performed by simulating multiple data sets structured as the one studied with *a priori* known effect sizes and analysis of them with and without accounting for a remifentanil effect. This was not attempted. Since the prediction error of propofol is independent from the corresponding remifentanil concentration (fig. 5), we speculate that the putatively missed remifentanil effect is of such a small magnitude to render it clinically insignificant. Even statistically highly significant interactions may have only partial clinical relevance (affecting only bolus kinetics, steady state kinetics, recovery, or any combination of them depending on the pharmacokinetic parameter influenced by the interacting drug).

The effect of propofol on remifentanil pharmacokinetics was highly significant, with the volume of distribution and distribution clearance affected by 41% and elimination clearance only to a very limited degree (15%). This directly translates into the conclusion that bolus kinetics will be significantly affected, whereas (pseudo) steady state infusions and recovery after cessation of a remifentanil infusion will basically be unchanged in the presence of propofol.

The mechanism by which propofol exerts this effect can only be speculated upon. First of all, the effect of propofol on alfentanil pharmacokinetics is surprisingly similar to the one on remifentanil pharmacokinetics, although both drugs differ completely in metabolism.[24] Propofol greatly decreases the (fast) distribution clearance and also minimally elimination clearance of alfentanil. Second, the effect of hemorrhagic shock on remifentanil kinetics in pigs is similar to that of propofol on remifentanil pharmacokinetics in our study, albeit more pronounced. The central and the fast equilibrating volumes of distribution and the elimination clearance were significantly decreased during hemorrhagic shock, and a trend toward decreased fast distribution clearances did not reach significance.[25] Taken together, these findings support the notion that the effect of propofol on remifentanil pharmacokinetics is caused by circulatory alterations (cardiac output or systemic vascular resistance).

Limitations of the Study

This investigation was performed to determine both the pharmacokinetic and pharmacodynamic interaction between propofol and remifentanil. The design was largely determined by pharmacodynamic considerations and therefore deviates substantially from the classic pharmacokinetic interaction design as, for example, recently used by Mertens *et al.*[24] to investigate the effect of propofol on alfentanil pharmacokinetics. Both approaches show distinct advantages. The classic pharmacokinetic interaction crossover design is time-proven (it worked before), very well controlled, and basically guarantees that an effect of reasonable size can be uncovered (power analysis possible, size of missed difference can be determined under the assumption of normally distributed pharmacokinetic parameters). It does not require fancy mathematics to come to meaningful conclusions. The raw data can be analyzed (does drug 2 alter C_{max}, T_{max}, area under the curve of drug 1), a noncompartmental–moment analysis can be performed (does drug 2 alter the terminal elimination half life, Cl, MRT, V_{ss} of

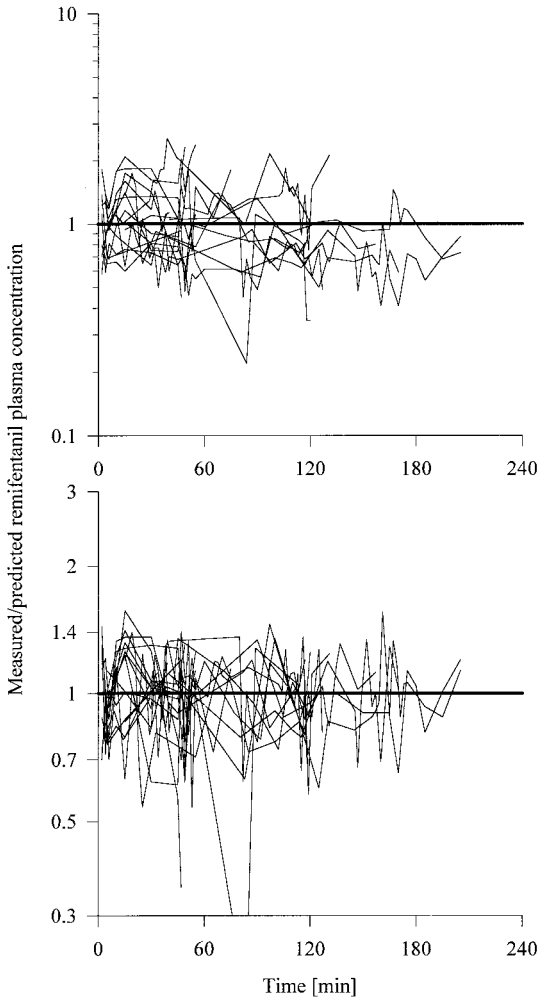

Fig. 8. Goodness-of-fit plots for remifentanil (all measured concentrations regardless of coadministration of propofol). The model used includes a scalar to account for the pharmacokinetic interaction between propofol and remifentanil. (*Top*) Predictions based on population means. (*Bottom*) Predictions based on Bayesian estimates.

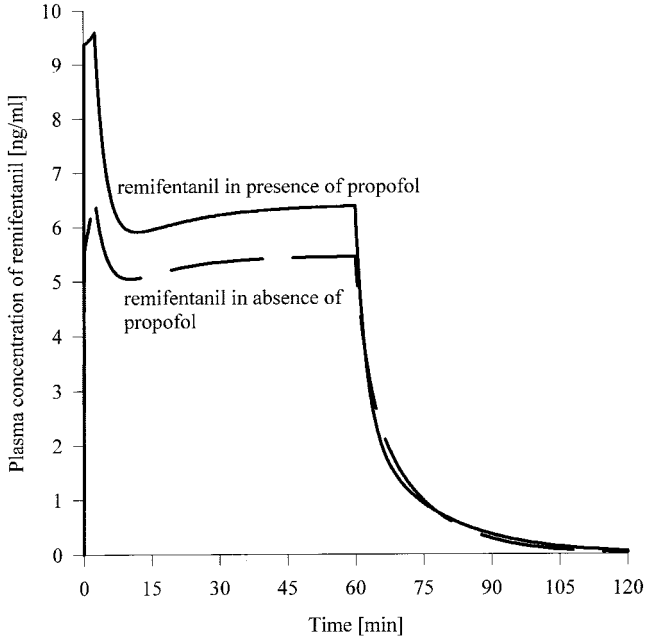

Fig. 9. Simulation of a typical dosing regimen for remifentanil (1-μg/kg bolus, 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 2.5 min, 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remaining period of administration [60 min]) in the presence and absence of propofol. Note the (expected) big difference of peak concentrations after the initial bolus, the small concentration difference during maintenance, and the negligible difference during recovery.

drug 1), a standard compartmental pharmacokinetic analysis with subsequent signed rank or paired *t* test for every parameter can be performed (does drug 2 alter the volume[s] of distribution– clearance[s] of drug 1). However, it is also remarkably inefficient. Two complete concentration–time courses spaced by a suitable washout period must be sampled for drug 1, one in absence and one in presence of a fixed concentration of drug 2. To ascertain steady state conditions and especially when enzyme induction is the suspected mechanism of interaction, a run in time for drug 2 must be maintained. Most important, this design only answers the questions of if, how much, and how a certain concentration of drug 2 alters the pharmacokinetics of drug 1 and not *vice versa*.

Our approach of dividing a study population into two groups receiving first drug 1 and thereafter drug 2 and *vice versa* within one session is complex, basically unproven, entirely depends on the ability to perform a compartmental population analysis, and cannot be tested for sensitivity by a simple power analysis. The apparently most striking problem of our design is the violation of random sequence of "treatments," making it impossible to distinguish between an effect of time *versus* drug 2 on the pharmacokinetic parameters of drug 1. However, contrary to the classic design, there is no appreciable time lag between administration of drug 1 and the addition of drug 2, and the effect of interoccasion variability balanced for by a randomized sequence of administration in the classic design should not be an issue. Implying that the pharmacokinetic parameters of drug 1 are not constant during an application of approximately 180 min challenges the "stationarity dogma" in pharmacokinetics and invalidates pharmacokinetic modeling (and pharmacokinetic parameter–based drug administration, *e.g.*, target controlled infusion) as a whole. Since clinical applications of pharmacokinetic modeling implying stationarity (and almost always linearity) work exceedingly well, we would like to reject this criticism.

Despite these problems, our approach shows distinct advantages. First, the design is very efficient. Only one study session per individual is required. Moreover, contrary to the classic approach, interaction between drugs 1 and 2 can be tested in both directions. Concentration effects can be uncovered, if sufficient and reasonably spaced concentrations of both drugs are investigated and appropriate samples are taken. Since there is only one occasion, interoccasion variability is not an issue at all

(see above). Pharmacodynamic interactions can be uncovered simultaneously with pharmacokinetic interactions without increasing the complexity of the study. The major open questions are whether the approach is statistically valid and works well enough to uncover small effects. The first step taken, building a population model from all propofol (remifentanil) pharmacokinetic data regardless of coadministration, is a standard procedure and can hardly be questioned. Information, whether a relevant pharmacokinetic interaction occurs at all can be obtained without explicit interaction modeling. Concentration measurements of propofol (remifentanil) were taken in absence and at different concentrations of remifentanil (propofol) from 18 volunteers. If remifentanil (propofol) alters the pharmacokinetic parameters of propofol (remifentanil) in a concentration-dependent fashion, the individual prediction errors based on Bayesian pharmacokinetic parameters must correlate with the corresponding concentration of remifentanil (propofol). As shown in figure 5, this is not the case. The exploratory analysis based on Bayesian parameters and evaluated with a signed rank test is equally straightforward. Since the pharmacokinetic parameters in this analysis are all weighted equally–treated as precisely measured characteristics of the respective individual (such as, *e.g.*, weight and height) regardless of the number of concentrations contributing to their estimation, this analysis must not be used for definitive statements about interaction or not. The subsequent definitive analysis of the pharmacokinetic parameters of propofol (remifentanil) affected by remifentanil (propofol) is performed by comparison of a population model not accounting for interaction and a population model accounting for interaction in complete analogy to uncovering an effect of a dichotomous variable, such as gender, on a pharmacokinetic parameter, yielding the typical magnitude of the interaction, its standard error, and interindividual variability. Therefore, we believe that our findings are as valid as those from a classic analysis. The only major problems of our approach are the inability to determine the maximum missed effect size by simple means and the inability to analyze interaction of drugs with long half-lives because of the prohibitive duration of the study session and perhaps introducing error due to chronobiological issues.[26]

In conclusion, we investigated the pharmacokinetic interaction of propofol and remifentanil based on a non–steady state design and analysis approach. The identified type of interaction was small but significant when tested in a population model. Remifentanil does not alter propofol pharmacokinetics, whereas propofol causes a 41% reduction of the central volume of distribution and distribution clearance and a 15% reduction of the elimination clearance of remifentanil. As long as bolus administration is avoided, propofol–remifentanil pharmacokinetic interaction does not require dosing adjustments of remifentanil during clinical practice.

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