Response Surface Modeling of Alfentanil–Sevoflurane Interaction on Cardiorespiratory Control and Bispectral Index

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Background: Respiratory depression is a serious side effect of anesthetics and opioids. The authors examined the influence of the combined administration of sevoflurane and alfentanil on ventilatory control, heart rate (HR), and Bispectral Index (BIS) in healthy volunteers.

Methods: Step decreases in end-tidal partial pressure of oxygen from normoxia into hypoxia (~50 mmHg) at constant end-tidal partial pressure of carbon dioxide (~48 mmHg) were performed in nine male volunteers at various concentrations of alfentanil and sevoflurane, ranging from 0 to 50 ng/ml for alfentanil and from 0 to 0.4 end-tidal concentration (ET%) for sevoflurane, and with various combinations of alfentanil and sevoflurane. The alfentanil–sevoflurane interactions on normoxic resting (hypercapnic) ventilation ($\dot{V}_i$), HR, hypoxic $\dot{V}_i$, and HR responses and BIS were assessed by construction of response surfaces that related alfentanil and sevoflurane to effect using a population analysis.

Results: Concentration–effect relations were linear for alfentanil and sevoflurane. Synergistic interactions were observed for resting $\dot{V}_i$ and resting HR. Depression of $\dot{V}_i$ by 25% occurred at 38 ± 11 ng/ml alfentanil (population mean ± SE) and at 0.7 ± 0.4 ET% sevoflurane. One possibility for 25% reduction when alfentanil and sevoflurane are combined is 13.4 ng/ml alfentanil plus 0.12 ET% sevoflurane. Additive interactions were observed for hypoxic $\dot{V}_i$ and HR responses and BIS. Depression of the hypoxic $\dot{V}_i$ response by 25% occurred at 16 ± 1 ng/ml alfentanil and 0.14 ± 0.05 ET% sevoflurane. The effect of sevoflurane on the BIS (25% reduction of BIS occurred at 0.45 ± 0.08 ET%) was independent of the alfentanil concentration.

Conclusions: Response surface modeling was used successfully to analyze the effect of interactions between two drugs on respiration. The combination of alfentanil and sevoflurane causes more depression of $\dot{V}_i$ and HR than does the summed effect of each drug administered separately. The effects of combining alfentanil and sevoflurane on hypoxic $\dot{V}_i$ and HR responses and BIS could be predicted from the separate dose–response curves. Over the dose range tested, the hypoxic response is more sensitive to the effects of anesthetics and opioids relative to resting ventilation.

ONE of the advantages of combining an opioid and an anesthetic over the use of single agents is the synergistic increase in desired anesthetic effect, such as absence of movement in response to a painful stimulus as defined by the minimal alveolar concentration (*i.e.*, anesthetic potency).[1] The consequence of this mechanism is the need for fewer drugs with possibly fewer side effects. Anesthesiologists make use of these fortuitous interactions by combining opioids and anesthetics during anesthesia. Because respiratory depression is a serious side effect of anesthetics,[2–4] hypnotics,[5] and opioids,[6,7] even at low doses, it is surprising that few studies in humans have addressed the issue of the impact of drug combinations on respiration. Especially the nature of the interaction (additive *versus* synergistic) of an anesthetic–opioid combination on the control of breathing remains unknown. Therefore, we studied the influence of the opioid alfentanil and the inhalational anesthetic sevoflurane on ventilatory control, heart rate (HR), Bispectral Index (BIS; as measure of the hypnotic state of the subjects), and the ventilatory and HR responses to hypoxia. The ability of the ventilatory control system to cope adequately with hypoxic episodes is of importance because hypoxic periods frequently occur perioperatively.

The alfentanil–sevoflurane interaction on ventilatory control, HR, and BIS was assessed by response surface modeling.[8–10] This approach enables us to construct three-dimensional representations of the concentration–response relation among combinations of alfentanil and sevoflurane and assess the nature of the interaction (additive, synergistic, or antagonistic) over the whole surface area (it is possible for the response surface to include all of these interactions in different regions).[8–10] This approach is superior to the construction of isoboles (or iso-effect curves), which allows assessment of the interaction at drug combinations yielding a constant effect, such as 25 or 50% reduction in effect parameter (*i.e.*, C_{25} and C_{50}).

In this study, we used the dynamic end-tidal forcing technique.[11] This technique enables us to assess the effect of drug combinations on ventilatory control at identical end-tidal partial pressures of carbon dioxide (P_{CO_2}s). Consequently, this makes a comparison among

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the respiratory effects of different drug combinations possible because the results are not confounded by changes in P_{CO_2}.

Methods

Subjects and Apparatus

Nine healthy male volunteers (aged 18–25 yr) participated in the protocol after approval was obtained from the local human ethics committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands). Oral and written consent was obtained from all volunteers. The subjects were healthy and did not have a history of tobacco or illicit drug use.

After arrival at the laboratory, two intravenous catheters were inserted in the left and right antecubital veins of the patients (one for alfentanil administration and one for blood sampling). Subsequently, electrodes for electroencephalographic measurement were placed on the head as specified by the manufacturer, and the subjects rested for 20–30 min. Next, a face mask was applied over the mouth and nose. Gas flow was measured with a pneumotachograph connected to a pressure transducer and integrated electronically to yield a volume signal. Corrections were made for the changes in gas viscosity caused by changes in oxygen concentration of the inhaled gas mixtures. The pneumotachograph was connected to a T piece. One arm of the T piece received a gas mixture from a gas mixing system consisting of three mass-flow controllers. A personal computer provided control signals to the mass-flow controllers so that the composition of the inspired gas mixtures could be adjusted to force end-tidal oxygen concentration (PET_{O_2}) and end-tidal carbon dioxide concentration (PET_{CO_2}) to follow a specified pattern in time. The oxygen and carbon dioxide concentrations of inspired and expired gases and the arterial hemoglobin–oxygen saturation (Sp_{O_2}) were measured with a gas monitor and pulse oximeter, respectively. Sevoflurane was measured at the mouth with a gas monitor, which was calibrated with an anesthetic gas of known concentration. End-tidal sevoflurane concentration, PET_{O_2}, PET_{CO_2}, tidal volume (V_T), respiratory frequency (RR), inspired minute ventilation ($\dot{V}_i$), Sp_{O_2}, and HR were collected and stored on disc.

The electroencephalograph was recorded using a monitor that computed the BIS over 2-s epochs. We averaged the BIS values over 1-min intervals and used data points obtained at 3-min intervals.

Study Design

Ventilatory response to isocapnic hypoxia (acute hypoxic response) was assessed during inhalation of sevoflurane, infusion of alfentanil, and the combined administration of both agents. Initially, two hypoxic control studies (*i.e.*, studies without the administration of

Table 1. Total Number of Paired Hypoxic Studies at Each of the Treatment Concentrations

ET Sevoflurane (%)	Target Alfentanil Concentration (ng/ml)					
	0	10	20	30	40	50
0	18	4	9	3	9	2
0.05	1	1	2	2	—	—
0.1	9	5	9	2	5	—
0.2	9	3	7	2	1	—
0.3	9	3	3	—	—	—
0.4	2	—	—	—	—	—

ET = end-tidal.

any agent) were obtained. Next, inhalation of sevoflurane was started, and hypoxic studies were performed during inhalation of sevoflurane. To achieve blood–brain equilibrium, sevoflurane hypoxic experiments were preceded by a 12-min equilibration period.[12] In table 1, the various imposed target end-tidal sevoflurane concentrations are given. After this set of studies, the subject rested for 30–45 min, and another two control studies were obtained. Next, intravenous infusion of alfentanil was started, and hypoxic studies were performed at various blood target concentrations (table 1). Subsequently, hypoxic studies during the combined administration of sevoflurane and alfentanil were performed (table 1). The sevoflurane and alfentanil target concentrations were chosen in such a way that at least 60% depression but preferably 80% depression of the ventilatory response to hypoxia was achieved. All experiments were performed on a single day, starting at 8:30 AM.

The Isocapnic Hypoxic Study. The PET_{O_2} waveform was as follows: (1) 10 min at 110 mmHg; (2) a rapid decrease to 50 mmHg; (3) 3 min at 50 mmHg; and (4) 4–5 min at 110 mmHg. At each treatment level (control, various concentrations of sevoflurane, alfentanil, and sevoflurane plus alfentanil), two hypoxic studies were obtained.

All hypoxic studies were performed at identical end-tidal P_{CO_2} concentrations, ~5–7 mmHg more than awake resting values. This high value was chosen to offset an increase in end-tidal P_{CO_2} caused by the alfentanil–sevoflurane–induced ventilatory depression.

Alfentanil Administration, Blood Sampling, and Assay. A target controlled infusion was used for the administration of alfentanil. A palm-top computer programmed with the population pharmacokinetic data set reported by Maitre *et al.*[13] was connected to a syringe pump, which was filled with alfentanil (0.5 mg/ml). This system allows a theoretical plasma concentration of alfentanil to be achieved rapidly and maintained. Hypoxic studies were performed 5–10 min after blood alfentanil concentrations reached their target levels. Because this equals 5–10 times the alfentanil blood–brain equilibration half-life of 1 min,[14] we assume that
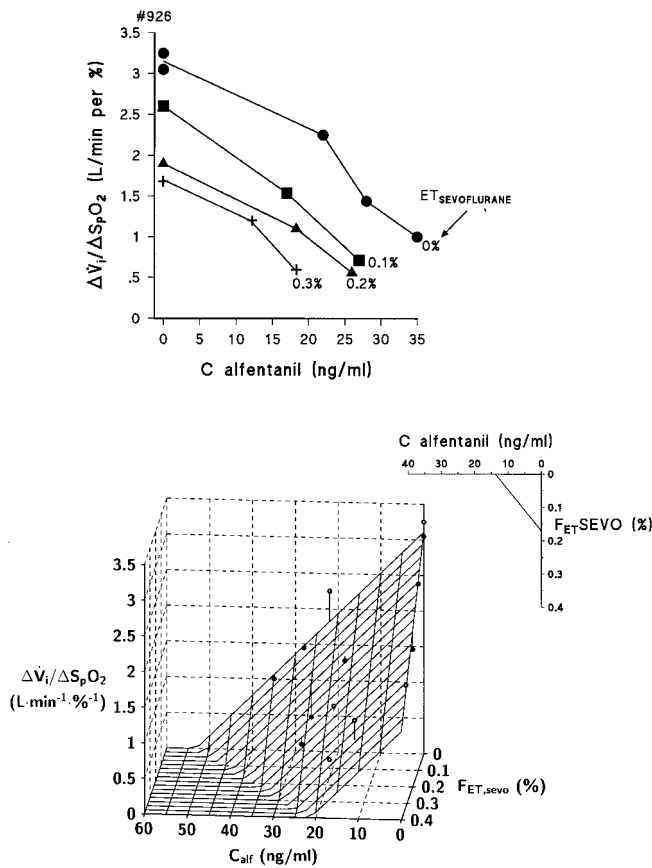
Fig. 1. (*Top*) The influence of plasma alfentanil concentration (x-axis) at fixed concentrations of end-tidal sevoflurane concentration (ET$_{SEVOFLURANE}$) on the hypoxic drive or $\Delta\dot{V}_i/\Delta Spo_2$ (y-axis) in one subject (subject 926). Note the parallel displacements of the alfentanil dose–hypoxic response curve caused by sevoflurane. (*Bottom*) A three-dimensional graph of the individual Bayesian estimate of the response surface of subject 926 for $\Delta\dot{V}_i/\Delta Spo_2$. The open and closed circles denote data points above and below the surface, respectively. The surface gives an impression of the nature of the interaction at all possible drug combinations, which, in this case, is additive. (*Inset*) A slice through the surface representing the concentrations of alfentanil and sevoflurane causing 25% depression of $\dot{V}_i$. C_{alf} = alfentanil blood concentration.

brain and blood alfentanil concentrations were in equilibrium.

Before and after changes in target alfentanil concentration, 3-ml blood samples for the measurement of alfentanil were collected. A capillary gas chromatographic technique was used to determine the plasma concentration.

Data Analysis and Statistics

Averaged values of the breath-to-breath data were chosen over identical time segments. Normoxic data points were the mean of the 10 breaths before the 3-min hypoxic period. Hypoxic data points were mean of the last 10 breaths of the hypoxic episode. Analysis was performed on the following variables: normoxic $\dot{V}_i$; normoxic V_T; normoxic RR; normoxic HR; normoxic BIS; normoxic and hypoxic end-tidal Pco_2; normoxic and

hypoxic end-tidal partial pressure of oxygen (Po_2); and the changes in $\dot{V}_i$, V_T, RR, and HR from normoxia to hypoxia relative to the absolute changes in arterial oxygen saturation (*i.e.*, $\Delta\dot{V}_i/\Delta Spo_2$, $\Delta V_T/\Delta Spo_2$, $\Delta RR/\Delta Spo_2$, and $\Delta HR/\Delta Spo_2$). Hypoxic sensitivities usually are defined as follows: [E(hypoxia) − E(normoxia)]/ΔSpo_2, where ΔSpo_2 is [100 − Spo_2 (hypoxia)], and E is the value of a measured parameter. Instead of 100, we used the actual Spo_2 value measured during normoxia to calculate ΔSpo_2. This definition results in positive hypoxic sensitivity values when the measured parameter E increases with the introduction of hypoxia (*i.e.*, E(hypoxia) > E(normoxia)). Only when the effect parameter decreases because of hypoxia (*i.e.*, E(hypoxia) < E(normoxia)) will the value of the hypoxic sensitivity be negative. The data sets (sevoflurane concentration, alfentanil concentration, E parameter) were analyzed using a pharmacodynamic model, which can be visualized in three-dimensional space as a "response surface." We used the following pharmacodynamic model:

$$f(x) = \alpha \cdot (1 - x^\gamma) \tag{1}$$

By substituting E_0, which is the baseline value (*i.e.*, pre–drug administration value) of a variable, for α and substituting $U^\gamma/2$ for x^γ and U = C/C_{50}, where C_{50} is the concentration causing 50% decrease in E, E is a measured variable, and C is the concentration of one drug, we obtain:

$$E(C) = E_0 \cdot (1 - U^\gamma/2) \tag{2}$$

Pure additive interactions of two drugs (alfentanil and sevoflurane) are modeled as follows:

$$E(C_A, C_S) = E_0 \cdot (1 - (U_A + U_S)^\gamma/2) \tag{3}$$

$$U_A = C_A/C_{50,A} \tag{4}$$

$$U_S = C_S/C_{50,S} \tag{5}$$

C_A is the alfentanil plasma concentration, C_S is the end-tidal sevoflurane concentration, $C_{50,A}$ is the alfentanil concentration causing a 50% decrease in E, and $C_{50,S}$ is the sevoflurane concentration causing a 50% decrease in E.

To include nonadditive interactions in the model, an interaction, I(Q), is introduced:

$$E(C_A, C_S) = E_0 \cdot (1 - [(U_A + U_S)^\gamma]/2 \cdot I(Q)) \tag{6}$$

I(Q) is a smooth function (spline) of Q (Appendix 1). Following Minto *et al.*,[10]

$$Q = U_A/(U_A + U_S) \tag{7}$$

Q ranges from 0 (sevoflurane only) to 1 (alfentanil only) and is the drug concentration ratio of alfentanil and sevoflurane normalized by their respective C_{50}s or potencies (equations 4 and 5). The smooth function has two parameters, I_{max} and Q_{max}. I_{max} is the maximum
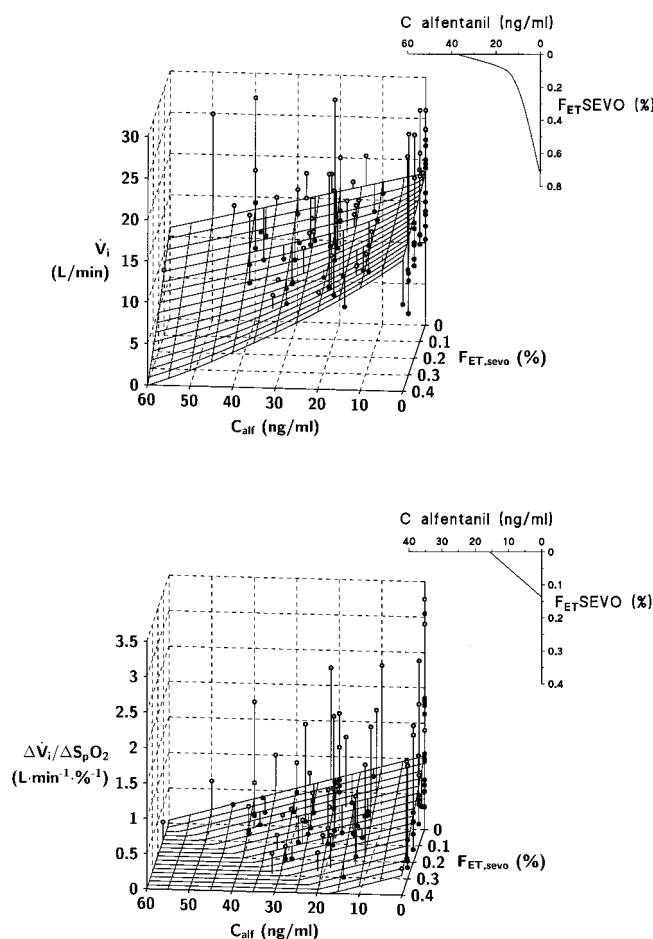
Fig. 2. (*Top*) **Response surface modeling of the influence of alfentanil (C$_{alf}$ = alfentanil blood concentration) and sevoflurane (FET$_{SEVO}$ = end-tidal sevoflurane concentration) on normoxic ventilation at a fixed end-tidal carbon dioxide concentration (PET$_{CO_2}$). The open and closed circles denote date points above and below the surface, respectively. (*Inset*) A slice through the surface; the isobole for 25% reduction of inspired minute ventilation ($\dot{V}_i$). A 25% reduction of $\dot{V}_i$ occurred at: an alfentanil concentration of ~38 ng/ml when no sevoflurane was present, at a sevoflurane concentration of ~0.73% when no alfentanil was present, and at ~0.1% sevoflurane when 15 ng/ml alfentanil was present. This indicates synergistic interaction (I(Q)) of ~1.9 at Q of ~0.7; P < 0.01). (*Bottom*) Response surface modeling of the influence of alfentanil and sevoflurane on the ventilatory response to acute hypoxia at a fixed PET$_{CO_2}$ (*i.e.*, the hypoxic drive). (*Inset*) The isobole for 25% reduction of hypoxic drive. A 50% reduction of hypoxic drive occurred at an alfentanil concentration of ~16 ng/ml when no sevoflurane was present, at a sevoflurane concentration of ~0.14% when no alfentanil was present, and at ~0.05% sevoflurane when 10 ng/ml alfentanil was present. This indicates additive interaction. Sp$_{O_2}$ = oxygen saturation.**
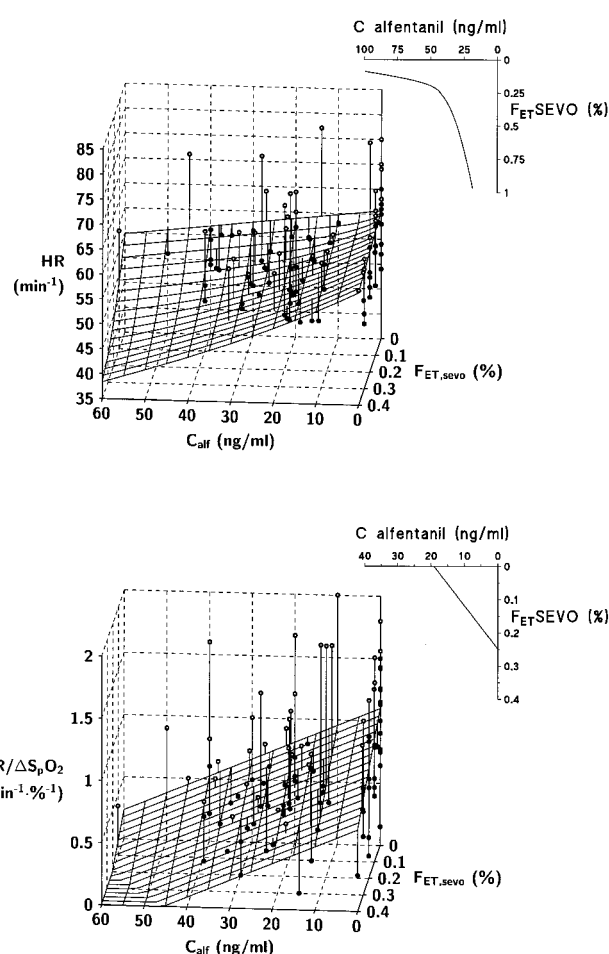
Fig. 3. (*Top*) **Response surface modeling of the influence of alfentanil and sevoflurane on normoxic heart rate (HR) at a fixed end-tidal carbon dioxide concentration (PET$_{CO_2}$). (*Inset*) A slice through the surface, which is the isobole for 25% reduction of HR. (*Bottom*) Response surface modeling of the influence of alfentanil and sevoflurane on the HR response to acute hypoxia at a fixed PET$_{CO_2}$. (*Inset*) The isobole for 25% reduction of ΔHR/ΔSp$_{O_2}$. C$_{alf}$ = alfentanil blood concentration; FET$_{SEVO}$ = end-tidal sevoflurane concentration; Sp$_{O_2}$ = oxygen saturation.**

value of the interaction term, and Q$_{max}$ is the value of Q (*i.e.*, concentration ratio) for which I attains I$_{max}$. When I$_{max}$ equals 1, the interaction is purely additive. An I$_{max}$ of less than 1 denotes antagonism, and an I$_{max}$ of more than 1 denotes synergy.

The model was fitted to the data with NONMEM (conditional estimation method), version V, level 1.1 (a data analysis program for nonlinear mixed effects modeling),[15] using a population approach. The interindividual

variability of each of the model parameters is characterized by the percentage coefficient of variation, which is a parameter derived from the variance of the logarithm of the individual model parameters. Likelihood-ratio tests were performed to determine whether γ did not equal 1 and whether I$_{max}$ did not equal 1. The intraindividual variability was quantified by the SD of the residuals. P values of less than 0.01 were considered significant.

Results

A total of 109 paired hypoxic responses were obtained at various treatment levels (table 1). The duration of the experiments ranged from 5 to 6 h. In figure 1, an example of the various drug combinations applied in a single subject is shown. This graph further illustrates that the maximum depression of the hypoxic drive

(= $\Delta\dot{V}_i/\Delta Sp_{O_2}$) was 70–80%, obtained at multiple drug combinations. This level of depression was one of the aims of the study protocol, which was met in all subjects.

End-tidal carbon dioxide values were equal in normoxia and hypoxia (PET_{CO_2} normoxia, 48.3 ± 0.5 mmHg [mean ± SEM] *versus* hypoxia, 48.2 ± 0.6 mmHg). These values are 6–7 mmHg more than individual resting values. The measured plasma alfentanil values averaged to 12.7 ± 0.9, 21.3 ± 1.6, 27.4 ± 1.2, and 35.6 ± 2.4 ng/ml for target concentrations of 10, 20, 30, and 40 ng/ml, respectively.

A three-dimensional graph of the conditional Bayesian estimate of the response surface of one subject for $\Delta\dot{V}_i/\Delta\%Sp_{O_2}$ is given in figure 1 (bottom). The value of γ was not different from 1. This indicates a linear relation between alfentanil, sevoflurane, and effect. The surface gives an impression of the nature of the interaction at all possible drug combinations, at least within the dose ranges tested, which, in this case, is additive in all regions of that part of the surface. It further predicts the interaction at concentrations higher than those we applied. Assuming that the concentration–effect relation remains linear, the model predicts the complete loss of the hypoxic response (*i.e.*, $\Delta\dot{V}_i/\Delta Sp_{O_2} = 0$) in this subject at combinations of alfentanil and sevoflurane on a line on the surface connecting the points (alfentanil = 55 ng/ml, sevoflurane = 0 ET%) and (alfentanil = 22 ng/ml, sevoflurane = 0.4 ET).

The population estimates of the response surfaces are given in table 2 and figures 2–4. The model fit the data well. For all variables, the model fits yielded values of γ not significantly different from 1. This indicates that alfentanil and sevoflurane, and combinations of alfentanil and sevoflurane at fixed ratios, cause changes of the measured variables in a linear manner. The C_{25} and C_{50} values (the concentrations causing 25% and 50% reduction of effect) are given in table 2. Note the absence of effect of alfentanil on BIS (table 2 and fig. 4) and of sevoflurane on normoxic breathing frequency (table 2; see also below).

Pure additive interactions were found for the following parameters: $\Delta\dot{V}_i/\Delta Sp_{O_2}$, V_T, $\Delta V_T/\Delta Sp_{O_2}$, and $\Delta RR/\Delta Sp_{O_2}$. Inert interactions were observed for RR and BIS. This leads to straight isoboles or iso-effect curves (the isoboles for EC_{25} are shown in the insets of figs. 2–4). Alfentanil, over the dose range studied, caused a modest reduction of normoxic breathing frequency. The C_{25} was 81.5 ng/ml, clearly outside the dose range we studied (table 2). Sevoflurane had no effect on RR when increasing from 0 to 0.4 ET%. Sevoflurane caused a linear reduction of the BIS with an EC_{25} of 0.45 ET% (table 2). The effect of sevoflurane on the BIS was independent of the alfentanil concentration.

Synergistic interactions were found for normoxic $\dot{V}_i$ and HR (table 2 and figs. 2 and 3). In figure 5, the
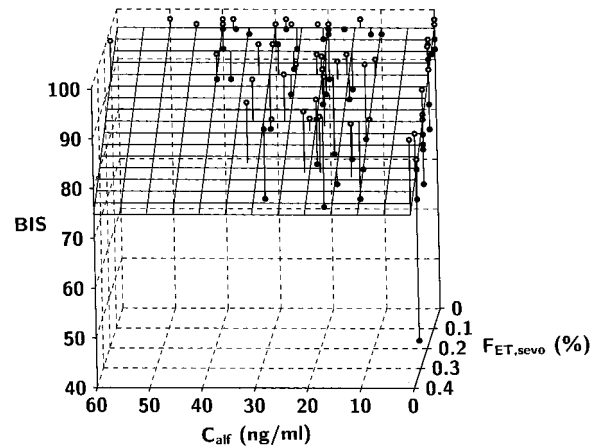

Fig. 4. Response surface modeling of the influence of alfentanil and sevoflurane on the Bispectral Index (BIS). A 25% reduction of the BIS occurred at a sevoflurane concentration of 0.43% (table 2), but no decrease was seen with increasing doses of alfentanil, even in the presence of sevoflurane. C_{alf} = alfentanil blood concentration; $F_{ET,sevo}$ = end-tidal sevoflurane concentration.

relations between Q (*i.e.*, the alfentanil–sevoflurane concentration ratio) and I(Q) (*i.e.*, the interaction) are given. For $\dot{V}_i$ and HR, synergistic interactions were observed, with maximum synergistic interactions (I_{max} in table 2) occurring at Q values of approximately 0.7 (Q_{max} in table 2). Depression of $\dot{V}_i$ by 25% occurred at an alfentanil concentration of 38 ng/ml and at a sevoflurane concentration of 0.7 ET%. The combinations of sevoflurane and alfentanil causing 25% reductions in $\dot{V}_i$ are given in the inset of figure 3 (top). The synergy is obvious from the concave form of the isobole. One possibility for 25% reduction is 13.4 ng/ml alfentanil plus 0.12 ET% sevoflurane (I(Q) of ~1.9 at a Q of ~0.7).

Discussion

The main findings in this study are as follows: (1) Alfentanil (up to a plasma concentration of 50 ng/ml) and sevoflurane (from 0 to 0.4 ET%), when administered separately, depress ventilation, HR, and the ventilatory and HR responses to acute hypoxia in a dose-dependent linear manner. (2) When combined, their depressant effect on ventilation and HR is synergistic, whereas their effect on the hypoxic responses is additive. (3) Relative to normoxic baseline parameters ($\dot{V}_i$, V_T, RR, and HR), the responses to hypoxia show greater sensitivity to the effects of alfentanil and sevoflurane (*i.e.*, depression occurs at lower drug concentrations) when the drugs are administered separately and when combined (C_{25} values differ by 2–8 times). (4) The BIS is sensitive to sevoflurane but not to alfentanil, even when these agents are combined (inert interaction).

The Pharmacodynamic Model
Although the relation between drug concentration and respiratory effect has been modeled previously using an

Table 2. Model Parameter Estimates for Ventilation ($\dot{V}_i$), Tidal Volume (V_T), Respiratory Frequency (RR), Heart Rate (HR), the Hypoxic Sensitivities ($\Delta E/\Delta Spo_2$), and Bispectral Index (BIS)

	$\dot{V}_i$	$\Delta\dot{V}_i/\Delta Spo_2$
Baseline		
Value ± SE	18.4 ± 1.5 l/min	1.04 ± 0.27 l · min^{-1} · %$^{-1}$
%CV	22	74
C_{25} alfentanil		
Value ± SE	37.7 ± 11 ng/ml	15.7 ± 1.4 ng/ml
C_{50} alfentanil		
Value ± SE	75.3 ± 23 ng/ml	31.3 ± 2.8 ng/ml
%CV	48	17
C_{25} sevoflurane		
Value ± SE	0.73 ± 0.44 ET%	0.14 ± 0.05 ET%
C_{50} sevoflurane		
Value ± SE	1.46 ± 0.88 ET%	0.27 ± 0.05 ET%
%CV	106	41
I_{max}		
Value ± SE	1.92 ± 0.28	
Q_{max}		
Value ± SE	0.68 ± 0.11 l/min	
SD of residuals	2.99 l/min	0.21 l · min^{-1} · %$^{-1}$

	V_T	$\Delta V_T/\Delta Spo_2$
Baseline		
Value ± SE	1150 ± 50 ml	46 ± 11 ml/%
%CV	11	62
C_{25} alfentanil		
Value ± SE	37.0 ± 6.5 ng/ml	18.4 ± 2.6 ng/ml
C_{50} alfentanil		
Value ± SE	74.0 ± 13.0 ng/ml	36.8 ± 5.2 ng/ml
%CV	30	28
C_{25} sevoflurane		
Value ± SE	0.39 ± 0.18 ET%	0.15 ± 0.05 ET%
C_{50} sevoflurane		
Value ± SE	0.79 ± 0.36 ET%	0.29 ± 0.10 ET%
%CV	80	70
SD of residuals	80 ml	10.9 ml/%

	RR	$\Delta RR/\Delta Spo_2$
Baseline		
Value ± SE	16.1 ± 1.1 min^{-1}	0.25 ± 0.07 min^{-1} · %$^{-1}$
%CV	16	86
C_{25} alfentanil		
Value ± SE	81.5 ± 24.7 ng/ml	11.6 ± 0.4 ng/ml
C_{50} alfentanil		
Value ± SE	163.0 ± 49.3 ng/ml	23.2 ± 0.7 ng/ml
%CV	*	*
C_{25} sevoflurane		
Value ± SE	*	0.24 ± 0.02 ET%
C_{50} sevoflurane		
Value ± SE	*	0.49 ± 0.04 ET%
%CV	*	*
SD of residuals	2.49 min^{-1}	0.18 min^{-1} · %$^{-1}$

Baseline = control parameter value (*i.e.*, before drug administration); C_{25} and C_{50} = concentrations of alfentanil (in ng/ml) or sevoflurane (in end-tidal concentration [ET%]) giving 25% and 50% reductions in E; %CV = percentage coefficient of variation, which is a measure of the interindividual variability; * = parameter not included in the statistical model; I_{max} and Q_{max} = interaction parameters: I_{max} values not significantly different from 1 are not included in the table (in these cases, the alfentanil–sevoflurane interaction is additive) and I_{max} values greater than 1 indicate synergy; SD of the residuals = measure of goodness of fit.

Table 2. Continued

	HR	$\Delta HR/\Delta Spo_2$
Baseline		
Value ± SE	60.7 ± 2.4 min^{-1}	1.10 ± 0.10 min^{-1} · %$^{-1}$
%CV	11	24
C_{25} alfentanil		
Value ± SE	155 ± 90 ng/ml	19.1 ± 3.0 ng/ml
C_{50} alfentanil		
Value ± SE	310 ± 180 ng/ml	38.2 ± 6.1 ng/ml
%CV	108	20
C_{25} sevoflurane		
Value ± SE	1.92 ± 1.35 ET%	0.25 ± 0.11 ET%
C_{50} sevoflurane		
Value ± SE	3.85 ± 2.70 ET%	0.50 ± 0.23 ET%
%CV	*	70
I_{max}		
Value ± SE	2.47 ± 0.90	
Q_{max}		
Value ± SE	0.69 ± 0.13	
SD of residuals	3.67 min^{-1}	0.33 min^{-1} · %$^{-1}$

	BIS	
Baseline		
Value ± SE	96.3 ± 0.8	
%CV	2.1	
C_{25} alfentanil		
Value ± SE	*	
C_{50} alfentanil		
Value ± SE	*	
C_{25} sevoflurane		
Value ± SE	0.45 ± 0.08 ET%	
C_{50} sevoflurane		
Value ± SE	0.90 ± 0.17 ET%	
%CV	53	
SD of residuals	3.32	

inhibitory sigmoid E_{max} model,[16] we refrained from such an approach. In contrast, we chose the function f(x) = $\alpha(1 - x^\gamma)$, which allows for linear and nonlinear concentration–effect relations (fig. 6). This was chosen for the following reasons:

1. Asymmetric sigmoidal relations between drug and effect may occur in complex systems, such as the ventilatory control system. For example, at high drug concentrations (higher than those studied by us), nonlinear threshold values may cause the respiratory oscillator to stop abruptly and may cause irregular or cyclic breathing and apnea.[17,18] In our model, effect becomes zero at the concentration $C_{50} \cdot 2^{1/\gamma}$ (fig. 6).

2. Some respiratory parameters, such as hypoxic ventilatory sensitivity ($\Delta\dot{V}_i/\Delta Spo_2$), may become negative above certain drug concentrations. For example, we previously observed in one male subject that although hypoxia caused an increase in $\dot{V}_i$ during alfentanil infusion (target, 40 ng/ml) in the awake state, it caused an immediate decrease in ventilation when the subject was asleep (*i.e.*, [$\dot{V}_i$(hypoxia) − $\dot{V}_i$(normoxia)]/Spo_2(normoxia) − Spo_2 (hypoxia)] < 0).[19] Our model predicts such behavior at concentrations greater than $C_{50} \cdot 2^{1/\gamma}$ (fig. 6). In some of the subjects in this study,
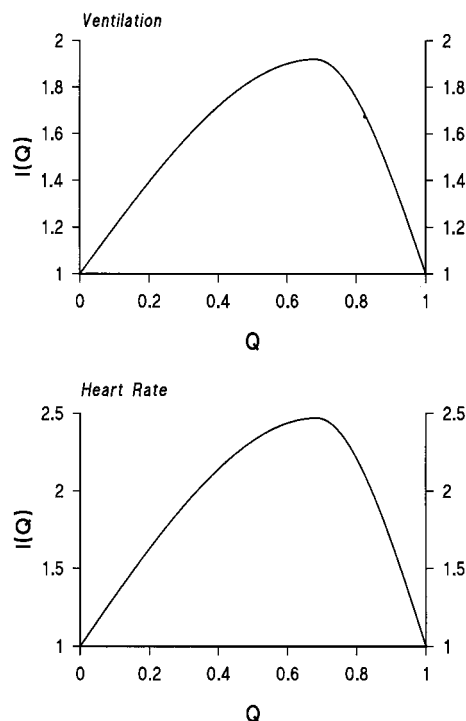
Fig. 5. The relations between Q (*i.e.*, the alfentanil–sevoflurane concentration ratio) and I(Q) (*i.e.*, the interaction) for ventilation (*top*) and heart rate (*bottom*). For both effects, synergistic interactions were observed over the range of concentration ratios from 0 to 1, with maximum synergistic interactions (I$_{max}$ in table 2) occurring at Q values of approximately 0.7 (Q$_{max}$ in table 2).
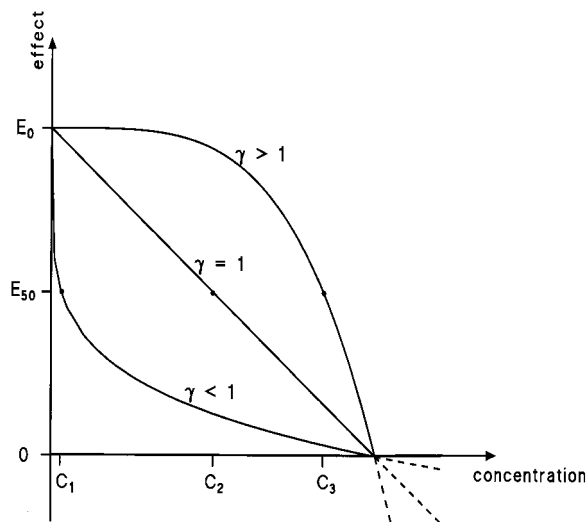

Fig. 6. Three examples of the concentration–effect relation predicted by the pharmacodynamic model f(x) = E$_0$(1 − x$^\gamma$), where x$^\gamma$ = U$^\gamma$/2 and U = C/C$_{50}$, obtained at three fixed values of γ (0.2, 1, and 4). When γ = 1, the model becomes linear. At all three γ values, negative effects are possible at drug concentrations x > C$_{50}$ · 2$^{1/\gamma}$. Note that the values for C$_{50}$ and γ were chosen in such a way that the zero crossing for all three examples occurred at the same value of C. As a consequence, the values of C causing 50% of the effect (*i.e.*, C$_{50}$) occur at different values of C (C$_1$ through C$_3$ are the C$_{50}$ values for the three different curves). Different values for C$_{50}$ and γ would result in the zero crossing at different values of C. E$_0$ = baseline effect; E$_{50}$ = 50% depression of effect.

negative responses were observed for $\Delta V_T/\Delta Sp_{O_2}$, $\Delta RR/\Delta Sp_{O_2}$, and $\Delta HR/\Delta Sp_{O_2}$ at high alfentanil concentrations.

3. Within a limited dose range (such as the range studied by us), some respiratory dose-response relations seem linear or almost linear. For example, halothane and isoflurane, over the dose range from 0 to 0.2 MAC, cause a linear decrease of the hypoxic ventilatory response (at 0.2 MAC, $\Delta \dot{V}_i/\Delta Sp_{O_2}$ is approximately 20% of control).[3,20] In our model, a linear function is obtained when γ = 1 (fig. 6). Interestingly, for all parameters our model, fits yielded values of γ not significantly different from 1. This indicates that at least within the dose range we tested, the data are well-described by a linear relation between drug (sevoflurane or alfentanil) and effect. This is also true for combinations of both agents, but only at fixed concentration ratios (Q). Incorporation of higher doses might have yielded values of γ significantly different from 1. This may be especially true for the BIS–sevoflurane relation.[12]

Response Surface Modeling. The response surface modeling method, as recently reported by Minto *et al.*,[10]

is based on two ideas. First, there is the notion that the combination of two drugs should be regarded as a new drug with its own properties,[21] with the concentration–effect relation E = f(CA/C$_{50,A}$ + CS/C$_{50,S}$; ψ), where the parameter vector ψ (in our model I(Q)) controls the properties of the interaction and specifically how it deviates from pure additivity. Second, ψ is assumed to depend only on the ratio of the concentrations of the two administered drugs.[22] These two ideas are crucial because they allow for a greatly reduced number of parameters necessary to describe a surface and thus make them estimable from a study of reasonable size.[10] A proper choice of ψ and f may further reduce the number of parameters while describing the concentration–effect relation in the range measured. We made two modifications to the model specified by Minto *et al.*[10] First, interaction was taken into account by the function I(Q), for which we chose a spline with two interpretable parameters (see Appendix 1 for details). Second, for f, we chose equation 1.

Although visual inspection of the residuals did not show remaining structure, other possibilities of modeling the concentration–effect relation and the nature of the interaction could be explored, for example, by using the function:[23]**

$$f(x) = \frac{\alpha}{(1 + \delta \cdot x^\gamma)^{1/\delta}} \quad (8)$$

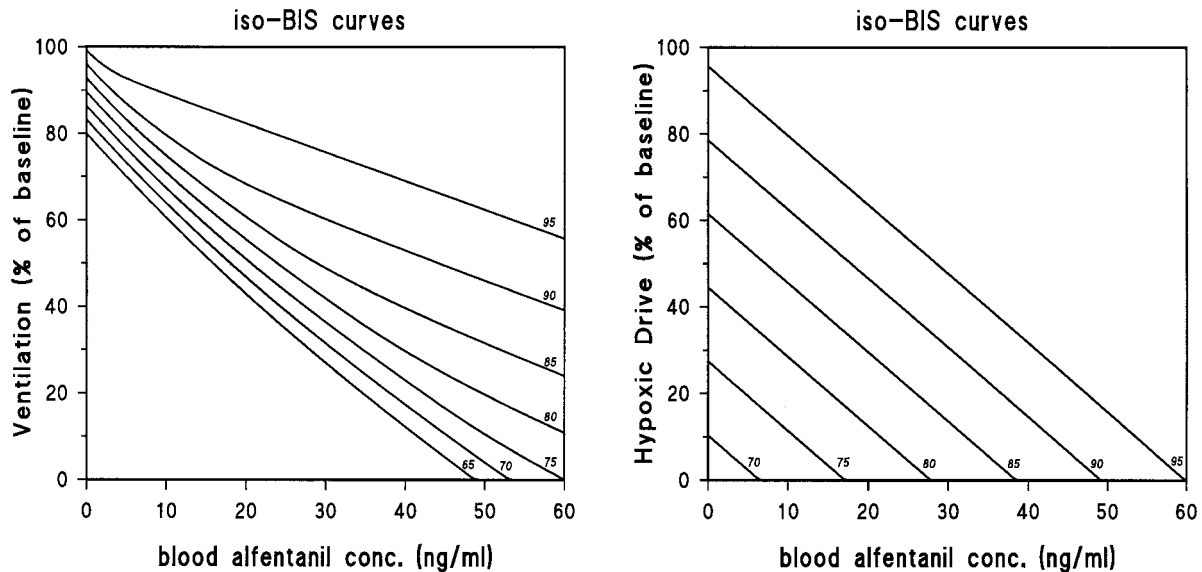** When δ is fixed to −1, equation 8 reduces to equation 1.

Fig. 7. The influence of alfentanil on ventilation (*left*; values are % of control) and hypoxic drive (*right*; values are % of control) at constant Bispectral Index (BIS) values (so-called iso-BIS curves). The BIS values are in italic and range from 95 to 65). The BIS values were fixed by inhalation of constant concentration of sevoflurane. The hypoxic drive is more vulnerable than $\dot{V}_i$ for the effects of alfentanil at all tested BIS values. conc. = concentration.

Now, a spectrum of linear, sigmoidal, and asymmetric sigmoidal concentration–effect relations is possible with varying values of γ and δ. However, because in our analysis γ never significantly differed from 1, inclusion of additional nonlinear parameters, such as in equation 8, does not seem necessary. Finally, when synergistic interactions were detected (*i.e.*, for $\dot{V}_i$ and HR), the SDs of the estimated parameters did not warrant a more complex form of I(Q).

$\dot{V}_i$ and HR versus $\Delta\dot{V}_i/\Delta Spo_2$ and $\Delta HR/\Delta Spo_2$

We observed synergistic alfentanil–sevoflurane interactions on $\dot{V}_i$ and HR. This indicates that the effect of the drug combination was greater than expected from the dose-response curves of sevoflurane alone and alfentanil [1]alone. Our analysis shows that for both variables, maximum synergy occurred at Q values of approximately 0.7. This indicates that, taking into account their respective C_{50} values, concentrations that give maximal synergy after reduction of $\dot{V}_i$ are at fractions (or multiples) of 26.7 ng/ml for alfentanil and 0.24 ET% for sevoflurane (maximum synergy causing 25% reduction of effect occurs at 13.4 ng/ml alfentanil + 0.12 ET% sevoflurane, maximum synergy causing 50% reduction occurs at 26.7 ng/ml alfentanil + 0.24 ET% sevoflurane, and maximum synergy causing 100% reduction occurs at 53.4 ng/ml alfentanil + 0.48 ET% sevoflurane).†† For HR, these concentrations are fractions of 86.6 ng/ml for alfentanil and 0.48 ET% for sevoflurane (= C_{50} values). Because we

explored only a relatively small part of the response surface for $\dot{V}_i$ and HR, C_{50} and C_{100} values are extrapolations. As indicated, nonlinearities of the ventilatory controller may cause apnea at concentrations higher than those explored in our protocol but lower than those estimated from our analysis. Moreover, we may have underestimated the magnitude of synergy in our study. Therefore, our results apply to the portion of the response surface analyzed, and extrapolation should be performed with caution (especially for those surfaces that are explored only marginally, *e.g.*, HR). The mechanism of the observed synergistic interactions remain elusive. Further studies (*e.g.*, identifying shared central effect sites for opioid- and anesthetic-induced respiratory depression) are needed to understand the synergistic effects of alfentanil and sevoflurane on ventilation and HR.

We observed additive alfentanil–sevoflurane interactions on $\Delta\dot{V}_i/\Delta Spo_2$ and $\Delta HR/\Delta Spo_2$. This indicates that the effect of the sevoflurane–alfentanil combination is expected from the concentration–response curve of the individual agents. The absence of synergy may be related to the different pathways through which sevoflurane and alfentanil depress the hypoxic response (inhalational anesthetics depress hypoxic response at sites within the peripheral chemoreflex loop,[2,20] and opioids depress hypoxic response through effects at the brainstem[18]). Another possibility is that because of the great sensitivity of the hypoxic response to both agents and consequently the early loss of the hypoxic response (*i.e.*, $\Delta\dot{V}_i/\Delta Spo_2 = 0$ occurring at 60 ng/ml alfentanil and 0.5 ET% sevoflurane), we are unable to unearth any synergy from the data.

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†† These values are obtained by simultaneously solving equations 6 and 7, with $E/E_0 = 0.75$ for 25% reduction, $E/E_0 = 0.5$ for 50% reduction, and $E/E_0 = 0$ for 100% reduction.

The observation that the hypoxic drive, relative to resting $\dot{V}_i$, is more sensitive to the effects of an opioid and an inhalational anesthetic suggests that the hypoxic test is the more sensitive tool to assess the effects of anesthetics and opioids on ventilatory control.

One of the many determinants of HR at rest and during hypoxia is stimulation and depression of lung receptors by increases and decreases in $\dot{V}_i$ (*i.e.*, HR effects are secondary to $\dot{V}_i$ effects).[4] This may explain the agreement in the nature of alfentanil–sevoflurane interactions for $\dot{V}_i$ and HR, and $\Delta\dot{V}_i/\Delta Sp_{O_2}$ and ΔSp_{O_2}.

Bispectral Index and Respiration

In contrast to sevoflurane, alfentanil, in the absence and presence of sevoflurane, had no effect on BIS. This indicates that the algorithm for calculating the BIS is not sensitive to the changes in arousal level from opioids and the combination of opioids and anesthetics (at least within the dose ranges we evaluated). Because we did not obtain other measures of sedation during the study (such as the subjective observers' assessment of alertness and sedation score) we remained uninformed about the level of arousal during the alfentanil–sevoflurane studies. However, because clinicians and researchers use BIS monitoring, we constructed iso-BIS curves (equivalent to iso-effect curves, fig. 7). We now are informed about the steady-state relation between alfentanil and $\dot{V}_i$ and $\Delta\dot{V}_i/\Delta Sp_{O_2}$ at varying BIS levels. Further studies are needed to examine whether these steady-state relations are independent of sevoflurane and also apply to other agents that affect the BIS (such as propofol, isoflurane, dexmedetomidine, midazolam) or whether separate BIS–opioid–$\dot{V}_i$ relations exist for each anesthetic–hypnotic.

Study Limitations

Some methodologic issues deserve further comment. We used an isohypercapnic design (PET_{CO_2} fixed to ~48 mmHg). This enables the comparison of the effect of various drug concentrations on $\dot{V}_i$ without the confounding influence of variations in PET_{CO_2}. However, because every drug effect on $\dot{V}_i$ is conditional on a certain PET_{CO_2} value, other results might be seen at different carbon dioxide concentrations. Furthermore, because we performed a steady-state study (drug concentrations, PET_{O_2}, and PET_{CO_2} were clamped during hypoxic testing), the time course of drug-induced variations in blood gases (such as those that may occur during bolus opioid infusions) and their translation into $\dot{V}_i$ and oxygen delivery were not modeled. Further studies are needed to examine the blood gas and $\dot{V}_i$ dynamics caused by the administration of opioids and anesthetics occurring in the clinical setting.

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Appendix 1

For the function I(Q), we use a spline with a piece $g_1(x)$ between knots at $x = 0$ and $x = Q_{max}$ and a piece $g_2(x)$ between knots $x = Q_{max}$ and $x = 1$, constrained by the following eight conditions:

$$g_1(0) = g_2(1) = 1 \tag{9}$$

$$g_1(Q_{max}) = g_2(Q_{max}) = I_{max} \tag{10}$$

$$dg_1(x)/dx|_{x=Q_{max}} = dg_2(x)/dx|_{x=Q_{max}} = 0 \tag{11}$$

$$d^2g_1(x)/dx^2|_{x=0} = d^2g_2(x)/dx^2|_{x=1} = 0 \qquad (12)$$

The first four constraints (equations 9 and 10) deal with the values of I(Q) at the three knots, constraints five and six (equation 11) make the second knot a maximum (or minimum), and constraints seven and eight (equation 12) are natural boundary conditions at the first and last knot and assure the absence of values outside $(1, I_{max})$. Because we specify eight conditions, we can use a cubic spline so that each piece is given by a third-order polynomial:

$$g(x) = a_0 + a_1x + a_2x^2 + a_3x^3 \qquad (13)$$

The parameters ai are such that the constraints are satisfied. Note that they need not be interpreted but are merely functions of I_{max} and Q_{max}. For $g_1(x)$, we have:

$$a_0 = 1$$

$$a_1 = -3(1 - I_{max})/(2Q_{max})$$

$$a_2 = 0$$

$$a_3 = (1 - I_{max})/(2Q_{max})/Q_{max}^2 \qquad (14)$$

For $g_2(1 - x)$, the parameters ai are obtained by substituting $(1 - Q_{max})$ for Q_{max}.