Pharmacokinetics and Pharmacodynamics of Remifentanil

II. Model Application

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Background: The pharmacokinetics and pharmacodynamics of remifentanil were studied in 65 healthy volunteers using the electroencephalogram (EEG) to measure the opioid effect.[1] In a companion article, the authors developed complex population pharmacokinetic and pharmacodynamic models that incorporated age and lean body mass (LBM) as significant covariates and characterized intersubject pharmacokinetic and pharmacodynamic variability. In the present article, the authors determined whether remifentanil dosing should be adjusted according to age and LBM, or whether these covariate effects were overshadowed by the interindividual variability present in the pharmacokinetics and pharmacodynamics.

Methods: Based on the typical pharmacokinetic and pharmacodynamic parameters, nomograms for bolus dose and infusion rates at each age and LBM were derived. Three populations of 500 individuals each, ages 20, 50, and 80 yr, were simulated base on the interindividual variances in model parameters as estimated by the NONMEM software package. The peak EEG effect in response to a bolus, the steady-state EEG effect in response to an infusion, and the time course of drug effect were examined in each of the three populations. Simulations were performed to examine the time necessary to achieve a 20%, 50%, and 80% decrease in remifentanil effect site concentration after a variable-length infusion. The variability in the time for a 50% decrease in effect site concentrations was examined in each of the three simulated populations. Titratability using a constant-rate infusion was also examined.

Results: After a bolus dose, the age-related changes in V_1 and k_{e0} nearly offset each other. The peak effect site concentration reached after a bolus dose does not depend on age. However, the peak effect site concentration occurs later in elderly individuals. Because the EEG shows increased brain sensitivity to opioids with increasing age, an 80-yr-old person required approximately one half the bolus dose of a 20-yr old of similar LBM to reach the same peak EEG effect. Failure to adjust the bolus dose for age resulted in a more rapid onset of EEG effect and prolonged duration of EEG effect in the simulated elderly population. The infusion rate required to maintain 50% EEG effect in a typical 80-yr-old is approximately one third that required in a typical 20-yr-old. Failure to adjust the infusion rate for age resulted in a more rapid onset of EEG effect and more profound steady-state EEG effect in the simulated elderly population. The typical times required for remifentanil effect site concentrations to decrease by 20%, 50%, and 80% after prolonged administration are rapid and little affected by age or duration of infusion. These simulations suggest that the time required for a decrease in effect site concentrations will be more variable in the elderly. As a result, elderly patients may occasionally have a slower emergence from anesthesia than expected. A step change in the remifentanil infusion rate resulted in a rapid and predictable change of EEG effect in both the young and the elderly.

Conclusions: Based on the EEG model, age and LBM are significant demographic factors that must be considered when determining a dosage regimen for remifentanil. This remains true even when interindividual pharmacokinetic and pharmacodynamic variability are incorporated in the analysis. (Key words: Analgesic, opioids: GI87084B; remifentanil. Pharmacokinetics: remifentanil; population. Pharmacodynamics: remifentanil. Computer simulations.)

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‡Statistical Sciences, Inc. *S-PLUS for Windows User's Manual, Version 3.1,* Seattle: Statistical Sciences, Inc., 1993. The PKPD Tools for EXCEL used for these simulations were written by Charles Minto and Thomas Schnider and are available via the WWW at URL: http://pkpd.icon.palo-alto.med.va.gov.

WE studied the pharmacokinetics and pharmacodynamics of remifentanil in 65 healthy volunteers between the ages of 20 to 85 yr using the EEG as the measure of opioid effect.[1] In the first article of this series, we

derived complex population pharmacokinetic and pharmacodynamic models based on a covariate analysis using a generalized additive model (GAM) as implemented in S-PLUS‡ and a mixed-effects modeling approach as implemented in the program NONMEM.§ The relative importance of the covariates in the pharmacokinetic model (age and lean body mass [LBM]) and the pharmacodynamic model (age), and the interindividual variability of the model parameters are difficult to interpret without using computer simulations. In this second article, we determined whether remifentanil bolus dose and infusion rates should be adjusted according to age and LBM or whether these covariate effects were overshadowed by the interindividual variability in the pharmacokinetics and pharmacodynamics.

Materials and Methods

The remifentanil parameters used for the simulations were those derived by NONMEM for the complex pharmacokinetic and pharmacodynamic models, which included age and LBM as significant covariates (in tables 3 and 5 of part I of our series of articles).[1] Three populations (n = 500 each) were simulated based on the typical values for individuals age 20, 50, and 80 yr and LBM of 55 kg and on the interindividual variances estimated by the mixed-effects modeling approach. The computer simulations were performed on an IBM-compatible personal computer using software written by the authors in the C programming language and Visual Basic for Applications (EXCEL) for Windows. The simulations used the simple analytical solution to the three-compartment model reported by Bailey and Shafer.[2]

Intravenous Bolus

The time to peak effect site concentration after an intravenous bolus is a function of both the rate of decline of blood concentration and the rate of equilibration of blood concentration with the site of drug effect. To calculate the bolus dose to reach a given EEG effect, we first calculated the volume of distribution at the time of the peak effect site concentration (Vd_{pe}) as proposed by Shafer and Gregg[3] and Henthorn and associates.[4] The Vd_{pe} was calculated as:

$$Vd_{pe} = \frac{V_1}{\text{percent decrease}} \qquad (1)$$

where "percent decrease" is the percentage of decrease in blood concentration from the initial concentration at time zero to the concentration at the time of the peak effect site concentration (t_{peak}). This is mathematically identical to calculating Vd_{pe} as the bolus dose divided by the blood concentration at the time of peak effect.

To examine differences in onset of remifentanil EEG effect with age, we plotted the unit disposition functions for the blood and effect site for three typical individuals with LBM of 55 kg ages 20, 50, and 80 yr. Age and LBM were then varied over the range of 20 to 80 yr and 35 to 75 kg, and their influence on Vd_{pe} was determined. Using the age- and LBM-adjusted Vd_{pe} and the age-adjusted EC_{50}, we derived a nomogram showing the bolus dose required to peak at 50% of the maximum EEG effect for typical individuals using equation 2:

$$\text{Bolus} = EC_{50} \times Vd_{pe} \qquad (2)$$

Typical values for Vd_{pe}, t_{peak}, EC_{50}, and the bolus dose for each EC_{50} for typical individuals ages 20, 50, and 80 yr were also tabulated.

NONMEM estimated a stochastic model, enabling simulations of the expected variability in response. To examine the relative importance of bolus-dose adjustment for increasing age in the presence of significant interindividual pharmacokinetic and pharmacodynamic variability, we simulated three populations of 500 individuals with LBM of 55 kg and ages 20, 50, and 80 yr based on the %CVs in part I of our series of articles (tables 3 and 5).[1] The simulations EEG effects were scaled so that baseline effect (E_0) was 0% and the maximum effect (E_{max}) was 100%. Thus variability in all volumes and clearances, EC_{50}, γ, and k_{e0} were used in these simulations. All individuals in both age groups were given the same bolus dose (calculated to cause a peak effect equal to 50% of the maximum EEG effect in the typical 50-yr-old). To examine the variability in the time course of EEG effect, we plotted the predicted response for these populations. This simulation was then repeated using the age-adjusted bolus dose for the 20- and 80-yr-old populations.

Intravenous Infusions

The steady-state blood concentration (C_{ss}) achieved with a constant-rate infusion is a function of the metabolic clearance (Cl_1) and the infusion rate (R):

$$C_{ss} = \frac{R}{Cl_1} \qquad (3)$$

We first calculated metabolic clearance as a function of age and LBM for a typical person. Using the age- and LBM-adjusted values for metabolic clearance and the age-adjusted EC_{50}, we derived a nomogram showing the infusion rate required to maintain 50% of the maximum EEG effect according to equation 4:

$$R = Cl_1 \times EC_{50} \qquad (4)$$

Typical values of Cl_1, and the infusion rate resulting in a steady-state concentration equal to the EC_{50} for typical individuals ages 20, 50, and 80 yr were tabulated.

To examine the relative importance of infusion rate adjustment for increasing age in the presence of significant interindividual pharmacokinetic variability, we simulated three populations of 500 individuals with LBMs of 55 kg and ages 20, 50, and 80 yr based on the %CVs described in part I of our series (tables 3 and 5). We scaled the effect so that E_0 was 0% and E_{max} was 100%. Thus only the interindividual variability on Cl_1, EC_{50}, and γ were used in this simulation. All individuals in each age group received the same infusion rate (calculated to cause 50% of the maximum EEG effect at steady state in the typical 50-yr-old). To examine the variability in the time course of EEG effect, we plotted the predicted response for the population of 20-, 50-, and 80-yr-olds to this infusion rate. This stimulation was then repeated using the age-adjusted infusion rate for the 20- and 80-yr-old populations.

For multicompartment drugs, the infusion rates required to maintain a steady-state concentration change over time. We calculated the infusion rates that would be administered by a computer-controlled infusion pump to maintain 50% of the maximum EEG effect at different ages. These rates were calculated after an initial bolus to rapidly achieve the targeted effect site concentration. This simulation was performed using the typical pharmacokinetic and pharmacodynamic parameters of persons ages 20, 30, 40, 50, 60, 70, and 80 yr and LBMs of 55 kg.

Recovery from Prolonged Infusion

To investigate the influence of age on recovery after a prolonged infusion, we calculated the 20%, 50%, and 80% effect site decrement times[5,6] for typical individuals ages 20 and 80 yr with LBMs of 55 kg. To assess the effect of the pharmacokinetic and pharmacodynamic

variability at each age, we calculated the 50% effect site decrement times for each of three populations of 500 individuals ages 20, 50, and 80 yr and with LBMs of 55 kg.

Titratability

Because of the evanescent nature of remifentanil, we wanted to assess the titratability of effect using a constant-rate infusion rather than a computer-controlled infusion pump. To compare the titratability of EEG effect at different ages, the response to stepped constant-rate infusions were simulated. For typical individuals ages 20 and 80 yr, the infusion rate required to achieve 20%, 50%, and 80% of the maximal EEG effect at steady state was calculated according to age-adjusted Cl_1 and EC_{50} (equation 4). The EEG effect over time for each person was graphed to compare the titratability of remifentanil in the elderly and the young.

Results

Intravenous Bolus

Figure 1 shows the unit disposition functions for the blood and effect site in typical individuals ages 20, 50, and 80 yr. When given the same dose (one unit), the initial concentrations are higher in the elderly because of their smaller V_1. The longer $t_{1/2} k_{e0}$ in the elderly slows the equilibrium between blood and effect site, resulting in an apparent peak effect site concentration that is approximately the same in all age groups. Thus Vd_{pe} changes little with increasing age. Lean body mass is the main factor influencing Vd_{pe}, which increased from approximately 14 to 20 l when LBM increased from 35 to 75 kg.

Figure 2 (upper graph) shows the nomogram to calculate the bolus dose required to peak at 50% of the maximum EEG effect for a particular age and LBM. The EC_{50} has been adjusted for age, reflecting the increased sensitivity of elderly individuals (table 5 of part I of our series).[1] For any given LBM, an 80-yr-old will require approximately one half the dose of a 20-yr-old to reach the same peak EEG effect. This figure also shows that the initial bolus dose should be adjusted for LBM. Typical values for t_{peak}, Vd_{pe}, EC_{50}, and bolus dose to cause 50% of maximum EEG effect are shown in table 1. The implication is that the initial bolus dose in elderly individuals needs to be adjusted for pharmacodynamic rea-

sons (increased sensitivity), and not because of the differences in pharmacokinetics or k_{e0}.

According to the complex pharmacokinetic and pharmacodynamic model, a 200-μg intravenous bolus will cause a peak effect equal to one half the maximum EEG effect in a typical 50-yr-old. Figure 3 (upper graphs) shows the expected range of responses to a 200-μg dose administered to a population (n = 500 each, LBM = 55 kg) of 20-yr-old and 80-yr-old individuals. The same 200-μg dose caused a skewed distribution of EEG effect in the young and old populations. The 20-yr-olds were typically underdosed (typical 20-yr-old peak effect was 30%), and the 80-yr-olds were typically overdosed (typical 80-yr-old peak effect was 75%). The 200-μg dose results in a peak EEG effect in a popualtion of 50-yr-old individuals that is approximately normally distributed

Fig. 1. Blood and effect site unit disposition functions after an intravenous bolus in typical 20-, 50-, and 80-yr-olds with lean body masses of 55 kg. Peak electroencephalographic effect and time of peak electroencephalographic effect are indicated by dashed lines.
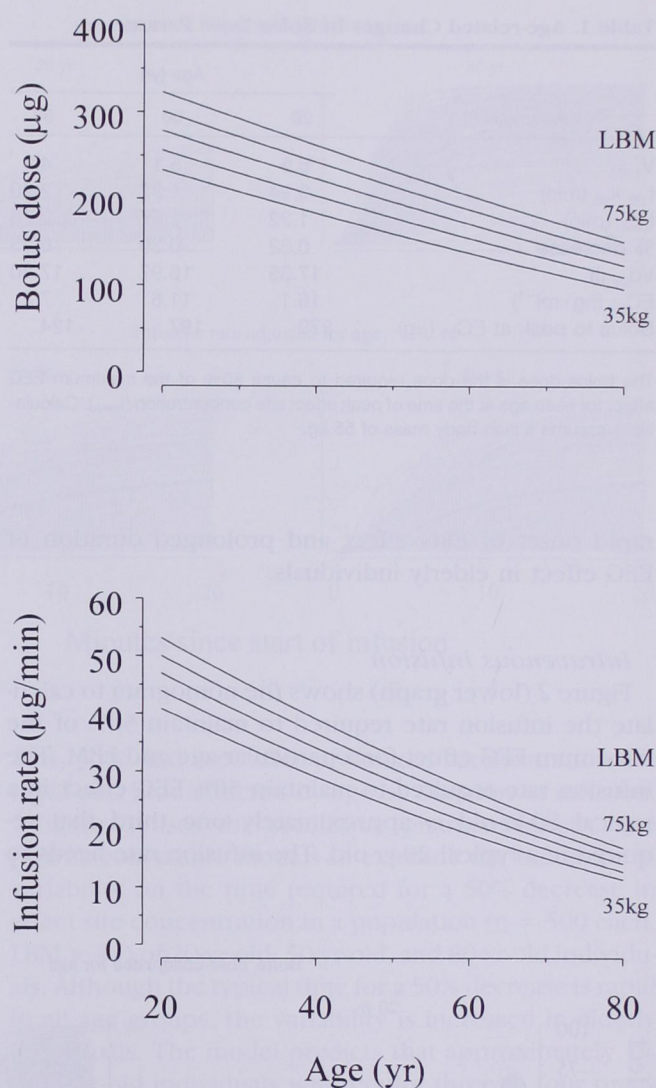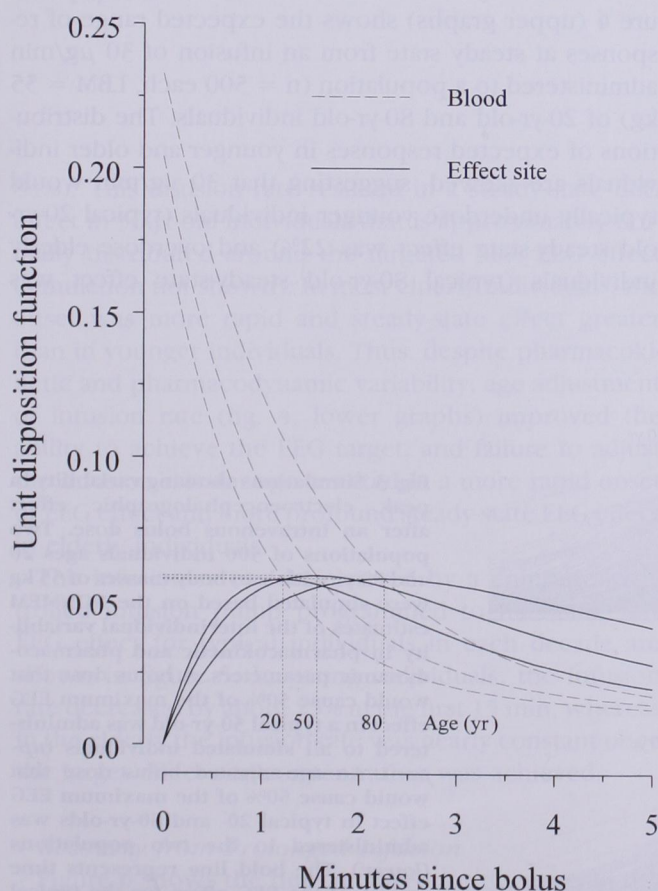

Fig. 2. Nomogram for calculating the intravenous bolus dose (*upper*) and intravenous infusion rate (*lower*) required to cause 50% of the maximum electroencephalographic effect as a function of age and lean body mass.

about the targeted EEG effect of 50% (simulation not shown). In most elderly individuals, the onset was more rapid and the duration of EEG effect was prolonged, with twice as many individuals having an effect greater than the targeted 50% EEG effect at 5 min after the bolus dose (55% vs. 24%). Therefore, despite pharmacokinetic and pharmacodynamic variability, age adjustment of a bolus dose (fig. 3, lower graphs) improved the ability to achieve the targeted EEG effect, and failure to adjust the bolus dose for age resulted in a more

Table 1. Age-related Changes in Bolus Dose Parameters

Parameter	Age (yr)		
	20	50	80
V_1 (l)	5.5	5.1	4.3
$t_{1/2} k_{e0}$ (min)	0.94	1.32	2.20
t_{peak} (min)	1.22	1.57	2.26
% decrease	0.32	0.30	0.25
Vd_{pe} (l)	17.35	16.97	17.30
EC_{50} (ng · ml^{-1})	16.1	11.6	7.2
Bolus to peak at EC_{50} (μg)	279	197	124

The bolus dose is the dose required to cause 50% of the maximum EEG effect for each age at the time of peak effect site concentration (t_{peak}). Calculations assume a lean body mass of 55 kg.

Table 2. Age-related Changes in Infusion Rate Parameters

Parameter	Age (yr)		
	20	50	80
Cl_1 (l · min^{-1})	2.9	2.4	2.0
EC_{50} (ng · ml^{-1})	16.1	11.6	7.2
Infusion rate (μg · min^{-1})	47	28	14

The infusion rate is calculated to cause 50% of the maximum EEG effect at steady state. Calculations assume a lean body mass of 55 kg.

rapid onset of EEG effect and prolonged duration of EEG effect in elderly individuals.

Intravenous Infusion

Figure 2 (lower graph) shows the nomogram to calculate the infusion rate required to maintain 50% of the maximum EEG effect for a particular age and LBM. The infusion rate required to maintain 50% EEG effect in a typical 80-yr-old is approximately one third that required in a typical 20-yr-old. The infusion rate needs to

be adjusted for LBM and age. Typical values for these infusion rates are shown in table 2.

According to the complex pharmacokinetic and pharmacodynamic model, an infusion rate of approximately 30 μm/min will cause a steady-state effect equal to one half the maximum EEG effect in a typical 50-yr-old. Figure 4 (upper graphs) shows the expected range of responses at steady state from an infusion of 30 μg/min administered to a population (n = 500 each, LBM = 55 kg) of 20-yr-old and 80-yr-old individuals. The distributions of expected responses in younger and older individuals are skewed, suggesting that 30 μg/min would typically underdose younger individuals (typical 20-yr-old steady-state effect was 22%) and overdose elderly individuals (typical 80-yr-old steady-state effect was

Bolus dose unadjusted for age

Bolus dose adjusted for age

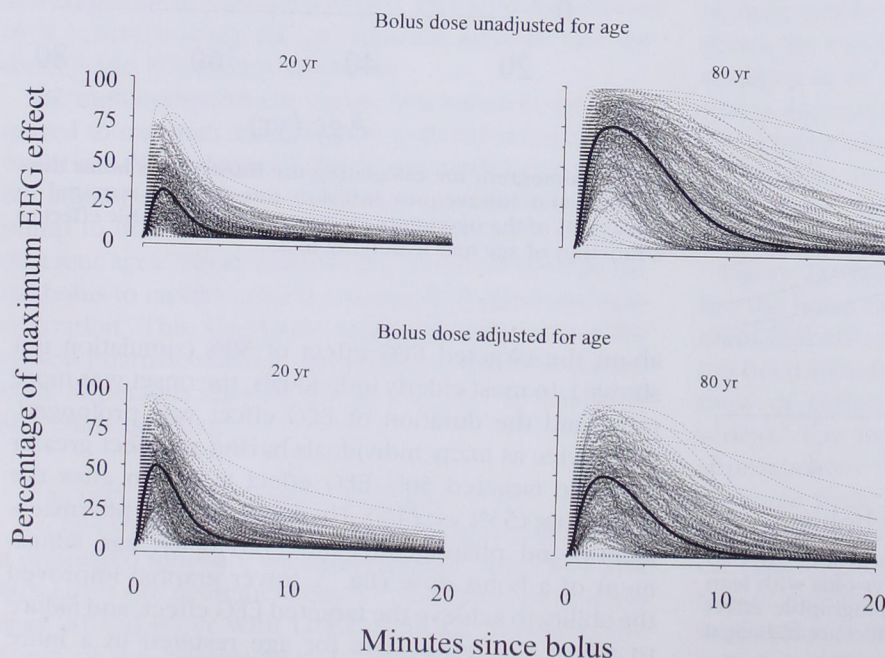Percentage of maximum EEG effect

Minutes since bolus

Fig. 3. Simulations showing variability in peak electroencephalographic effect after an intravenous bolus dose. Two populations of 500 individuals ages 20 and 80 yr with lean body masses of 55 kg were simulated based on the NONMEM estimates of the interindividual variability in pharmacokinetic and pharmacodynamic parameters. A bolus dose that would cause 50% of the maximum EEG effect in a typical 50-yr-old was administered to all simulated individuals (*upper*). An age-adjusted bolus dose that would cause 50% of the maximum EEG effect in typical 20- and 80-yr-olds was administered to the two populations (*lower*). The bold line represents time course of the EEG effect for the typical person in each simulated population.

Fig. 4. Simulations showing variability in steady-state electroencephalographic effect after a constant-rate infusion. Two populations of 500 individuals ages 20 and 80 yr and with lean body masses of 55 kg were simulated based on the NONMEM estimates of the interindividual variability in pharmacokinetic and pharmacodynamic parameters. An infusion rate that would cause 50% of the maximum electroencephalographic effect in a typical 50-yr-old individuals was administered to all simulated individuals (*upper*). An age-adjusted infusion rate that would cause 50% of the maximum electroencephalographic effect in typical 20 and 80 yr olds was administered to the two populations (*lower*). The bold line represents the typical person in each population.

84%). This infusion rate resulted in a steady-state EEG effect in 50-yr-old individuals that is approximately normally distributed around the targeted 50% EEG effect (simulation not shown). In most elderly individuals, the onset was more rapid and steady-state effect greater than in younger individuals. Thus, despite pharmacokinetic and pharmacodynamic variability, age adjustment of infusion rate (fig. 4, lower graphs) improved the ability to achieve the EEG target, and failure to adjust the infusion rate for age resulted in a more rapid onset of EEG effect and more profound steady-state EEG effect in elderly individuals.

The infusion rates administered by a computer-controlled infusion pump programmed to maintain 50% EEG effect for typical individuals in each decade are shown in figure 5. In young individuals, the infusion rate decreased by about 25% in the first 15 min, whereas in the elderly the infusion rate was nearly constant once the target effect site concentration was achieved.

Recovery from Prolonged Infusion

Figure 6 shows the time required for deceases in the effect site concentration after termination of a pseudo-steady-state infusion for typical individuals with LBMs of 55 kg and ages 20 yr and 80 yr. The typical times required for remifentanil concentrations to decrease by

20%, 50%, and 80% after prolonged administration are rapid and little affected by age or duration of infusion.

Figure 7 uses the stochastic pharmacokinetic and pharmacodynamic models to examine the influence of variability on the time required for a 50% decrease in effect site concentration in a population (n = 500 each, LBM = 55) of 20-yr-old, 50-yr-old, and 80-yr-old individuals. Although the typical time for a 50% decrease is rapid in all age groups, the variability is increased in elderly individuals. The model predicts that approximately 1% of 80-yr-old individuals will require three to four times longer than the typical 80-yr-old person to achieve a 50% decrease in effect-site concentrations.

Titratability

Figure 8 shows the EEG effect *versus* time profiles for typical 20- and 80-yr-old individuals receiving stepped constant rate infusions targeting 20%, 50%, and 80% of maximum EEG effect. Within 15 min, the predicted effect approaches the targeted effect at both ages, although the rate of change is slightly faster in the young compared with the elderly.

Discussion

These simulations have used age- and LBM-adjusted pharmacokinetic and pharmacodynamic models to de-
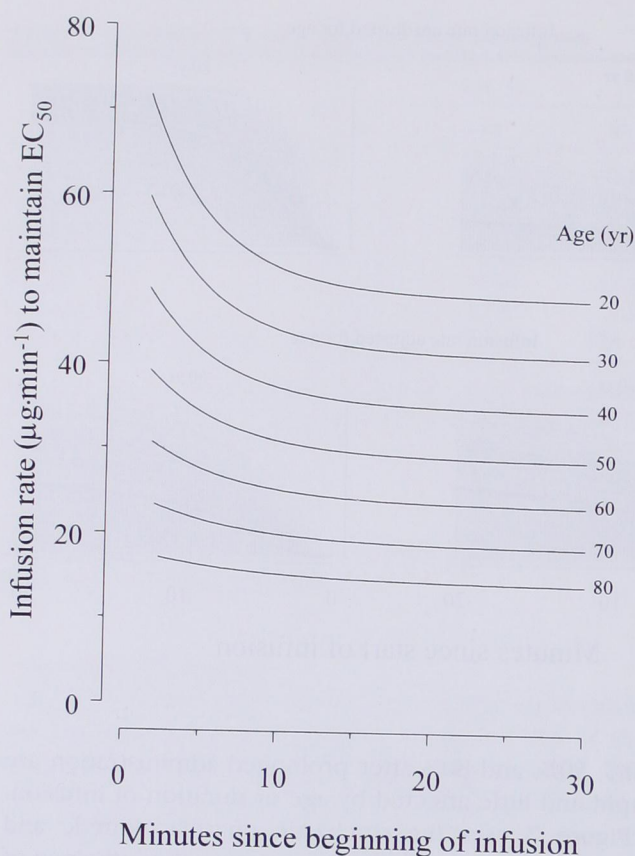
Fig. 5. Remifentanil infusion rates required to maintain 50% of the maximum electroencephalographic effect as a function of age for typical individuals with LBM of 55 kg.

rive dosing guidelines based on an EEG model of drug effect, and to examine the influence of interindividual variability on the dosing guidelines and predicted time course of drug effect. It must be emphasized that all the simulations of remifentanil's effect are based on the EEG model. For example, figures 3 and 4 indicate that some individuals would have little EEG effect from the remifentanil bolus or infusion rates used in the simulation. This does not imply that the models predict no opioid effect. For fentanyl, alfentanil, and sufentanil, the concentrations necessary for various anesthetic techniques have been reviewed.[5] The EC_{50} for opioid-induced EEG depression were approximately three to five times greater than the concentrations required for adequate ventilation on emergence from a general anesthetic. More recently Kapila and associates[7] used depression of minute ventilation to 7.5% ET_{CO_2} as a measure of remifentanil effect. They targeted a blood con-

centration of 1 ng/ml, much lower than the typical EC_{50} values for remifentanil's EEG effect (table 1). Thus, although the simulations predict little EEG response in some individuals to the particular bolus and infusion rates used, there could be significant ventilatory depression. As an additional caveat, note that we have included the tails of the distributions in all simulations. As discussed recently by Schnider and Shafer,[8] whether these tails represent real expectations in a population is not clear, because they are extrapolated from the normal distribution and not directly observed.

The simulations we made in this study show that elderly individuals should receive one half the bolus dose and one third the infusion rate of young individuals. These conclusions depend on both pharmacokinetic and pharmacodynamic factors. The reduction in the volumes, clearances, and k_{e0} that occur in the elderly result in little change in the Vd_{pe}. The decreased bolus requirement in the elderly is due to the age-related decrease in EC_{50} found using the EEG model of drug effect. The lower infusion rate requirement in the elderly is a result of the age-related decrease in both metabolic clearance and EC_{50}. Although the time to the peak effect site concentration is almost twice as long in the elderly as the young, the bolus and infusion simulations (figs. 3 and 4) revealed a rapid onset (and more prolonged duration) of EEG effect in the elderly, when the dose was not adjusted for age. These findings are explained by the sigmoid E_{max} model. The age-related changes
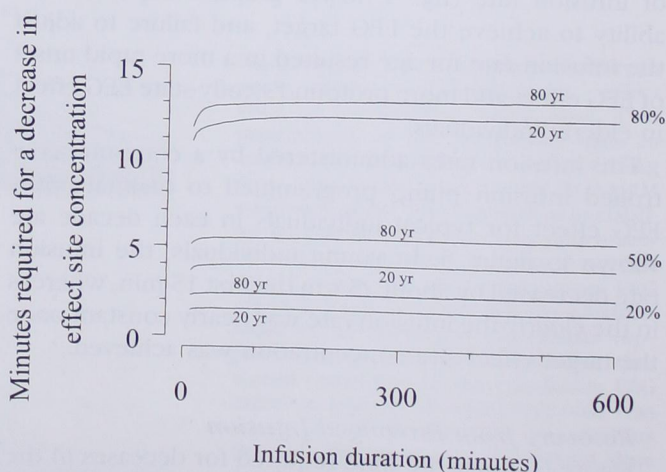

Fig. 6. A simulation of the time necessary to achieve a 20%, 50%, and 80% decrease in effect site drug concentration after a variable-length infusion. For each percentage decrease, curves are drawn for typical individuals ages 20 and 80 yr with LBMs of 55 kg.

Fig. 7. A simulation showing the variability in the 50% effect site decrement curves. Three populations of 500 individuals ages 20, 50, and 80 yr with LBMs of 55 kg were simulated based on the NONMEM estimates of the interindividual variability in pharmacokinetic and pharmacodynamic parameters. The curve for the typical individual in each age group is shown with an arrow. Some individuals show an initial decrease in the context-sensitive decrement times (see the discussion).
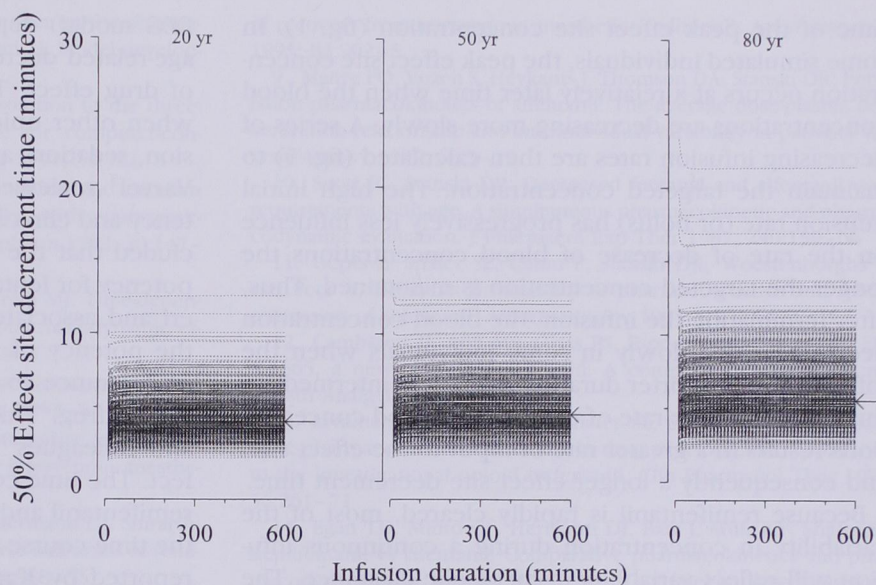
in pharmacokinetics and pharmacodynamics, together with the relative overdose, result in effect site concentrations that increase more quickly and stay higher (relative to the EC_{50}) for a much longer period. The adjustment of bolus and infusion rates according to the nomograms presented resulted in a similar distribution of peak EEG effect after a bolus, steady-state EEG effect after an infusion, and time course of EEG effect in all age groups.

Even when interindividual variability is included in

the simulation, the time required for a given percentage (20–80%) decrease in effect site concentration remains short at all ages. Interestingly, there are several instances in figure 7 in which the 50% effect site decrement time is longer for short infusions than for long infusions. The algorithm[3] used for these simulations initially calculates a brief rapid infusion rate (or bolus) to reach the targeted effect site concentration without overshoot. This results in high initial blood concentrations, which decrease rapidly to equal the target at the

Fig. 8. A simulation showing the predicted electroencephalographic effect resulting from several stepped constant-rate infusions. Infusion rates were chosen to achieve the targeted effect at steady state for typical individuals ages 20 and 80 yr.
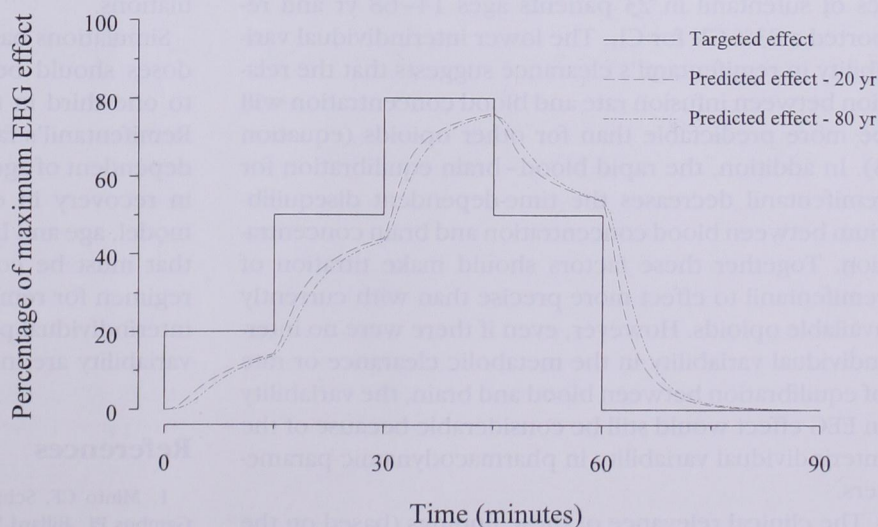
time of the peak effect site concentration (fig. 1). In some simulated individuals, the peak effect site concentration occurs at a relatively later time when the blood concentrations are decreasing more slowly. A series of decreasing infusion rates are then calculated (fig. 5) to maintain the targeted concentration. The high initial infusion rate (or bolus) has progressively less influence on the rate of decrease of blood concentrations the longer the targeted concentration is maintained. Thus, after terminating the infusion, the blood concentration decreases more slowly in some individuals when the infusion is of a shorter duration than of an intermediate duration. A slower rate of decrease in blood concentrations results in a greater rate of input to the effect site, and consequently a longer effect site decrement time.

Because remifentanil is rapidly cleared, most of the variability in concentration during a continuous infusion will reflect variability in metabolic clearance. The variability of remifentanil metabolic clearance is less than other intravenous opioids. The %CV on Cl_1 is reduced from 23% CV to 14% CV when age and LBM are included in the model (table 3 of part I of our series). After correction for age, body weight, and sex, Maitre and coworkers[9] reported a 48% CV for the clearance of alfentanil in a population pharmacokinetic analysis of 45 patients ages 19 to 91 yr who were undergoing general anesthesia. Scott and Stanski[10] reported individual clearance estimates for fentanyl (20 patients ages 20–88 yr) and alfentanil (17 patients ages 20–89 yr). The calculated %CVs for fentanyl and alfentanil clearance in their study were 59% and 32%, respectively. Gepts and associates[11] investigated the pharmacokinetics of sufentanil in 23 patients ages 14–68 yr and reported a 23% CV for Cl_1. The lower interindividual variability in remifentanil's clearance suggests that the relation between infusion rate and blood concentration will be more predictable than for other opioids (equation 3). In addition, the rapid blood–brain equilibration for remifentanil decreases the time-dependent disequilibrium between blood concentration and brain concentration. Together these factors should make titration of remifentanil to effect more precise than with currently available opioids. However, even if there were no interindividual variability in the metabolic clearance or rate of equilibration between blood and brain, the variability in EEG effect would still be considerable because of the interindividual variability in pharmacodynamic parameters.

The clinical relevance of these findings (based on the

EEG model) depend in part on the demonstration of age-related decreases in the EC_{50} for clinical measures of drug effect. The influence of age may be different when other opioid effects such as ventilatory depression, sedation, and analgesia are examined. Shafer and Varvel[5] reviewed EEG-based measures of opioid potency and clinical measures of opioid potency and concluded that the EEG was a useful predictor of opioid potency for fentanyl, alfentanil, and sufentanil. Cambareri and associates[12] found no significant difference in the potency of alfentanil and trefentanil as measured by tolerance to tibial pressure 3 min after a bolus of either drug. This finding was confirmed by Lemmens and colleagues[13] using EEG as a measure of opioid effect. The time course of EEG response observed in our remifentanil and alfentanil trials[13,14] has correlated with the time course of ventilatory depression and analgesia reported by Kapila and colleagues.[7] They found that after a 3-h infusion of remifentanil or alfentanil, designed to closely maintain a constant drug concentration and drug effect, the measured times to 50% recovery from drug effect (as measured by recovery from respiratory depression) was 5.4 min for remifentanil and 54 min for alfentanil.[7] The measured context-sensitive half-lives for remifentanil and alfentanil corresponded closely to those modeled based on the EEG model parameters. Thus the available data suggest that the EEG is a useful surrogate measurement of opioid drug effect that permits identification of both drug potency and the time course of blood-effect site equilibration and would suggest that the EEG is a sensitive method for developing dosing guidelines in special populations.

Simulations based on the EEG model show that bolus doses should be halved and infusion rates decreased to one third in the elderly compared with the young. Remifentanil's favorable titration characteristics are independent of age, although there is increased variability in recovery in elderly individuals. Based on the EEG model, age and LBM are significant demographic factors that must be considered when determining a dosage regimen for remifentanil. This remains true even when interindividual pharmacokinetic and pharmacodynamic variability are incorporated in the analysis.

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