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Technique for Quantifying the Duration of Intravenous Anesthetic Effect

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Background: **Several recent studies have analyzed the relationship between pharmacokinetic parameters and the rate of decrease in concentration after discontinuation of a continuous drug infusion. Although these studies have clarified our understanding of those aspects of pharmacokinetics most relevant to anesthesia practice, they do not directly address the issue of the duration of drug effect, which will be a function of both pharmacokinetic and pharmacodynamic variables. This paper extends these concepts by presenting a method to unify pharmacokinetics and pharmacodynamics in a measure of duration of drug effect that is applicable when the drug effect is assessed in a binary, response/no response fashion.**

Methods: **The parameter proposed to quantify duration of drug effect is the area under the curve expressing probability of drug effect as a function of time after the agent is discontinued. This parameter is denoted the mean effect time. It is calculated using the logistic (or Hill) equation to relate the probability of drug effect to drug concentration, which in turn can be calculated as a function of time by pharmacokinetic simulation. Mean effect times were calculated for sufentanil, alfentanil, propofol, and midazolam using the logistic equation describing recovery and by assuming that drug blood concentrations during maintenance of anesthesia were sufficient to reduce the probability of responsiveness to surgical stimulation to 10% (C_{90}). Published pharmacokinetic and pharmacodynamic parameters were used for these calculations. These results were compared to the relevant decrement times (as defined in this paper, the time required for the concentration to decrease from C_{90} to the concentration at which 50% of patients are responsive and/or able to maintain adequate ventilation, denoted C_{50}). It was assumed that C_{90} and C_{50} were independent variables.**

Results: **Mean effect times for midazolam and propofol, for which the steepness parameter δ for recovery (responsiveness and adequate ventilation) is less than 4, are significantly greater than the decrement time. Mean effect times for sufentanil and alfentanil (δ = 6 and 10, respectively) are close to decrement times. The discrepancy between mean effect time and decrement time becomes greater as the duration of drug administration increases. The incorporation of pharmacokinetic variability into the calculations had little effect on the results.**

Conclusions: **Context-sensitive half-times or other decrement times have been shown to be the most useful measures of the kinetics of drug concentrations. Mean effect time may be a useful concept for understanding the recovery from drug effects. (Key words: Anesthetics, intravenous: alfentanil; fentanyl; midazolam; propofol; sufentanil. Computer simulation. Pharmacodynamics. Pharmacokinetics.)**

THE duration of drug effect is a function of both pharmacokinetic and pharmacodynamic properties. The influence of pharmacokinetic variables has been significantly clarified by papers by Shafer and Varvel[1] and Hughes *et al.*[2] These authors have demonstrated, using computer simulation, that the rate of decrease of either the effect site (Shafer and Varvel) or plasma (Hughes *et al.*) concentration after continuous intravenous infusion cannot be simply related to any one pharmacokinetic parameter and is highly dependent on the duration of infusion. Hughes *et al.* introduced the term context-sensitive half-time to indicate the time necessary for a 50% decrease in plasma drug concentration. This parameter is a function of the "context", *i.e.*, the duration of drug administration before its discontinuation. This concept can be generalized to "decrement times," whereby, for example, the 80% decrement time is the time needed for the plasma or effect site concentration to decrease by 80%.[3] The duration of drug effect can be identified with the appropriate decrement time if the drug effect can be measured by a continuous variable for which there is a well defined value of recovery. An example is recovery from muscle relaxants, as was demonstrated by Kern.[4] However, in anesthesiology, we often deal with binary data, *i.e.*, the patient is responsive or not, ventilation is adequate or not, and

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so on. At any specific drug concentration, there is a probability of drug effect, and it usually is assumed that this probability can be described within the framework of the logistic distribution as $P = C^{\delta}/(C^{\delta} + C_{50}{}^{\delta})$, where P is the probability of drug effect, C is the drug concentration, C_{50} is the concentration at which the probability of drug effect is 50%, and δ is a parameter determining the steepness of the relationship. If δ is very large, the probability of drug effect is nearly 1 when C is larger than C_{50} (even if only slightly larger) and nearly 0 when C is less than C_{50}. In this case, the duration of drug effect will be the decrement time between the drug concentration maintained during anesthesia and C_{50}, because the transition between effect and no effect is very sharp. However, for smaller values of δ, this may not be true, because there will still be a finite probability of drug effect even when the concentration is less than C_{50}. In this paper, I extend the context-sensitive half-time/decrement time concept and propose a parameter, mean effect time (MET), which can be used to quantify the duration of drug effect when dealing with binary (response or no response) data and consider the implications of this approach for several commonly used intravenous anesthetic agents.

Methods

Mean effect time (MET) is defined as

$$\text{MET} = \int_0^{\infty} P(t) \cdot dt$$

where $P(t)$ is the probability of drug effect at time t. The mathematical rationale for this parameter is as follows. The probability of drug effect, P, is a function of drug concentration, C, and because C is time-dependent, P may be viewed as a function of time. During the time span from t to t + dt, the probability of drug effect is $P(t)$. The sum of drug effect for all time spans is then given by integrating $P(t)$ over t. Note, because $P(t)$ (as a probability) is unitless, the unit of MET is time.

An intuitive understanding of this parameter is illustrated in figure 1 for the hypothetical recovery from a continuous infusion of fentanyl that has maintained a plasma concentration of 10 ng/ml for 60 min. Figure 1 presents the plasma concentration of fentanyl as a function of time after the infusion is discontinued, as well as the probability of drug effect predicted for these plasma concentrations using the logistic equation with

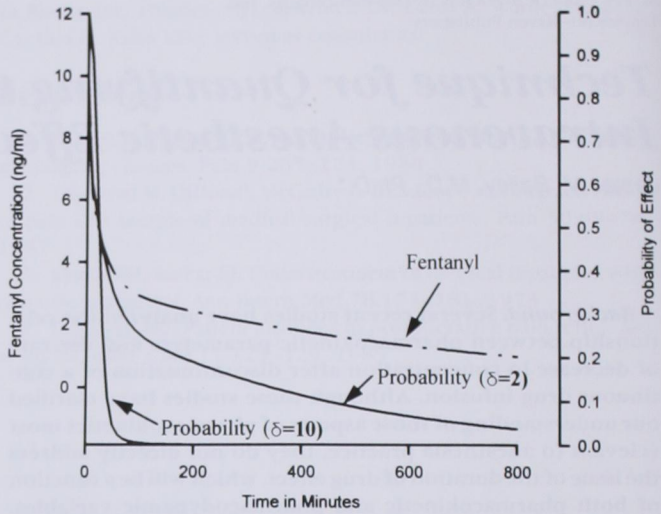

Fig. 1. The plasma concentration of fentanyl, as a function of time, after an infusion maintaining a concentration of 10 ng/ml for 60 min is discontinued. Also shown are the corresponding probabilities of drug effect calculated from the logistic equation with C_{50} = 5 ng/ml and δ = 2 or δ = 10.

C_{50} = 5 and δ = 2 or 10. It is seen that the area under the probability of effect curve when δ = 10 is nearly rectangular. Because the probability of effect is nearly 1 when C is greater than C_{50} and nearly 0 when C is less than C_{50}, the area under the curve, which is MET by definition, is 25 min, a value nearly equal to the time needed for the plasma concentration to decrease from 10 ng/ml (the concentration during anesthesia maintenance) to 5 ng/ml (C_{50}), *i.e.*, the context-sensitive half-time (23 min). In contrast to this case for fentanyl, where δ is relatively large, note the probability of drug effect as a function of time (fig. 1) when δ = 2. In this case, the curve is not nearly as rectangular. The area under the curve (MET) is 130 min, whereas the decrement time from 10 to 5 ng/ml is only 23 min. In this case, MET is considerably larger than the context-sensitive half-time because there is still a significant probability of drug effect when the concentration is less than C_{50}.

In the above example, MET was calculated assuming the fentanyl concentration during maintenance of anesthesia was 10 ng/ml. This was an arbitrary assumption. Clearly, the value of MET will depend on the drug concentration during maintenance. For the simulations in this paper, drug concentrations during maintenance were calculated by assuming that the probability of response to surgical stimulation was only 10% (this concentration will be denoted C_{90}). This is

comparable to the clinical practice of maintaining patients with 1.3 MAC of an inhaled agent, rather than 1.0 MAC, to avoid the possibility of movement in 50% of patients.[5] C_{90} was calculated by using the drug concentration-response relationship for maintenance of surgical anesthesia, where available (this, in general, may be different from the drug concentration-response curve describing recovery of responsiveness and adequate spontaneous ventilation). Pharmacodynamic parameters were taken from Wessen *et al.*[6] for propofol (using their data for propofol supplemented with alfentanil), from Jacobs *et al.*[7] for midazolam, from Sear and Gavaghan for sufentanil,† and from Ausems *et al.*[8] for alfentanil (calculating C_{90} from their data for upper-abdominal surgery). Calculations were performed with an IBM-compatible personal computer using an Excel 5.0 spreadsheet. Plasma concentrations after the discontinuation of bolus-elimination transfer-type infusions were simulated by convoluting the infusion rate with the unit disposition function, as described by Hughes *et al.*[2] The term bolus-elimination transfer infusion refers to a dosing regimen comprised of a bolus followed immediately by an infusion(s) with exponentially declining rate(s) and is designed to achieve and maintain a constant plasma concentration.[9] The unit disposition functions, which describe the concentration as a function of time after a unit bolus dose, were assumed to have the form $udf(t) = A_1\exp(-k_1{}^*t) + A_2\exp(-k_2{}^*t) + A_3\exp(-k_3{}^*t)$, and the pharmacokinetic parameters used in these functions were taken from Hughes *et al.* for fentanyl, sufentanil, alfentanil, midazolam, and propofol.[2] The logistic equation $P = C^\delta/(C^\delta + C_{50}{}^\delta)$ was used to calculate the probability of drug effect (P) at any concentration C, and MET was calculated by integrating P over time using the Euler technique with a step size of 15 s for 1,000 min after discontinuing the bolus-elimination transfer-type infusion and directly integrating the terminal term tail of the curve by assuming the concentration was well approximated by the terminal exponential term and that P could be approximated as $(C/C_{50})^\delta$ when C was much less than C_{50}.

The simulations performed as described above assumed "average" pharmacokinetic parameters and do not take into account pharmacokinetic variability. It is shown in the appendix that pharmacokinetic variability can be approximately accounted for by assuming that the probability of drug effect is better described by an extension of the logistic equation;

$$P = \langle C\rangle^\delta/(\langle C\rangle^\delta + C_{50}{}^\delta) + K(var_c)$$

where $\langle C\rangle$ is the average concentration (as a function of time); K is a complicated function of $\langle C\rangle$, C_{50}, and δ (derived in the appendix); and var_C is the variance of C in the population at any given time. Simulations were performed by assuming that var_C could be described by a simple constant coefficient of variation model,[10] where $var_C = \alpha^2\langle C\rangle^2$ and α^2 was assumed to be 0.2.

Simulations also were performed in which MET was calculated by assuming that the probability of drug effect is related to the effect-site concentration, using the logistic equation (but not taking into account pharmacokinetic variability). The effect-site concentration was calculated as described by Shafer and Varvel,[1] with values of k_{e0} (the blood effect-site equilibration rate constant) for sufentanil and alfentanil taken from this reference and for midazolam from Buhrer *et al.*[11] A value of 0.243 was used for k_{e0} of propofol.‡

Results

Figure 2 presents a comparison of MET and decrement time (defined as the time required for the plasma concentration to decrease from C_{90} for surgical anesthesia to C_{50} for recovery) for sufentanil, alfentanil, propofol, and midazolam. There is little difference between decrement time and MET for alfentanil and sufentanil for which δ (for recovery) is 9.2 and 5.99, respectively. In contrast, for propofol and midazolam (δ = 3.28 and 3.054, respectively), there are significant differences between decrement time and MET. The magnitudes of these differences tend to increase with increasing duration of administration, although this difference does reach a plateau for midazolam.

Figure 3 compares MET calculated from plasma drug concentration and MET calculated by assuming that the probability of drug response should be related to the effect-site concentration. It can be seen that, for the drugs under consideration, the differences between MET_{plasma} and $MET_{effect\text{-}site}$ are minor.

Figure 4 compares MET calculated by assuming no pharmacokinetic variability with results using a mod-

† Sear JW, Gavaghan D: Dynamic-kinetic relationships for sufentanil during nitrous oxide-oxygen anaesthesia (abstract). Br J Anaesth 65: 290P–291P, 1990.

‡ Shafer SL: Private communication.

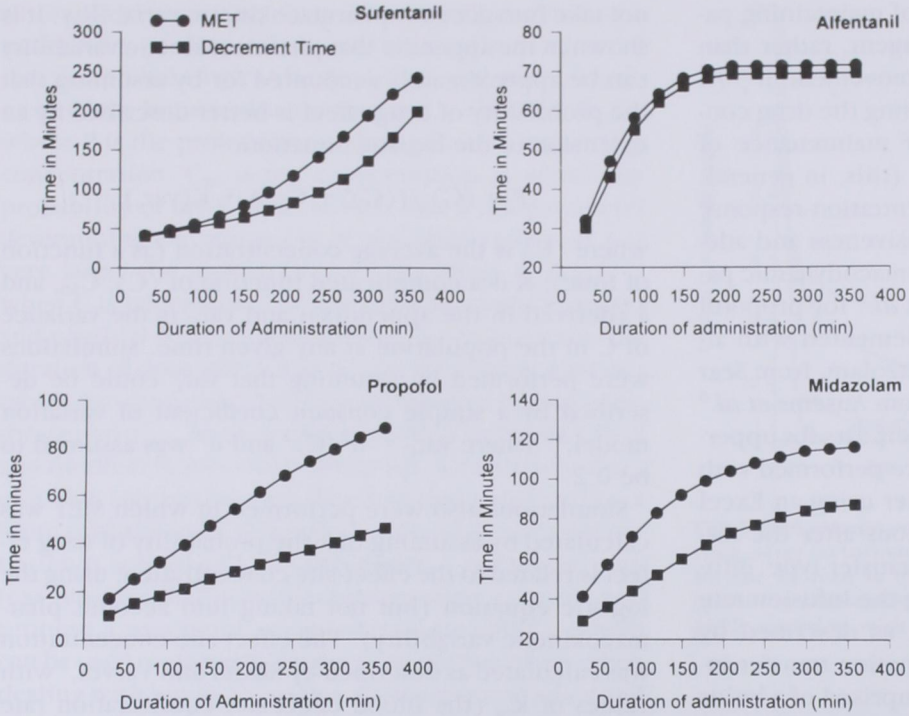

Fig. 2. Comparisons of mean effect time (solid circles) and decrement time (solid squares) as a function of length of administration for sufentanil, alfentanil, propofol, and midazolam. Note differences in the range of the y-axis between panels.

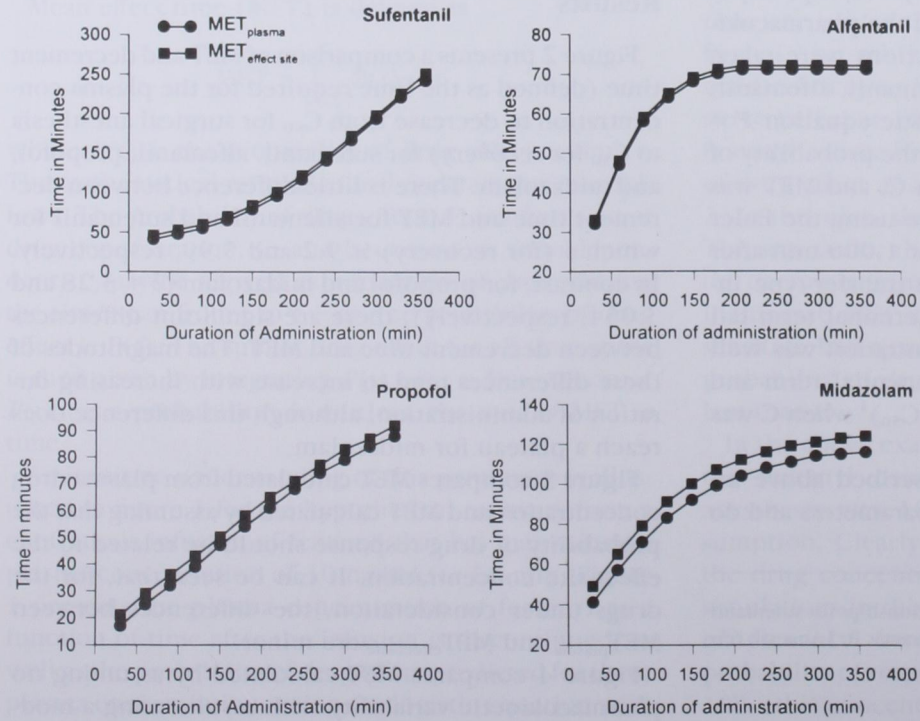

Fig. 3. Comparisons of MET_{plasma} (solid circles) and $MET_{effect\ site}$ (solid squares) as a function of length of administration for sufentanil, alfentanil, propofol, and midazolam. Note differences in the range of the y-axis between panels.

ified logistic equation that incorporates pharmacokinetic variability in an approximate manner. There are only minor differences between the two methods (less than 15%). It also can be noted that accounting for pharmacokinetic variability may either shorten or lengthen MET, depending on the drug and duration of administration.

Figure 5 presents MET for the hypothetical case of administration of propofol, with titration to response, to an individual for whom $\delta = 5$.

Discussion

When a well defined endpoint (*e.g.*, train-of-four recovery) can be identified, the duration of drug effect can be simply calculated as the decrement time to the plasma or effect-site concentration that is associated with that endpoint. However, it is common to describe drug effects as binary, yes or no, variables. In this case, the concentration-effect relationship is defined in terms of probabilities, and it may be difficult to identify an endpoint defining the termination of drug effect. As an example of this difficulty, consider the suggestion of using the decrement time needed to reach the concentration associated with a 5% or 10% probability of drug effect (the 90% or 95% decrement time) as a measure of drug duration. This suggestion seems plausible because, at these concentrations, the patient has only a 5% or 10% probability of drug effect. If the effect-concentration relationship is sharply defined (δ is large), as illustrated by figure 1, this method of defining drug effect duration is meaningful. However, if the concentration-effect relationship is not steep (δ is small), as illustrated in figure 1, this parameter is ambiguous, because at concentrations greater than C_5 or C_{10}, there may be a substantial cumulative chance that there will be no drug effect. Mean effect time is a method of quantifying the duration of drug effect in this situation.

In this paper, decrement time denotes the time required for the drug concentration to decrease from C_{90}, the concentration used for maintenance of anesthesia in the presence of surgical stimulation, to the C_{50} for recovery (*e.g.*, adequate spontaneous ventilation, responsiveness). As such, it is the median recovery time, *i.e.*, half the patients will recover in less than the decrement time and half will require more time. In contrast, MET is a mean (''average'') recovery time. It is based on a ''frequentist'' interpretation of probability that assumes that an x% probability of an event implies that x% of patients will have the effect and (100 − x)% will not. One might expect the effects of patients re-

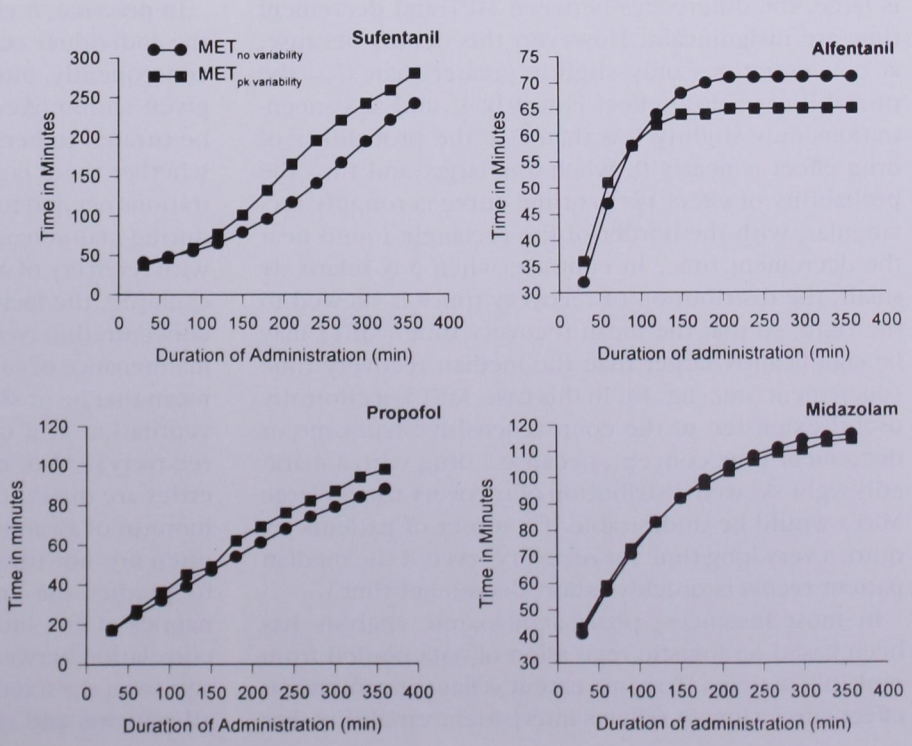

Fig. 4. Comparisons of mean effect time (MET) calculated with incorporation of pharmacokinetic variability as described in the appendix (solid squares) and MET calculated without consideration of pharmacokinetic variability (solid circles) as a function of length of administration for sufentanil, alfentanil, propofol, and midazolam. Note differences in the range of the y-axis between panels.

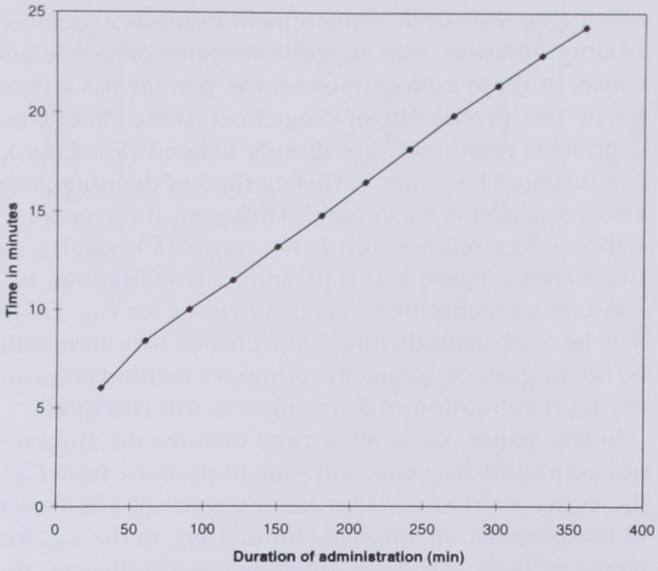

Fig. 5. Mean effect time as a function of the duration of administration of propofol for the hypothetical case of an individual patient for whom $\delta = 5$. It is assumed that the same logistic equation describes the probability of drug effect during both surgical stimulation and recovery.

quiring less than the decrement time for recovery and of those requiring more than the decrement time for recovery to approximately cancel, so that decrement time and MET would be nearly equal. Indeed, when δ is large, the differences between MET and decrement time are insignificant. However, this occurs because, at concentrations only slightly greater than C_{50}, the probability of drug effect is nearly 1, and at concentrations only slightly less than C_{50}, the probability of drug effect is nearly 0, when δ is large, and thus the probability of effect *versus* time curve is roughly rectangular, with the border of the rectangle found near the decrement time. In contrast, when δ is relatively small, the distribution of recovery times is skewed to the right, so that the mean recovery time (MET) may be significantly larger than the median recovery time (decrement time; fig. 1). In this case, MET is a clinically useful extension of the context-sensitive half-time or decrement time concept, because a drug with a markedly right-skewed distribution of recovery times (large MET) would be undesirable if a subset of patients require a very long time for recovery, even if the median patient recovers quickly (short decrement time).

In most instances, pharmacodynamic analysis has been based on logistic regression of data pooled from multiple patients. To some extent, a flat concentration-effect curve (low δ) reflects interpatient variability. For any individual patient, the concentration-effect relationship may be steep. If so and if the clinician has titrated the drug dose to the specific concentration-effect relationship of the individual patient, the mean effect time concept is not uniquely significant. This is an important clinical point, graphically illustrated in figure 5, which presents MET as a function of the duration of administration of propofol, with titration to response, for the hypothetical case of an individual patient for whom $\delta = 5$. Comparison to figure 2 shows that recovery is much faster in this situation. This reflects both the steep concentration-effect curved during recovery and the small decrement between C_{90} and C_{50} when δ is large. It is clear that, if individual concentration-effect curves are steep and if one titrates to effect, very large savings in recovery time may be realized.

The extent to which individual concentration-effect relationships are steep ($\delta > 5$) is unclear. In general, we would expect variation in the drug concentrations associated with specific events during recovery if the drug were administered to the same patient on multiple occasions. In other words, the concentration-effect relationship for an individual patient is probabilistic. Although these individual concentration-effect relationships are often steep for alfentanil,[8] a recent study has shown that, in some patients, δ may be as low as 2.1.[12] There are no data available for other drugs.

In practice, it can be difficult to fully titrate drugs to the individual concentration-effect relationship, and, consequently, intravenous anesthetic agents usually are given within fixed dose ranges. Although opioids may be titrated to hemodynamic response, it is not known whether there is any correlation between the concentrations needed to prevent tachycardia or hypertension during maintenance and the concentrations associated with recovery of adequate spontaneous ventilation. For example, the fact that an individual requires a plasma concentration twice that of the average patient during maintenance of surgical anesthesia does not of necessity mean that he or she will resume adequate spontaneous ventilation at a concentration equal to $2 \times C_{50}$ (for recovery). Also, drugs given for their hypnotic properties are difficult to titrate because we have no direct monitor of awareness. Consequently, anesthetic agents often are not titrated sufficiently during maintenance to predict the specific recovery-phase pharmacodynamics of any individual patient. There may be little correlation between the plasma concentrations that result from the fixed dose range used for maintenance in all patients and the concentration at which the indi-

vidual patient emerges. Hence, the average recovery time for the population may be predicted best by a mean effect time calculated from data pooled from multiple patients.

MET is a function of C_{90}, C_{50}, δ, and the pharmacokinetic parameters. Strictly, it should be calculated as an average of this function over the distribution of individual values of C_{90}, C_{50}, δ, and pharmacokinetic parameters in the population. This is currently impossible because these distributions are unknown. In this study, MET has been evaluated using the common statistical approximation of replacing an average function of parameters by the function of the average parameters. The accuracy of this approximation cannot be evaluated without further knowledge of the distributions of individual values of C_{90}, C_{50}, and δ.

To calculate the mean effect time, the concentration-effect relationship must be known. This is the major limitation to use of this parameter, because these data are scarce. However, based on the limited data available, some tentative observations can be made. Wessen *et al.* presented a pharmacodynamic study of emergence in patients who received propofol and either an infusion of alfentanil or a lumbar epidural injection for maintenance of anesthesia.[6] The calculations of MET for propofol reported in this paper are based on their data for the propofol-alfentanil group. However, Wessen *et al.* report a steeper concentration-effect relationship for the lumbar epidural group than the alfentanil group with $\delta = 5.66$ and 3.28 (in the logistic equation) at extubation, respectively. Referring to figure 2, we see that, for $\delta = 3.28$, there is a significant difference between MET and the decrement time, particularly after longer use. In contrast, for $\delta = 5.66$, MET is indistinguishable from the decrement time. Wessen *et al.* report a statistically significant prolongation of recovery in the patients receiving alfentanil, which they attribute to a left shift of the concentration-effect curve. However, there was less than a 20% difference in C_{50} between these two groups. It is plausible that the prolongation of recovery may be due to the much larger difference in δ between the two groups, as reflected in the increased MET.

Jacobs *et al.* published a pharmacodynamic study of midazolam and report that $\delta = 3.054$ with logistic equation analysis of their responsiveness *versus* concentration data.[7] As seen in figure 2, this implies a significant difference between MET and decrement time.

In contrast to propofol and midazolam, there are only insignificant differences between MET and decrement time for alfentanil and sufentanil. For both of these drugs, δ for recovery is relatively high. However, it should be noted that the decrement time for sufentanil is longer than that for alfentanil, a reversal of the relation of their context-sensitive half-times. This is a reflection of the flat concentration-effect relationship for maintenance of surgical anesthesia with sufentanil reported by Sear and Gavaghan† and used to calculate C_{90} in this paper. Because the concentration-effect relationship is flat, the drug concentration during maintenance must be relatively large to reduce the probability of response to noxious stimuli to 10%. C_{90} is higher in relation to C_{50} for sufentanil than for alfentanil, which has a steep concentration-effect relationship during maintenance of anesthesia. In other words, based on the available pharmacodynamic data, recovery from sufentanil will require a larger decrement (73%) than from alfentanil (56%). This conclusion must be viewed as tentative, because the data on sufentanil pharmacodynamics are relatively sparse and electroencephalographic investigations do not suggest significant differences between the concentration-effect relationships of sufentanil and alfentanil. However, this tentative conclusion underscores the fact that understanding the duration of drug effect requires pharmacodynamic as well as pharmacokinetic data.

Calculation of MET for fentanyl was not done because a complete analysis of the pharmacodynamics of recovery from fentanyl was not found in the literature. Although values of C_{50} have been reported, the analyses do not include a description of the steepness of the concentration-effect relationship, *i.e.*, δ has not reported for recovery from fentanyl. However, the simulations shown in figure 1 suggest there will be significant differences between MET and decrement time for fentanyl if δ is low.

MET did not change significantly when calculated by relating the probability of drug response to the effect-site concentration. The differences were comparable to the respective blood effect-site equilibration half-times. However, it should be emphasized that this study did not consider drugs that slowly equilibrate with their effect sites, such as morphine. Furthermore, the study did not consider drugs that have active metabolites.

The effect of pharmacokinetic variability was incorporated into the calculations using a well known mathematical technique, the truncated Taylor's series. This leads to an expression for the probability of drug effect, which is a linear function of the variance of the drug concentration. To calculate MET, one must have a

mathematical representation of this variance. In this study, the concentration variance was calculated using the simple constant coefficient of variation model, $var_C = \sigma^2 C^2$.[10] With this model, the change in MET due to pharmacokinetic variability will be proportional to the constant δ^2. In pharmacokinetic studies using the constant coefficient of variation model, σ^2 is equal to the mean squared prediction error.[10] The simulations shown in figure 4 were performed with $\sigma^2 = 0.2$, which is somewhat larger than reported values.[10,13–15] This should tend to magnify the effects of pharmacokinetic variability. Despite this, figure 4 indicates that pharmacokinetic variability had little effect on MET. It should be noted that the MET concept provides a framework for evaluating the effect of pharmacokinetic variability on context-sensitive half-times, because in the limit of increasing δ, MET and context-sensitive half-time are equal. MET was evaluated for fentanyl, sufentanil, alfentanil, midazolam, and propofol for $\delta = 20$ and $C_{50} = (0.5)C_{90}$. In this case, MET is equal to context-sensitive half-time for all of these drugs. Adding pharmacokinetic variability with $\sigma^2 = 0.2$ had an insignificant effect on the value of MET (less than a 10% difference). It appears that, although pharmacodynamic variability tends to skew the distribution of recovery times to the right, pharmacokinetic variability has a symmetric effect on the distribution, such that the mean recovery time, MET, is not significantly altered. However, this conclusion must be viewed as tentative until the results of pharmacokinetic analysis that more accurately model pharmacokinetic variability[16,17] are incorporated into the calculation of MET.

The applicability of the MET concept to drugs whose effects can be measured in a continuous manner is unclear. If there is a level of effect that can be accepted as a clinical endpoint, the pertinent measure of drug duration is simply the time needed for the drug concentration to decline from maintenance levels to the level associated with this endpoint. In this case, the area under the effect *versus* time curve is not relevant, whereas the decrement time to this endpoint is the appropriate measure of duration of effect.

The results of this study demonstrate the importance of complete pharmacodynamic characterization of drugs. Although determination of single points on the concentration-effect curve, *i.e.*, C_{50}, is obviously important, a complete analysis of the drug requires an understanding of the shape of the curve, often embodied in the parameter δ. Unfortunately, these latter data sometimes are not evaluated or reported.

In summary, MET, as defined in this paper, is a parameter that extends the context-sensitive half-time/decrement time concept to use both pharmacokinetic and pharmacodynamic data to quantify the duration of drug effect when the effect is a binary, response/no response variable. When the concentration-effect relationship is steep, MET equals the relevant decrement time. However, there can be significant differences between MET and decrement times when there is a flatter concentration-effect relationship. Based on available data, MET for propofol (when used in conjunction with alfentanil) and midazolam is significantly greater than decrement time, and MET for sufentanil and alfentanil is nearly equal to the respective decrement time. The inclusion of pharmacokinetic variability into the calculation seems to have little effect on MET.

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Appendix

Calculation of MET using the logistic equation

$$P = C^{\delta}/(C^{\delta} + C_{50}{}^{\delta})$$

implicitly assumes that the drug concentration at any time is the same for all patients. To take pharmacokinetic variability into effect, note that the probability of drug effect, P, can be expressed in a Taylor's series expansion around the mean concentration in the population, $\langle C \rangle$ as follows:

$$P = P(\langle C \rangle) + (dP/dC)\Delta C + (1/2)(d^2P/dC^2)(\Delta C)^2 + \text{higher order terms} \quad (A1)$$

In this equation,

$$P(\langle C \rangle) = \langle C \rangle^{\delta}/(\langle C \rangle^{\delta} + C_{50}{}^{\delta});$$

$$\Delta C = C - \langle C \rangle;$$

and the derivatives dP/dC and d^2P/dC^2 are evaluated at $C = \langle C \rangle$. The probability of drug effect, averaged (in the sense of a mean) over the population and ignoring higher order terms, is then;

$$\langle P \rangle = P(\langle C \rangle) + (1/2)(d^2P/dC^2)\ var_c \quad (A2)$$

since

$$\langle \Delta C \rangle = \langle C - \langle C \rangle \rangle = 0$$

and

$$\langle (\Delta C)^2 \rangle = \langle (C - \langle C \rangle)^2 \rangle = var_c$$

by definition. Because MET is a mean parameter, pharmacokinetic variability is accounted for by calculating MET using equation A2. It is a straightforward exercise in differentiation to show that

$$(1/2)(d^2P/dC^2) = (1/2)\langle P \rangle^3[\delta^2(C_{50}{}^{\delta} - \langle C \rangle^{\delta}) - \delta(C_{50}{}^{\delta} + \langle C \rangle^{\delta})](C_{50}{}^{\delta})/(\langle C \rangle)^{2\delta+2}$$

This term is denoted K in the text.