

Intravenous Anesthesia: Concepts and practice

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The practice of intravenous anesthesia was popularized by the introduction of intravenous anesthetic drugs that meet the criteria for rapid onset/offset and, thus, ideal for administration by continuous infusion. In addition, there have been technological advances that will make intravenous drug delivery as convenient as the administration of volatile anesthetics. This review will provide the reader with a rational basis for the administration of intravenous anesthetics as we move into the new millennium. This will be based on our increasing understanding of the pharmacological processes that provide anesthesia. The goal of any anesthetic drug is to rapidly render the patient unconscious, maintain adequate anesthesia (irrespective of any surgical intervention), and then allow a rapid recovery to an awake state. To achieve this, the drug needs to provide a rapid onset/offset and have a delivery system that can readily alter the effective concentration of the drug. Over the past 30 years we have gained a greater appreciation of the pharmacokinetic principles that determine onset and offset of intravenous drugs.

Classically, intravenous anesthetics have been given either as a large single dose or by multiple smaller intermittent doses for induction and maintenance of anesthesia. Why should intravenous drugs be given by continuous infusion? When administering an intravenous anesthetic, the physician is aiming to obtain a predetermined therapeutic goal; i.e., anesthesia or analgesia. The response is dependent on achieving the concentration of the drug necessary to elicit this response at the site that the drug produces its effect. The concentration achieved is dependent on the dose administered and the disposition of the drug in the body. The process that describes this disposition (i.e., how the body handles the drug) is called the pharmacokinetics of the drug. Thus, the dose is based on the pharmacokinetics of the drug such that a therapeutic level of the agent is obtained. The ability to achieve and maintain a therapeutic concentration is best achieved utilizing a variable rate continuous infusion that accounts for the time varying changes in drug distribution and elimination. Clinical studies have demonstrated that intravenous anesthetics given by variable rate continuous infusions provide several advantages over intermittent bolus administration. These include: a) greater hemodynamic stability, b) fewer incidences of hemodynamic breakthrough and other signs of patient responsiveness, c) reduced need for supplemental anesthetics or vaso-active drugs, d) more rapid awakening, e) decreased incidence of requirements for naloxone or need for postoperative ventilatory support, f) decreased incidence of side effects, and g) lower total dose of drug given.¹⁻⁶ Pharmacokinetics relates dose to concentration; however, the therapeutic concentration varies according to the desired response and between individuals for the same response. The relationship between concentration and response is known as pharmacodynamics and describes what the drug does to the body. Therefore, to achieve the desired result (i.e., therapeutic effect) the clinician needs to appreciate the relationship between dose and concentration (pharmacokinetics) and concentration and effect (pharmacodynamics).

PHARMACOKINETIC PRINCIPLES

The importance of pharmacokinetics is its ability to make use of mathematical descriptions of the disposition process (i.e., how the drug is distributed, redistributed and eliminated by the body) to predict the resultant drug concentration within the plasma. From this, dosing schemes can be calculated to obtain a desired concentration.

Infusion Regimes

Classically, texts on designing infusion schemes for intravenous anesthetics recommend that the initial loading dose be calculated as

$$\text{Loading Dose} = Vd_1 \times C_p \quad \text{equation 1}$$

and maintenance infusion as

$$\text{Maintenance infusion} = C_p \times Cl \quad \text{equation 2}$$

where Vd_1 is the initial volume of distribution and C_p is the desired plasma drug concentration and Cl is systemic clearance. This classical description of obtaining a target concentration is flawed for several reasons.

The Biophase

For intravenous anesthetics the plasma is not the site of drug effect. Even if the precise concentration for the desired effect is known, calculating the loading dose according to equation 1 would obtain the target plasma drug concentration but the desired biophase concentration (and thus effect) would not be achieved. The site at which a drug produces its effect is termed the biophase. For a drug to reach the biophase it must distribute from the plasma/blood to the tissue of the biophase. Whilst this is occurring drug is also distributing into other tissues. Thus the loading dose necessary to produce the desired effect cannot be calculated using the initial volume of distribution (that includes primarily the blood volume), but should rather use the volume into which the drug has distributed when it has equilibrated with the biophase⁷. When a rapid infusion of drug is administered and its plasma concentration is simultaneously measured along with a measure of the drugs' effect (e.g., spectral edge of the electroencephalogram or minute ventilation), the rapid rise and fall in plasma concentration is not paralleled by the change in effect. There is hysteresis of this relationship. It is possible by continuously measuring the effect of the drug and its plasma concentration to relate plasma concentration to the effect it produces in the biophase⁸. From this, the volume of distribution that incorporates the effect compartment can be obtained. Also, by mathematical manipulation, the hysteresis loop can be collapsed so that there is a linear relationship between concentration and effect. The value that causes the hysteresis loop to collapse represents the rate of equilibration of the drug concentration between the plasma at its biophase. This value is termed the k_{e0} .^{7,9}

The $t_{1/2 k_{e0}}$ ($0.693/k_{e0}$) is the time it takes for half of the equilibration to occur between the biophase and the plasma concentration. For example, the $t_{1/2 k_{e0}}$ for fentanyl is 4.7 min (Table 1). If an infusion regime is started to obtain a plasma concentration of exactly 1 ng/ml, at 4.7 minutes the effect achieved will be equal to 0.5 ng/ml, and it will take approximately 20 minutes to achieve an effect of 1 ng/ml. The time to the peak effect of a drug following a bolus is also a function of its k_{e0} (and its disposition). A drug having a short $t_{1/2 k_{e0}}$ will have a rapid onset to peak effect. For optimal dosing it is important for clinicians to be knowledgeable of the time to peak effect for each of the intravenous drugs. (Table 1) For example, with a rapid sequence induction, it is desirable to use drugs with a rapid onset like thiopental (time to peak effect-100 seconds) and alfentanil/remifentanil (82 seconds) so that both peak at the same time causing loss of consciousness and ablating the response during laryngoscopy and endotracheal intubation. If fentanyl (216 seconds) rather than alfentanil is administered at the same time as thiopental and succinylcholine, its effect will not be maximal at the time of the greatest stimulus (intubation), and this is likely to result in initial hypertension following laryngoscopy and then hypotension as fentanyl reaches its peak effect when stimuli are minimal. In addition, when giving intravenous drugs by intermittent bolus dosing, the interval between doses needs to be of sufficient duration so that the peak effect of the drug is observed prior to administering the next dose of the drug. This principle is utilized for the lock out interval with patient-controlled analgesia.

When inducing loss of consciousness, it is important to be cognizant of both the times to peak effect of the drugs being used and the impact of drug combinations on loss of consciousness and hemodynamic parameters. In general, the common drug combinations (barbiturate or propofol plus opioid and/or benzodiazepine) used for induction of anesthesia result in a synergistic interaction allowing the clinician to markedly reduce the amount of propofol or barbiturate used. Illustrated is the interaction between propofol, midazolam and alfentanil for loss of consciousness either alone or as a double or triple combination (Figure 1).¹⁰ These drug interactions also have to be interpreted in terms of the time to peak effect of each drug used in combination. For example, when administering fentanyl or sufentanil at the same time as thiopental or propofol, the dose required to provide loss of consciousness is not markedly reduced as the effect of the hypnotic peaks well before the opioid. However, when combining these hypnotics with a rapid onset opioid, their dose should be markedly reduced as the effects of the opioid and hypnotic will peak at the same time.

Multi-compartment Models in Dosing Strategies

The infusion scheme as shown in equation 2 will maintain the precise plasma drug concentration if the decrease in plasma drug concentration only occurs as a result of clearance processes (i.e. the drug does not distribute from the blood/plasma to other tissues, a 1 compartment drug). This is not true for most of the drugs used for anesthesia (with the notable exceptions of remifentanyl and mivacurium) and thus any infusion scheme must account for distribution of drug into peripheral tissues. As drugs distribute into various other tissues from the blood/plasma (e.g. muscle, fat etc.) their distribution into these tissues occurs at different rates and these tissues will contain different volumes of drug. Thus depending on how the drug is disposed of in the body, the drugs' pharmacokinetic parameters can be best described by either a 2 or 3 compartment model. When designing an infusion scheme to maintain a target concentration in the plasma, the infusion scheme must not only replace drug lost from the plasma due to the terminal clearance of drug, but also due to loss from the plasma as a result of distribution into peripheral tissues. The infusion scheme to exactly maintain a target concentration has been termed the **BET** scheme. The **B** is the loading bolus dose as described above. **E** is for the infusion to replace drug removed due to its terminal elimination (clearance), and **T** is for an exponentially declining infusion proportional to the rate of transfer of drug to peripheral tissues¹¹. In practical terms this implies that when administering an intravenous anesthetic one starts with a high infusion rate and decreases it with time to maintain a stable plasma concentration. A typical example of a BET scheme used in daily practice is the infusion scheme for propofol to obtain a concentration of 3.5µg/ml. An initial load of 2 mg/kg is followed by 70 ml/hr for 10 minutes, 55 ml/hr for 10 minutes and then 40 ml/hr thereafter.¹² Thus to maintain a stable target concentration a decreasing infusion rate as based on both drug disposition into peripheral tissues and terminal clearance is required.

Another important pharmacokinetic principle to bear in mind when administering a continuous infusion is that pharmacokinetics is based on linear models. An infusion administered at a rate double the initial will result in a steady state plasma concentration twice that produced by the original infusion rate. The time taken for a new infusion rate to obtain a new plasma concentration is long (and determined by the elimination half-life of the drug). During anesthesia rapid increases in plasma concentration are required. Therefore to achieve this, a combination of a bolus dose plus an increase in infusion rate is used to rapidly establish a new central compartment/ effect site concentration.

Our understanding of the pharmacokinetic processes within a 2-3 compartment model that determine the recovery from drug effect have also recently been elucidated. The concentration of a drug in the plasma and the biophase is dependent on those processes adding drug to the body and the

disposition of drug within the body. When the administration of drug to the body is terminated the concentration of the drug in the plasma (and biophase) will decrease due to both the irreversible elimination of drug from the body and the redistribution of drug from the plasma to peripheral tissues.

Conventional wisdom has been that the elimination half-life of the drug represents the measure of how rapidly recovery from drug occurs. The elimination half-life represents the terminal clearance of the drug and does not incorporate any redistribution of drug and thus clearly does not provide any quantitative measure of how long it will take for the drug to decrease by 50%. To provide an estimate of the time for recovery to occur with intravenous anesthetics the concept of “context-sensitive half-time” has been proposed and represents the time required for the plasma concentration of a drug to decrease by 50% (for an infusion designed to maintain a constant concentration) for any given duration of the infusion.¹³ The ‘amount’ of distribution available when the infusion is terminated is dependent on how long the drug has been administered for. Thus the duration of the half-time depends on how long the infusion is administered (i.e., context sensitive to the duration of the infusion). This is well demonstrated in Figure 2 that illustrates the context sensitive decrement times, of the most commonly used intravenous opioids. Pharmacokinetic simulations demonstrate that the time for e.g. 20%, 50%, or 80% decrease in plasma drug concentration is not linear (i.e., a 20% decrease may take 5 minutes, a 50% decrease 20 minutes and a 80% decrease 120 minutes).

It must also be understood that if a continuously varying plasma concentration has been administered the context-sensitive half-time no longer will accurately reflect the time for a 50% decrease in plasma drug concentration once the infusion is terminated. The context-sensitive half-time rather than the elimination half-life provides a guide for both the choice of drug with respect to the desired rate of recovery from drug effect and an indication of when to terminate an infusion prior to the end of surgery.

Delivery Systems

At present the most commonly used administration system for the delivery of intravenous anesthetics is a syringe and needle. It is quite obvious that the intermittent administration of drug via a syringe will result in a continuously varying drug concentration and thus therapeutic effect. As continuous infusion of an intravenous anesthetic provides superior outcomes there is increasing popularity of infusion pumps for the administration of intravenous anesthetic drugs. The pumps have been specially modified for the administration of intravenous anesthetics by the inclusion of calculator features. If the pharmacokinetic parameters that describe the disposition of the drug have been determined it is possible to utilize these to calculate a dosing scheme to provide a target concentration. This is described above in terms of the BET scheme. To calculate, oneself, accurately and continuously the infusion rate for a desired target concentration is virtually impossible. However, computers (microchips) can easily be programmed to provide accurate and rapid calculations of these complex mathematical tasks, thereby providing automated drug delivery devices.

Automated Drug Delivery

Automated drug delivery implies that some form of electronic and/or mechanical instrumentation performs dose rate adjustments independent of human intervention². The desired target (e.g., drug concentration or clinical response) is still chosen by the clinician. Generally, two methods may be applied for automated target anesthetic drug delivery: either model-based (a form of open loop control) or closed-loop. Although closed-loop is the ideal means of automated drug delivery, there is not always a measurable feedback signal. Recently the introduction of the Bispectral Index and other measures of hypnosis have increased interest in developing closed loop devices for anesthesia. (See below) Model-based drug delivery utilizes a mathematical equation that

can simulate the process that produces the set point. Several investigators implemented model based automated intravenous drug delivery systems. This stimulated the commercial development of the “Diprifusor” which consists of software developed by Astra Zeneca and hardware (the pump) by several manufacturers. These devices enable the clinician to simply select a target plasma concentration of propofol. Investigator designed devices provide both target plasma or effect compartment concentration delivery. For all these devices the infusion rate is automatically computed and delivered to the patient via an infusion pump. Within the software the infusion rate required to either obtain or maintain the target concentration over the next time interval; e.g., 10 seconds is computed. This information is fed to the infusion pump, which then infuses drug at the calculated infusion rate. The amount of drug delivered is communicated back to the software so that the infusion rate for the next 10 seconds can again be computed based on the target concentration and the amount of drug already administered.²

The ability of target controlled infusion devices to precisely obtain the target concentration is dependent primarily on how well the pharmacokinetic parameters utilized describe the disposition of the drug in the given patient. The pharmacokinetic parameters used in such devices are derived from the literature and represent the average values of generally a small group of volunteers or patients. It is therefore impossible that they exactly match those of all patients. It is expected that there will be a difference between the target value and the actual measured concentration. When target controlled infusion devices have been used for the administration of intravenous anesthetics, such systems work well clinically if there is not a predominant over or under prediction between the measured and the target concentration (i.e., the pharmacokinetic parameters do not result in either a positive or negative bias.). Also, the absolute difference between the target concentration and the measured concentration should not on average exceed 30% (this value is termed the median absolute prediction error).²

Although target-controlled infusion devices do not result in a measured concentration exactly equal to the target concentration, it does provide an excellent tool to proportionally adjust the concentration of drug, thereby enabling an easier and probably smoother titration of drug to provide the desired effect. Target-controlled infusion devices can also calculate, on line, the time required for the drug concentration to decrease to any new concentration if the infusion is terminated. This provides the actual context-sensitive time for the desired percent decrease. Commercial target-controlled infusion devices are likely to facilitate the ability of the clinician to administer intravenous anesthetics to continuously provide the desired effect.

Closed Loop Drug Delivery Systems

The next step in automated drug delivery is to feed the measured drug effect directly back into the automated drug delivery device and to permit the model to be updated based on observed measures of drug effect, thus providing a closed-loop system¹⁴. In this instance the set point is the measured effect rather than drug concentration. It has been proposed that closed loop control of anesthesia may provide several advantages: Increased stability of the control variable because of more frequent sampling of the effect with more frequent adjustment of drug delivery, more customized dose delivery accounting for both inter-individual pharmacokinetic and pharmacodynamic differences, improvement because of the above of hemodynamic stability, inadvertent awareness and recovery.

The simplest form of a closed loop system is an on-off controller. The infusion pump is programmed to give only 1 infusion rate. Where the effect of the drug reduces the measured effect, the pump will turn on when the measured effect is greater than the set point (positive error) and switch off when the error is negative. Such a system will oscillate around the targeted effect. Several

modifications of this simple closed loop system have been developed. This is especially important for their implementation in complex biological systems. The next engineering modification that has been implemented to improve the performance of closed loop devices is by adjusting the infusion rate according to the error. A (P)roportional controller will adjust the infusion rate in accordance with the size of the error. Depending on the rapidity with which the error changes this may also lead to over or undershoot of the target and thus the (I)ntegral of the error is used to minimize this. This leads to a reduction in the error but may lead to a systemic bias. To prevent this the (D)erivative of the error is also used. Most mechanical closed loop systems are PID controllers. Biological systems are more complex in that there is a second or third order relationship between infusion dose and effect and sensitivity between individuals may vary by a factor of 10 fold. To deal with these, two further modifications for control have been used. The first is that the changes in dose, based on the error, is determined by a pharmacokinetic/pharmacodynamic model. Secondly as the system learns the sensitivity of the individual the model 'adapts' to that individual. Adaptation may be simply by adjusting the gain, by adjusting the relationship between concentration and effect, or using fuzzy logic. Several investigators have developed closed-loop target control systems for blood pressure and neuromuscular blockade which have demonstrated an ability to provide excellent control with zero bias and a median performance error and median absolute performance error of within 10%. As mentioned earlier, the ability to measure adequacy of anesthesia is limited. Rather anesthesia is a composite of several effects; hypnosis or loss of consciousness, amnesia and analgesia. There are now several derivatives of the EEG who show a strong correlation with hypnosis/ loss of consciousness. The major component of anesthesia for which we do not have a monitor of effect is analgesia. This continues to constitute an impediment to the general application of closed loop anesthesia. Noxious stimuli during surgery are extremely variable. Intravenous anesthetics (with the exception of Ketamine) have limited or no analgesic activity. Thus the closed loop system based on a derivative of the EEG may provide perfect hypnosis in the absence of a stimulus but awakening will occur as soon as a noxious stimulus is administered. To overcome this hurdle investigators have taken several approaches to test closed loop systems for anesthesia in patients. They have been used in combination with a regional anesthetic thereby ablating any painful stimulus reaching the brain. Others have used low dose constant opiate concentration for superficial surgery or high dose opiate for more extensive surgery. Another interesting approach is a combination of an analgesic concentration of opiate and applying at regular short intervals a noxious stimulus (e.g. tetany) thus minimizing oscillations due to surgical stimuli.

Struys et al also performed a study to determine if there are any advantages of a closed loop system to manual administration of propofol for lower abdominal surgery ¹⁵Anesthesiology 2001 July;95(1):6-17. Their approach was to have the anesthesiologist in the manual control have as the target of control clinical criteria of adequate anesthesia whereas for the closed loop system the Bispectral Index was used as the set point. Struys and colleagues also used a model based adaptive control system. During induction the system administered a staggered increasing propofol concentrations so that it could construct a sigmoid Emax model thereby 'learning' the individuals concentration effect relationship. The sigmoid e max model developed during induction could change based on the degree of noxious stimulation and opiate concentration. To account for this the investigators allowed a left or right shift of the Emax curve that corresponded with the new Bispectral Index value and the predicted concentration. A new target concentration was determined from this new Emax curve and this was then delivered to return the Bispectral Index to its target. That is just like surface maps can be created for hypnotic and opiate interaction one can also think of a surface map that relates degree of noxious stimulus and level of consciousness. This approach will also help account for changes due to tolerance etc. As the noxious stimulus may vary rapidly this

approach can also lead to oscillations of the target. A differential factor is applied to dampen this. All patients received 0.5 $\mu\text{g.kg.min}^{-1}$ remifentanyl. The closed loop control group achieved statistically significant better control of both its control variable (BIS Index 89 \pm 10%) and systolic pressure (51 \pm 27%) compared to the manual group (Systolic pressure 34 \pm 31%, BIS Index 49 \pm 29%). In addition recovery was also improved in the closed loop group. This study does not definitively answer if closed loop delivery of anesthesia is better than any manual system, nor does it define what an optimal closed loop control system is, however its results are encouraging and should further stimulate work on developing closed loop anesthetic drug delivery for day to day anesthesia.

PHARMACODYNAMICS

Pharmacodynamics is largely the understanding of the relationship between drug concentration and observed effect (i.e. what the drug does to the body). Only by defining the concentration effect relationship can the appropriate dosing schemes be determined from the drug pharmacokinetics. Table 2 provides the concentration effect relationships that have thus far been defined for intravenous anesthetics.

MAC (end-tidal concentration of the volatile anesthetic in equilibrium with its effect site in the brain that prevents a purposeful somatic response in 50% of patients to a skin incision) provides for the volatile anesthetics a benchmark of their concentration-effect relationship. A similar measure is required of the concentration-effect response of the intravenous anesthetics. This measure has been termed the $\text{Cp}_{50 \text{ skin incision}}$ and represents the plasma concentration (once equilibration between the plasma and biophase has occurred) that will prevent a pre-defined response (e.g., movement) to a given stimulus (e.g., skin incision) in 50% of patients. Aulsems et al defined the Cp_{50} of alfentanil in the presence of 66% nitrous oxide for a variety of anesthetic and surgical stimuli.¹⁶ From these results it is evident that the required anesthetic concentration for adequate anesthesia varies markedly according to the surgical stimulus. The highest concentrations are required for endotracheal intubation. The concentration of alfentanil required to prevent a response for skin closure is less than that required for skin incision or spontaneous ventilation. This allows the opioid to be gradually titrated downwards towards the end of the procedure. For the intravenous hypnotics the $\text{Cp}_{50\text{LOC}}$ for loss of consciousness has been determined.²

Although the Cp_{50} can be defined, it is important to realize that this only represents the 'average' concentration for a given effect and different patients will require different concentrations of an intravenous anesthetic to achieve the same desired effect. Thus Cp_{50} values simply provide a guide to intravenous drug dosing. It is imperative with intravenous (and volatile) anesthetics that they are titrated to each individual's need for the surgical stimulus they are experiencing.

Newer Concepts of Anesthesia

To truly provide rational dosing schemes with intravenous anesthetics it is important also to understand drug interactions in providing anesthesia. Initial studies by Murphy and Hug in dogs demonstrated a marked reduction in the MAC of volatile anesthetics by the administration of opioids¹⁶. The MAC reduction of isoflurane by opioids in humans has been repeated.¹⁷⁻²¹ These studies demonstrated, as illustrated in Figure 3, very small doses of opioid (fentanyl, alfentanil, sufentanil and remifentanyl) within their analgesic range, markedly reduced the MAC of isoflurane (or desflurane). As the opioid is increased a ceiling effect on the MAC reduction of the volatile anesthetic occurs. In studies examining the interaction between propofol and opioids an identical pattern is obtained.^{22,23} The ceiling effect produced by the opioid is seen at propofol concentrations similar to those required for loss of consciousness. Similarly the lowest concentration of isoflurane associated with absence of movement irrespective of the opioid concentration (i.e., at the ceiling

effect) was 0.2-0.4% which also is close to its MACawake concentration. Recently it has also been shown that in such drug interaction studies the ability to prevent an autonomic response is largely dependent on increasing the amount of opioid. The results of these interaction studies indicate that to prevent a purposeful or autonomic response to a noxious stimulus requires effective analgesia combined with a concentration of the volatile or intravenous anesthetic (hypnotic) that is sufficient to provide loss of consciousness. These interaction studies further suggest that anesthesia may not be a single entity, but rather a process requiring both the inhibition of the noxious stimulus by means of an analgesic and the provision of loss of consciousness by an hypnotic.

Probably the most commonly used combination of anesthetics is isoflurane and fentanyl. A 50% MAC reduction is achieved with 1.7ng/ml fentanyl- (loading dose of 4 µg/kg followed by 1.75 µg/kg/min.). The minimum effective analgesic concentration of fentanyl is 0.6 ng/ml so that the steepest reduction in MAC occurs within the analgesic concentration range of fentanyl (i.e., 1-2ng/ml). Clinically, significant respiratory depression may occur with plasma fentanyl concentrations above 2ng/ml. Beyond 5 ng/ml a plateau or ceiling effect is seen with a maximum MAC reduction of approximately 80%. Fentanyl concentrations of 5 ng/ml also are sufficient to ablate the autonomic response to a noxious stimulus. Once the ceiling effect is reached there is very little advantage in increasing the opioid concentration. For fentanyl and remifentanyl, this is a concentration of approximately 5 ng/ml, for alfentanil 400 ng/ml and for sufentanil 0.5 ng/ml. (See table 3 for dosing schemes to achieve these concentrations). Each combination of opioid and hypnotic actually results in a unique new drug for which one can determine the 20, 50 or 90% etc response rate within the population. Using the drug interaction and response rate one can develop a response surface for the drug interaction for the population. An example of such a response surface for the interaction of propofol and remifentanyl for skin incision is illustrated in figure 4.

As one adds increasing opioid to the anesthetic regimen the dose of the hypnotic can and should be reduced. This illustration of the interaction between opioid and hypnotic serves as a guideline for drug dosing. However, there is considerable variability in the concentration required to insure loss of consciousness in any given individual. To insure adequate dosing the clinician uses a variety of clinical signs. These may not always be reliable in preventing awareness. Thus other monitors of adequate anesthesia have been sought. The most promising have been those dependent on electroencephalograph (EEG) signals either through direct recording or via evoked responses. The BIS has been shown to provide a very strong correlation between increasing sedation and loss of consciousness for both intravenous and volatile anesthetics.^{24,25} Several investigators have shown when the BIS is used to guide the titration of propofol or volatile anesthetics a 20-30% reduction in propofol and volatile anesthetic is observed together with a more rapid recovery.^{26,27}

From the drug interactions shown above it is possible to provide adequate anesthesia by any combination of hypnotic and opioid. Our responsibility is not only to provide adequate anesthesia intra-operatively, but also to insure rapid recovery. Rapid recovery implies return of consciousness and adequate spontaneous ventilation. In general, terms the objective is thus to provide an ED95 of the combination for adequate anesthesia during surgery and then return the patient to a concentration of the combination that is associated with an ED95 for consciousness and adequate spontaneous ventilation. The time to recovery is dependent on the context-sensitive decrement time required for the concentrations of both drugs used intraoperatively to decrease to that required for consciousness and spontaneous ventilation. The less the opioid used, the more this time is dependent on the hypnotic, and as the dose of opioid exceeds the concentration resulting in respiratory depression, the more recovery is dependent on the context-sensitive decrement times of the opioid. Therefore, there is an ideal combination that provides adequate intraoperative anesthesia and will result in the most rapid recovery.

Figure 5 illustrates the interaction between hypnotic and opioid for providing anesthesia and the implication of where one is on this interaction line to return to a state of consciousness and adequate respiration. This was well illustrated by Vuyk, et al who performed studies determining the interaction of alfentanil and propofol as illustrated in the Figure 6.²³ However they took this interaction one step further in that they also measured the time to awakening at each of these combinations (solid line on z-axis). The time for awakening correlated closely with the required context-sensitive decrement time required for propofol and alfentanil. Thus, not only were they able to define the optimal interaction for the prevention of a response to skin incision, but also the implication of these concentrations on recovery. The differences in recovery time according to the amount of which drug (i.e., opioid or propofol) was administered is well illustrated in this study. They showed that the shortest recovery time occurs at an alfentanil concentration of approximately 80ng/ml and propofol concentration of approximately 3µg/ml. When the concentration of propofol is increased, the concentration of alfentanil can be decreased, but the overall time for recovery increases. Similarly, as the concentration of alfentanil increases, the concentration of propofol can be decreased, but the time for recovery increases. It can be seen that when the concentration of alfentanil is increased beyond 80 ng/ml, even though the concentration of propofol can be reduced, there is a marked increase in the time for recovery. This increase in recovery time is much larger than the increase in recovery time that occurs when propofol is increased beyond 3µg/ml. As the context-sensitive decrement time varies according to the duration of drug administration, the impact of increasing either the opioid or hypnotic component to provide adequate anesthesia varies according to the duration of the anesthetic. In essence, the shorter the duration of the anesthetic, the less impact increasing one or other drug has on delaying recovery. However, the longer the duration of the anesthetic, the more important it is to maintain the patient within a narrow therapeutic window to ensure prompt recovery. The recovery profile (offset or context-sensitive decrement times) of isoflurane is very similar to that of propofol. Thus, the clinical implications of the drug interaction between volatile anesthetics with fentanyl, alfentanil or sufentanil to provide anesthesia with the most rapid recovery are identical to that between propofol and the opioids. If the objective at the end of anesthesia is to have an awake, spontaneously breathing patient at the end of surgery for all of these drug combinations, the infusion regimen should provide an analgesic concentration of the opioid equivalent to 1-2ng/ml of fentanyl (see table 3). Propofol or the volatile anesthetic should provide an absolute minimal Cp50awake concentration or end-tidal concentration equivalent to its MACawake value (e.g., for propofol 3µg/ml produced by a loading dose of 1-2 mg/kg followed by an infusion rate of 80µg/kg/min., or for isoflurane a minimal concentration of 0.3-0.4%). The infusion schemes for intravenous hypnotics to provide sedation and loss of consciousness are listed in Table 4.

If the patient demonstrates signs of inadequate anesthesia there are several issues to be considered. If the response is intense rapid re-establishment of anesthesia is required and drugs with a rapid onset will be required e.g. propofol, thiopental, remifentanyl or alfentanil. In such situations it is the authors preference to give a dose of both hypnotic and opioid. If the response is less intense it is preferable to initially increase the hypnotic component (i.e., volatile anesthetic or propofol), as increasing these has less of an effect on prolonging wake-up time than increasing the opioid and reduces the risk of possible awareness. Often in such situations where repeated increases in heart rate and blood pressure occur in conjunction with surgical stimulation, the author will also consider giving a small bolus of an opioid to ascertain within that individual if the adequate concentration of opioid is being delivered. If the opioid ablates the responses, a small ($\pm 20\%$) increase in the infusion rate is then made. When using the BIS, the hypnotic is titrated to a BIS of ± 60 during the procedure and 70 at termination. Increase in opioid is given if autonomic responses occur in the presence of a

BIS value of <60. An important corollary to this is, that if the blood pressure remains elevated with a BIS <60 and 1 to 3 increases in opioid dosing, an anti-hypertensive should be given rather than persisting with increasing either opioid or hypnotic.

Remifentanyl has an extremely short context-sensitive half-time of only 3-5 minutes and a context-sensitive 80% decrement time of 10-15 minutes irrespective of the duration of the infusion. This offset is quicker than achieved with most of the volatile anesthetics. When combining remifentanyl with an hypnotic or volatile anesthetic, a high-dose opioid technique minimizing the amount of volatile anesthetic will provide the most rapid recovery. This relationship holds true independent of the duration of the anesthetic. Thus, it may be preferable to administer remifentanyl to high opioid concentrations of 3-6 ng/ml (0.15-0.3µg/kg/min.) with just sufficient hypnotic to ensure an unconscious patient. If the patient responds, recovery time is prolonged less by increasing the remifentanyl than by increasing the hypnotic/volatile anesthetic. However, it must be reiterated that, although for optimizing recovery time, it is preferable to increase the opioid; the primary goal is to ensure the patient is not conscious, and this is only achieved with propofol or the volatile anesthetic.

In surgery in which immediate recovery is not required (e.g., cardiac procedures where post-operative ventilation is planned) and where surgical stimulation is profound, it is preferable to administer the opioid to its ceiling effect, thereby ablating any stress response to surgery. Thus, for cardiac anesthesia and similar procedures to minimize the stress response and yet provide fast-track recovery (i.e., ability to extubate within 6 hours of surgery), it is optimal to use a combination of propofol or volatile anesthetic and opioid rather than a pure high-dose opioid technique. In this instance, the opioid should be administered at a dose that will be just at the ceiling effect of the opioid (fentanyl equivalent of 4-6 ng/ml see table 3).

Although one can provide a guide to appropriate dosing of intravenous anesthetics, the combined affect of variability in sensitivity from patient to patient, the differing concentrations required for different stimuli, and the variable interaction between various intravenous anesthetics makes it imperative that the clinician closely and continuously observes his patient and titrates the intravenous anesthetics to achieve the desired dynamic effect within each individual.

Intravenous anesthetics are an important component in providing safe and effective anesthesia for our patients. With knowledge of both pharmacokinetics and pharmacodynamics of intravenous drugs, the clinician is capable of a more rational use of these drugs for the most optimal outcome during anesthesia.

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TABLE 1. The $t_{1/2 ke0}$, time to peak drug effect following a bolus dose, and volume of distribution (Vd) incorporating the effect compartment.

Drug	Time to Peak Effect (min.)	$t_{1/2 ke0}$ (min.)	Vd(L) incorporating the effect compartment
Fentanyl	3.6	4.7	75
Alfentanil	1.4	0.9	5.9
Sufentanil	5.6	3	89
Remifentanil	1.2	1	
Propofol	2.2	2.4	37
Thiopental	1.7	1.5	
Midazolam	2.8	4	
Etomidate	2	1.5	

TABLE 2. Steady State Concentrations For Pre-defined Effects

Drug	IC50 (±SD)	Cp50 incision or painful stimulus (± SD)	Cp50 LOC (±SD)	Cp50 Spont Vent (±SD)	50% Reduction in Isoflurane MAC	
Alfentanil (ng/ml)	520±123	241±16		226±10	50	10
Fentanyl (ng/ml)	6,9±1.9	4.2		(3-4)	1.67	0.7
Sufentanil (ng/ml)	0.68±0.31	(0.3-0.4)		(0.3-0.4)	0.145	0.0
Remifentanil (ng/ml)	14.7	3-6		(3-4)	1.3	(0.
Thiopental (µg/ml)	17.9	39.8±3.3	15.6±1.1			
Propofol (µg/ml)		15.8	3.4			

IC50 is the steady state serum concentration in equilibration with the effect compartment that causes a 50% slowing of the maximal EEG. Cp50 skin incision is the steady state plasma concentration in equilibration with the effect compartment that will prevent a somatic or autonomic, response in 50% of patients. Cp50 LOC is the steady state plasma concentration in equilibration with the effect compartment which provides absence of a response to a verbal command in 50% of patients. Cp 50 Spont Vent is the steady state plasma concentration in equilibration with the effect compartment that is associated with adequate spontaneous ventilation in 50% of patients. MEAC is the minimum effective plasma concentration providing post-operative analgesia. Values in () are estimated by scaling to the alfentanil Cp50 (see text for details).

Table 3.
Manual Opioid Infusion Schemes

Drug	Plasma Target Concentration (ng/ml)	Bolus (ug/kg)	Infusion Rate (ug/kg/min.)
Fentanyl	1	3	.020
Fentanyl	4	10	.070
Alfentanil	40	20	0.25
Alfentanil	160	80*	1.00
Sufentanil	0.15	0.15	0.003
Sufentanil	0.50	0.50	0.010
Remifentanil	2	0.5-1*	0.1
Remifentanil	8	1*	0.3-0.4

*Give as a rapid infusion over 1-2 minutes.

Table 4.

MANUAL INFUSION SCHEMES FOR HYPNOTICS

DRUG	<u>HYPNOSIS</u>		<u>SEDATION</u>	
	LOADING DOSE $\mu\text{g.kg}^{-1}$	MAINTENANCE INFUSION $\mu\text{g.kg}^{-1}.\text{min}^{-1}$	LOADING DOSE $\mu\text{g.kg}^{-1}$	MAINTENANCE INFUSION $\mu\text{g.kg}^{-1}.\text{min}^{-1}$
Ketamine	1500 - 2500	25 - 75	500 - 1000	10 - 20
Propofol	1000 - 2500	50 - 150	250 - 1000	10 - 50
Midazolam	50 - 150	0.25 - 1.5	25 - 100	0.25 - 1.0
Methohexital	1500 - 2500	50 - 150	250 - 1000	10 - 50

Figure 1

Figure 1

The ED50 isobolograms for the hypnotic interactions between midazolam, alfentanil and propofol. Shown on the right is the interaction between 2 of the above drugs and on the left both the double and triple interaction. The shaded line represents the additive plane for the triple interaction. Reproduced with permission from reference 10.

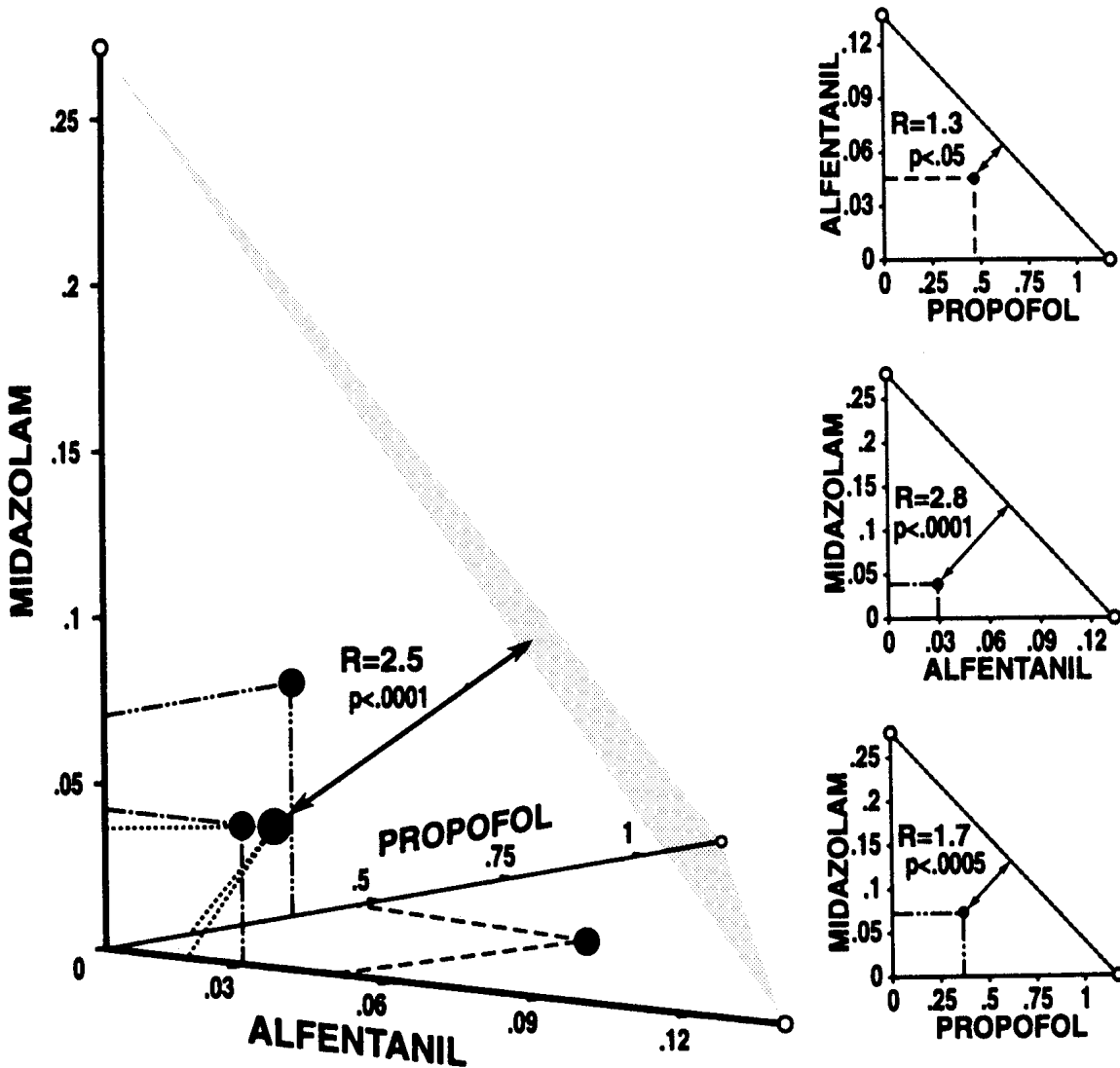


Figure 2

The 20%, 50% and 80% context-sensitive decrement times for fentanyl, alfentanil, sufentanil, and remifentanyl.

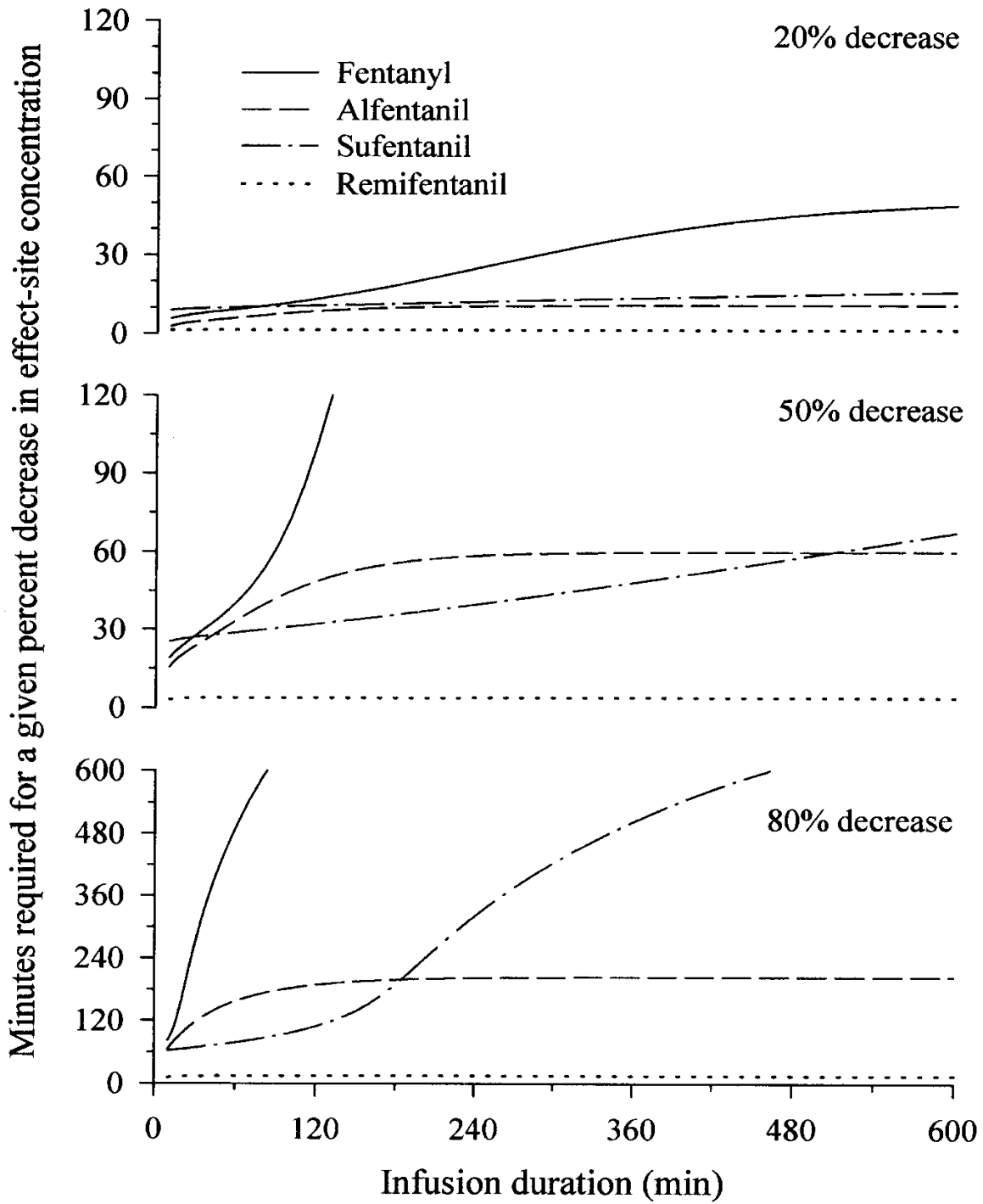
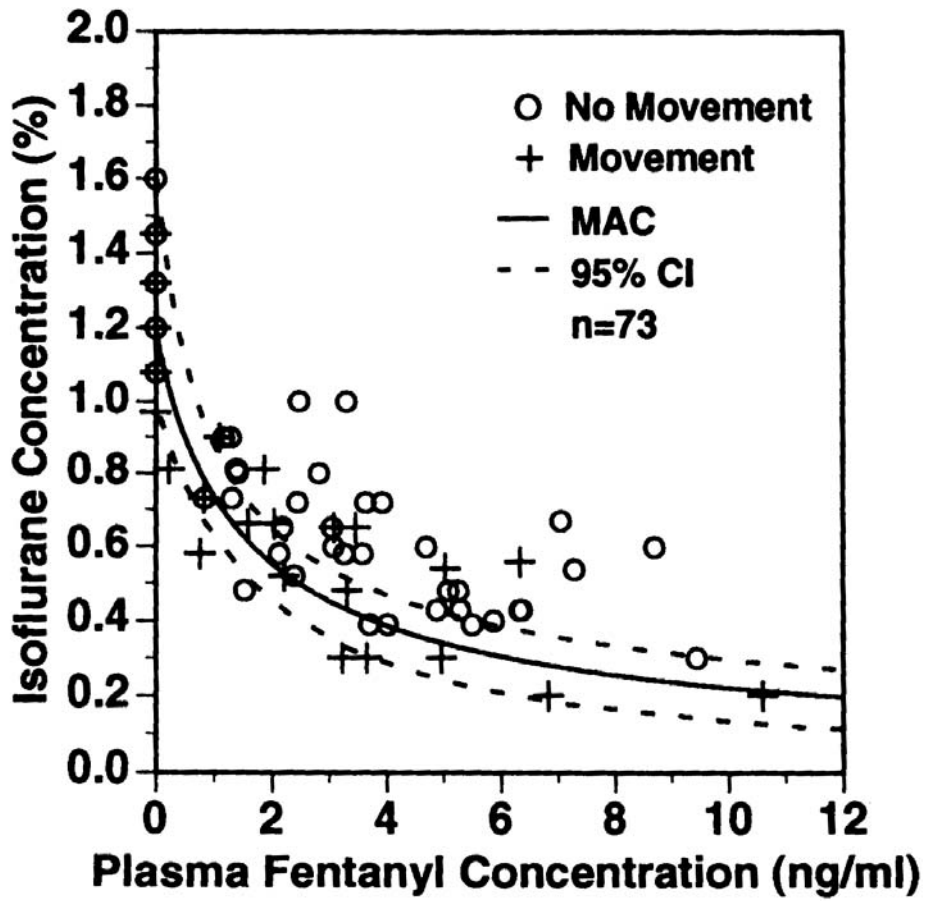


Figure 3

The reduction in the MAC of isoflurane by increasing concentrations of fentanyl. Each circle or cross represents the drug concentration of isoflurane and fentanyl in an individual at the time of skin incision. The solid line represents the concentration of the combination of isoflurane and fentanyl that prevents a somatic response to skin incision in 50% of patients



Surface Map of Midazolam Alfentanil for LOC

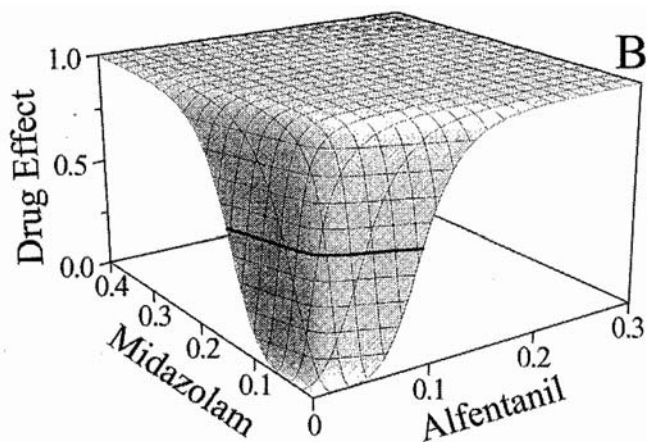
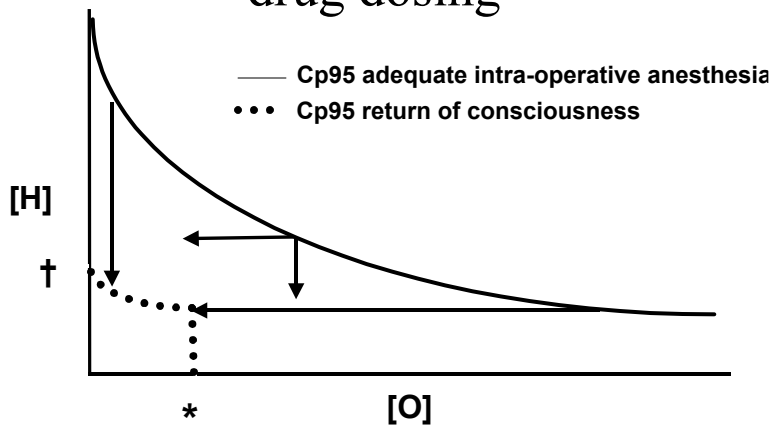


Figure 4. Surface map of the interaction of Midazolam and and Alfentanil for Loss of Consciousness. The Z axis represents the percent of patients likely to loose consciousness for the combination represented by the x and y axis. The solid horizontal line represents the Cp50 for the combination.

Figure 5

Drug interactions for optimizing drug dosing



[H], hypnotic concentration; [O], opioid concentration

* Cp50 for clinically significant respiratory depression

† Cp50 for loss of consciousness

This figure illustrates anesthetic requirements of the combination of an hypnotic and opioid for adequate anesthesia and the required decrease in both to return the patient to an awake state with adequate respiration. The greater the amount of hypnotic used to achieve anesthesia the lower the opioid but the longer to return to wakefulness. There is an ideal combination of opioid and hypnotic that will provide the most rapid recovery. This is usually just above the MAC_{awake} and just below the concentration of opioid that results in clinically significant respiratory depression.

Figure 6

The reduction in the concentration of propofol by alfentanil to prevent movement at skin incision. The solid line on the z axis represents the time for awakening and spontaneous ventilation following a 90 minute infusion when the combination of alfentanil and propofol concentrations from the xy axis are administered. Note the most rapid recovery occurs when 3 $\mu\text{g/ml}$ propofol is combined with 85 ng/ml alfentanil. Reproduced with permission from reference 31.

