Advances in the Clinical Pharmacology of Intravenous Anesthetics: Pharmacokinetic, Pharmacodynamic, Pharmaceutical and Technological Considerations

Talmage D. Egan, M.D Salt Lake City, Utah,

Over the last several decades we have witnessed dramatic advances in the scientific underpinnings of intravenous anesthesia. Having been rapidly translated into the clinical domain, the ultimate result of these advances is that total intravenous anesthesia (TIVA), once an impractical fantasy, is now an appealing, workable alternative to the traditional practice of inhalation anesthesia.

This refresher course presentation is intended to provide a broad overview of recent advances in the scientific foundation of intravenous anesthetic pharmacology. Drawing upon a "surfing" analogy as a theoretical framework, we will briefly review conceptual advances in pharmacokinetics and pharmacodynamics, developments in pharmaceutics such as designer drugs and innovative formulations, and improvements in intravenous drug delivery technology.

THE "SURFING ANALOGY" IN ANESTHESIA DRUG SELECTION AND ADMINISTRATION

Anesthesia and reanimation necessitate a standard of precision and accuracy in drug administration not required in most areas of clinical medicine. Anesthetists profoundly depress the central nervous system to maintain the anesthetized state but then must rapidly reanimate the patient after the operation is complete. Although over-dosing every patient within the constraints of acceptable hemodynamic variables is one approach to assuring the patient is adequately anesthetized, it comes at the cost of slow emergence from anesthesia, among others. Anesthetists must therefore target drug levels that are within a relatively narrow therapeutic window to achieve the competing clinical imperatives of adequate anesthesia (without toxicity) and rapid emergence.

A surfing analogy is helpful in conceptualizing the approaches that can be applied to the problem of rational drug administration in anesthesia. The anesthesiologist typically targets the upper portion of the steep part of the concentration-effect relationship; that is, the anesthesiologist targets a concentration that produces considerable drug effect but from which drug effect will recover quickly once drug administration is terminated. This can be visualized as a surfer riding near the crest of a wave as in Figure 1. Targeting ("surfing") the steep portion of the concentration-effect relationship makes it possible to achieve large reductions in effect with relatively small decreases in concentration.

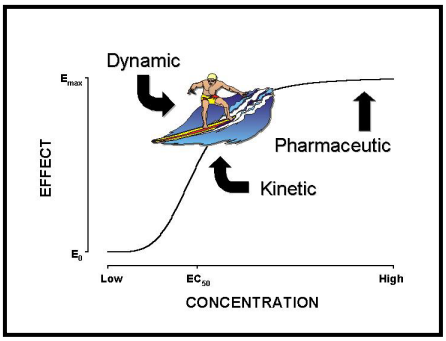

Figure 1. A surfing analogy as a graphical explanation of how anesthesiologists use a combination of three approaches to administer anesthetics to maintain the anesthetic effect while making rapid recovery possible. Anesthesiologists target the upper portion of the "steep" part of the concentration-effect relationship so that small decreases in concentration translate into large decrements in drug effect at the end of the anesthetic; this can be visualized as a surfer riding the crest of a wave. The pharmacodynamic approach relies on the measurement of pharmacologic effect to guide drug administration. The pharmacokinetic approach relies on knowledge of a drug's pharmacokinetics to deliver the drug to a specified target concentration. The pharmaceutic approach makes use of pharmacokinetically responsive agents, rendering the need to have exactness in the measurement of drug effect or drug delivery less important.

There are essentially three approaches to targeting this area of the concentration-effect relationship. Perhaps chief among them is the pharmacodynamic approach, wherein a drug effect measure is employed as a feedback mechanism to guide drug administration. Propofol titrated to a specific processed electroencephalogram target or a muscle relaxant administered to maintain a specific degree of twitch depression as measured by a peripheral nerve stimulator are examples of this pharmacodynamic approach.

While perhaps less appealing because it ignores drug effect, another common approach in targeting the steep portion of the concentration-effect relationship is the pharmacokinetic approach. Drawing upon knowledge about the concentration-effect relationship (i.e., therapeutic windows), the pharmacokinetic approach targets specific drug concentrations that are known to be appropriate for a given anesthetic application. The use of an agent specific vaporizer to deliver some multiple of the agent's minimal alveolar concentration (MAC) and the use of a target controlled infusion (TCI) device to infuse propofol to a specified concentration (e.g., the Diprifusor) are sophisticated examples of this approach. Of course even in situations where an advanced delivery technology is not employed, standard dosage regimens for most drugs in anesthesia are devised to achieve concentrations that are within the drug's therapeutic window based on the drug's pharmacokinetics.

A third approach to targeting the steep portion of the concentration-effect relationship can be referred to as the "forgiving drug" or "pharmaceutical" approach. The forgiving drug approach takes advantage of the responsive pharmacokinetic profiles of modern anesthetic agents. With this approach, within the constraints of acceptable adverse effects such as hemodynamic depression, it is unnecessary to hit the target with as much precision and accuracy as with the other approaches. Because short acting agent concentrations can be manipulated up or down rapidly, adjustments can be made quickly as suggested by pharmacodynamic feedback. If the empirical dosage scheme is obviously too aggressive or too conservative, the anesthetist can achieve a more appropriate level of drug effect in short order. Short acting agents essentially make it unnecessary to hit the target right on.

As a practical matter, of course, anesthetists combine all three approaches (e.g., the pharmacodynamic, pharmacokinetic and pharmaceutic approaches). Increasingly, pharmacokinetically responsive agents are administered by advanced, target controlled delivery devices according to pharmacodynamic feedback. Adjusting the Diprifusor propofol target based on feedback from the Bispectral Index Scale monitor is an example of this combined approach to anesthesia drug delivery. The scientific advances supporting this three pronged approach to rational drug selection and administration for intravenous anesthesia is the focus of this review.

PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

Pharmacologic Modeling

Pharmacokinetic-dynamic (PK-PD) modeling is the quantitative description of drug behavior and constitutes the scientific foundation for the clinical use of anesthetics.(1) Using computerized, nonlinear regression techniques, PK-PD models are constructed by fitting mathematical equations to raw pharmacologic data, resulting in a set of numeric parameters that describe in quantitative terms a drug's disposition and effect in the body.(2, 3) Pharmacokinetic (PK) parameters such as

clearance, distribution volumes and half-lives characterize "what the body does to the drug." Pharmacodynamic (PD) parameters such as potency characterize "what the drug does to the body." The ultimate goal of PK-PD modeling is to provide the practitioner with the knowledge necessary to formulate rational dosing schemes, accurately predicting the duration and magnitude of drug effect in any type of patient.

The central thrust of PK-PD modeling is to move beyond simple dose-response analysis. Earlier, more primitive experimental methods characterized drug behavior by measuring in qualitative terms the patient's response after a dose of drug. The more modern modeling methods separate drug behavior into pharmacokinetic and pharmacodynamic components and provide a quantitative description of each. The pharmacokinetic component describes the relationship between the drug dose and the time course of drug concentrations in the body. The pharmacodynamic component describes the relationship between the drug concentration in the site of action and the drug effect. Because most drugs do not act in the blood, the pharmacokinetic and pharmacodynamic components of the overall model must be linked so that concentrations in the blood can be translated into concentrations in the effect site.

Predictions regarding latency to peak effect, magnitude of effect and duration of effect can be made using PK-PD models. In this sense, PK-PD modeling studies provide the scientific foundation for drug administration in anesthesiology.(4) Although clinicians may not refer to PK-PD modeling studies specifically in everyday practice, dosage regimens outlined in textbooks and package inserts are based on modeling studies.

Because of the rapid development of PK-PD modeling techniques over the last several decades, PK-PD modeling papers now constitute a huge part of the anesthesia literature. This literature is the most sophisticated source for predictions regarding the latency to peak effect, magnitude of effect and duration of effect for intravenous anesthetics.

The Importance of Simulations in Understanding Pharmacokinetics

Recognizing that little insight into a drug's pharmacokinetic profile can be gleaned from simple inspection of its multicompartment pharmacokinetic parameters,(5) computer simulation of the expected rise and fall of drug concentrations utilizing a drug's pharmacokinetic parameters has assumed an important role in modern pharmacokinetic research and analysis.(4) Making use of population pharmacokinetic parameters estimated in research studies, computers can be programmed to simulate the concentration *versus* time profile that results from any type of drug input (e.g., various routes, doses, etc.). Although such simulations are subject to certain limitations, they are intuitively comprehensible, graphic representations of the time course of drug concentration. Combined with knowledge about the concentration effect relationship (i.e., potency of a drug), this specific information regarding the expected course of drug concentration can aid the clinician in predicting the magnitude of and recovery from drug effect. Without the aid of a computer it would be very difficult to draw such specific conclusions regarding the time course of drug effect.(1)

The Biophase Concept and Latency to Peak Effect

Equilibration delay between peak drug concentration in the blood and peak drug effect must be considered in understanding the implications of pharmacokinetic simulations. For many drugs, there is a significant time lag between peak concentration in the plasma and peak drug effect because most drugs do not act in the bloodstream. This time lag, or hysteresis, is a function of drug movement into and action within the effect site, or "biophase."(6, 7) The time lag is particularly important when giving drugs by bolus injection such as during patient controlled analgesia therapy, whereas for long infusions the time lag assumes less importance because the biophase and plasma are generally closer to equilibrium.

For many drugs used in anesthesiology and pain management, the equilibration delay between peak concentration in the plasma and peak effect has been characterized. Flow of drug to the effect compartment is a first order process and can be elucidated by estimating k_{e0}, a first order rate constant for elimination of drug from the effect compartment.(8) When the k_{e0} parameter is available for a drug, theoretical effect compartment concentrations can be simulated along with plasma or blood concentrations, thus making the effect of the time lag easily appreciated.

The opioids and the benzodiazepines are good examples of drug classes in anesthesia for which this issue assumes great clinical importance. In general, the fentanyl congeners (especially alfentanil and remifentanil) rapidly equilibrate with the site of action, while morphine's biophase equilibration time is much longer.(9) Hence, when administered in "equipotent" doses, the fentanyl congeners reach peak effect considerably faster than morphine. The very rapid acting fentanyl congeners (i.e., alfentanil and remifentanil) actually reach peak effect and the effect begins to decline before the slower acting fentanyl congeners (i.e., fentanyl and sufentanil) have even reached peak effect.(10) Failure to appreciate the slower latency to peak effect of midazolam compared to diazepam contributed to the epidemic of midazolam associated deaths in the clinical setting of conscious sedation in the late 1980s.(11, 12)

Context Sensitive Half-Times: A New Pharmacokinetic Concept

A recently introduced computer simulation illustrates how conclusions about drug concentration based on terminal half-lives can be misleading.(13) This new simulation technique predicts the time necessary to achieve a 50% decrease in drug concentration after termination of a variable length continuous infusion to a steady state drug level. Using concepts developed by Shafer and Varvel,(9) these simulations are an attempt to provide "context sensitive half times" (CSHT) as proposed by Hughes, et al.(14) In this case the "context" is the duration of a continuous infusion. The CSHT has also been referred to as the 50% decrement time.(15) Such simulations are intended to provide more clinically relevant meaning to pharmacokinetic parameters.

Figure 2 is a graphical representation of the context sensitive half-times of the previously marketed fentanyl family of opioids using parameters from the literature.(9) Contrary to previously established notions, alfentanil does not exhibit the most rapid 50% decrease in plasma concentration after termination of a continuous infusion until after many hours of infusion. Thus, sufentanil appears to have more favorable pharmacokinetics for infusions lasting less than eight hours when the goal is to achieve a rapid 50% decrease in concentration. In terms of pharmacokinetic theory, this surprising difference between alfentanil and sufentanil can be explained by the fact that sufentanil's pharmacokinetic model has a large, slowly equilibrating peripheral compartment that continues to fill after termination of an infusion, thus contributing to the faster decrease in sufentanil central compartment concentration. In other words, central compartment sufentanil concentrations fall rapidly after an infusion of less than 8 hours is stopped because of continued elimination and distribution.(9)

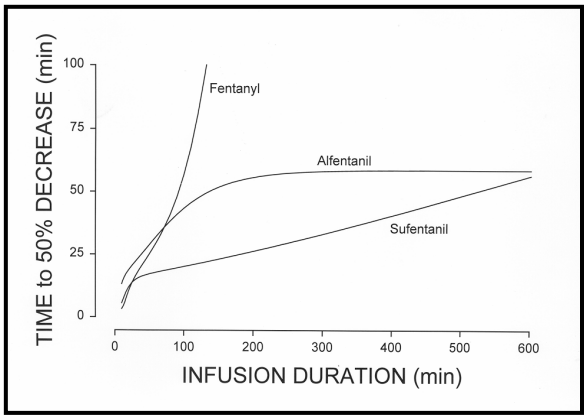

Figure 2: A simulation of the time required to achieve a 50% decrease in plasma concentration for the previously marketed fentanyl congeners after termination of a continuous infusion (i.e., the context sensitive half-times or 50% decrement time); from Shafer and Varvel.(9)

Unlike sufentanil and alfentanil, fentanyl exhibits an early time dependent increase in the CSHT. While fentanyl would be a poor choice for clinical situations in which a rapid decrease in concentration after infusion termination is desirable, in clinical scenarios in which prolonged opioid effect is the goal, fentanyl might well be the drug of choice. For example, fentanyl is well suited for cases after which the patient's trachea will remain intubated for a period of time after the procedure in order to promote a gradual emergence from anesthesia and a long lasting level of significant analgesia.

Note that for cases of very brief duration, the CSHTs for sufentanil, alfentanil and fentanyl are nearly identical. Thus, for brief applications, when the opioid is administered by infusion (or by frequent, small bolus doses), there would not be any substantial differences among the three drugs in the time to a 50% decrease in concentration after stopping a continuous infusion. Also note that the shapes of these curves vary depending on the percentage decrease in concentration required.

The Slope of the Concentration-Effect Relationship & Prediction of Clinical Response

While clinicians have traditionally relied upon pharmacokinetic parameters in predicting the time course of drug effect, the duration of drug effect is a function of both pharmacokinetic and pharmacodynamic parameters. Recent computer modeling research has focused attention on the steepness of the concentration-effect relationship as an important parameter in predicting the duration of drug effect.(16)

For most anesthetics and analgesics, the concentration-effect relationship is described graphically by a sigmoidal "maximum-effect" curve in which drug concentration in the site of action is plotted against drug effect. This sigmoid curve is represented mathematically by the equation:

$$E = E_0 + \frac{E_{max} \cdot C_e^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}}$$

where E is the predicted effect, E_0 is the baseline effect level, E_{max} is the maximal effect, C_e is the effect site concentration, gamma (γ) is a measure of curve steepness, and EC_{50} is the effect site concentration that produces 50% of maximal effect. EC_{50} is the measure of drug potency, which can be compared to other drugs of the same class.

This mathematical representation of the concentration-effect relationship is appealing not only because it is harmonious with experimental observations but also because it is consistent with the receptor concept of drug action. Drugs exert pharmacologic effect by binding with specific cellular receptors and activating a series of chemical changes within the cell that culminate in drug action. When a substantial number of receptors have been activated the maximal possible effect is achieved; that is, biologic systems are not capable of an infinite response. Thus, the concentration-effect relationship is well described by a sigmoidal maximum-effect curve in which a plateau in drug effect is eventually observed despite enormous increases in drug concentration.

The gamma (γ) parameter of the sigmoidal, maximum-effect equation is a measure of curve steepness. When gamma is large, the concentration-effect relationship is steep. For drugs with a steep concentration-effect relationship, small changes in drug concentration produce large changes in drug effect. For drugs that exhibit a concentration-effect relationships in which gamma is small, a small change in concentration does not result in such obvious changes in the magnitude of drug effect.

For drugs that have a steep concentration-effect relationship, the correlation of effect with concentration is often observed to be binary in nature.(16) In other words, the degree of drug effect is either substantial or it is negligible. This is because when drug concentration drops much below the EC_{50}, the probability of substantial drug effect is minimal, whereas when concentrations are much above the EC_{50} the probability of near maximal drug effect is high. When the concentration-effect relationship is less steep, the correlation of concentration with effect is more linear in nature.

The practical application of this concept is that pharmacokinetic parameters cannot be interpreted in isolation in predicting the duration of drug effect. While knowledge of the predicted decline in drug concentration based on pharmacokinetic parameters is helpful (i.e., the CSHT), it must be interpreted with knowledge about the drug potency and steepness of the concentration-effect relationship.

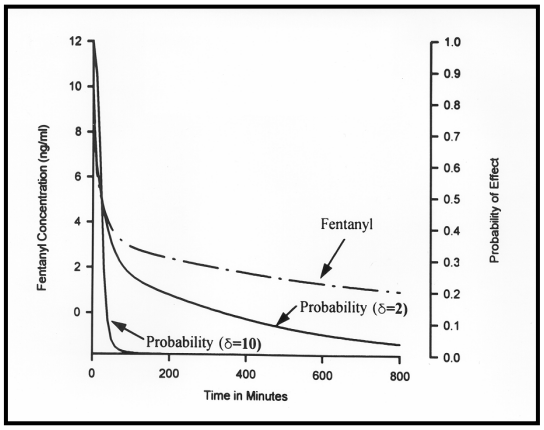

Figure 3. The decline in fentanyl concentration in the plasma (after stopping a 60 minute infusion targeting a concentration of 10 ng/ml) versus time compared to the probability of drug effect for 2 concentration-effect relationships, one steep (γ=10), the other less steep (γ=2). Note that when the slope of the concentration-effect relationship is steep the probability of substantial drug effect as a function of concentration is nearly a binary response (see text for complete explanation); from Bailey.(16)

For example, in Figure 3, the predicted decline in fentanyl concentration after a steady state infusion is terminated is plotted *versus* time. The probability of drug effect is also plotted for two different theoretical concentration-effect relationships; one that is steep (gamma = 10) and another that is less steep (gamma = 2). When the concentration-effect relationship is steep, there is a rapid dissipation in the probability of drug effect with declining drug concentration, whereas when the concentration-effect relationship is not steep, there is a much more gradual decline in the probability of drug effect with falling drug concentration.

Perhaps the most common clinical application of these concepts in anesthesia and pain management relates to the steepness of the concentration-effect relationship of opioids. Opioids are known to be drugs of relatively steep concentration-effect relationships; that is, the gamma parameter is relatively large.(17) Thus, very small changes in opioid concentration can produce large changes in the degree of drug effect. This means that for patients who fail a typical analgesic regimen, sometimes very small increases in dosage can result in adequate analgesia.(18) Patient response to opioids is often binary in nature. Analgesia is either adequate or it is not.

The Importance of Covariate Effects

Data gathered over the last twenty years from pharmacokinetic-pharmacodynamic modeling studies have provided part of the necessary scientific foundation to characterize the impact of patient covariates on drug behavior.(19) Of the frequently considered patient covariates (e.g., gender, age, body weight, kidney function, hepatic function, etc.), age and body weight are perhaps the most practically valuable in terms of developing a therapeutic, non-toxic dosage strategy for many drugs. Age and body weight are easily measured (i.e., just ask the patient) and their influence on the pharmacokinetics and pharmacodynamics of many

drugs has been described in some detail. The recently introduced, short acting opioid remifentanil can be used as a prototype example to examine the influence of age and body weight on anesthetic dosage regimens.

With regard to age, it is clear that older adults require less remifentanil to produce the desired spectrum of opioid effects. The reduced dosage requirement is a function of both pharmacokinetic and pharmacodynamic mechanisms, although pharmacodynamic factors dominate.(20) Remifentanil's EC_{50}, the concentration necessary for 50% of maximal effect as measured by the electroencephalogram (EEG), is markedly decreased in the elderly; in addition, remifentanil's central clearance and central distribution volume are also decreased. Interestingly, a slower equilibration between plasma and effect site concentrations in the elderly mitigates the clinical impact of the decreased central volume of distribution. All in all, these age related changes translate clinically into the need for a very substantial dosage reduction in the elderly (i.e., as much as 50-70%) that is based largely on the increased potency of remifentanil in older patients (i.e., a pharmacodynamic difference).(21)

As with age, the impact of obesity on remifentanil's clinical pharmacology has also been well described. Remifentanil's pharmacokinetic parameters are more closely related to lean body mass (LBM) than to total body weight (TBW).(22) To the clinician in everyday practice, this simply means that remifentanil dosing regimens should be calculated based on LBM and not TBW. Even substantially overweight and morbidly obese patients should receive remifentanil based on LBM as a starting point. Although the obese do indeed require somewhat more medication than lean patients, the dosage increase is significantly less than what would be indicated by TBW. For practical purposes, because the estimation of LBM requires a somewhat cumbersome calculation that is not well suited to the clinical environment, ideal body weight (IBW), a parameter closely related to LBM and one that is perhaps more easily "guestimated" by the clinician is probably an acceptable alternative.(23, 24)

As illustrated by the clinical pharmacology of remifentanil, age and body weight are easily measured patient covariates that have a substantial influence on anesthetic clinical pharmacology and thus the formulation of rational dosage schemes. Similar data exist to guide the rational administration of other opioids and hypnotics in the older adult and obese patient populations.(25, 26, 27)

The Importance of Pharmacodynamic Drug Interactions and Synergy

In anesthesiology, unlike most medical disciplines, pharmacodynamic drug interactions are frequently produced by design. Anesthesiologists take advantage of the pharmacodynamic synergy that results when two drugs with different mechanisms of action but similar therapeutic effects are combined. These synergistic combinations can be advantageous because the therapeutic goals of the anesthetic can often be achieved with less toxicity and faster recovery than when the individual drugs are used alone in higher doses.

In fact, except for specific, limited clinical circumstances wherein a volatile agent or propofol alone are acceptable approaches (e.g., a brief operation in a pediatric patient such as tympanostomy tubes), modern day anesthesia is at least a two drug process consisting of an analgesic (typically an opioid) and an hypnotic agent. Therefore, from a strictly pharmacological perspective, anesthesiology is the practice of pharmacologic synergism using central nervous system depressants.(28)

Propofol-opioid interactions are characterized using "EC_{50}" reduction study methodology with a clinical effect measure such as hemodynamic or movement response to surgical stimuli. Like MAC reduction studies, propofol-opioid interaction studies exhibit a general pattern irrespective of the opioid that is used. Opioids produce a marked reduction in the level of propofol required (and vice versa); as the opioid concentration increases, the propofol requirement decreases asymptotically toward a non-zero minimum.

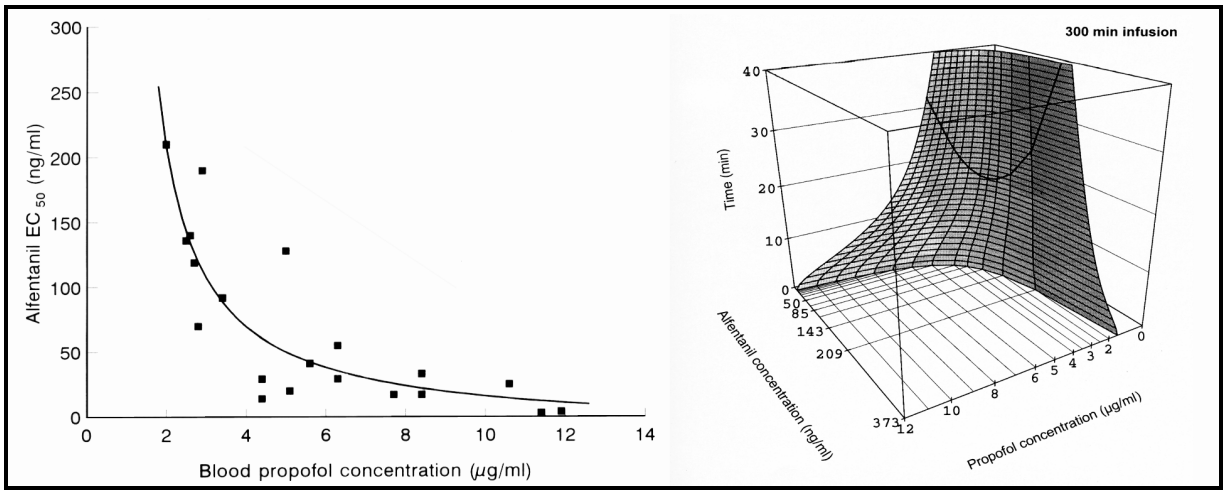

Figure 4. An example of the interaction between propofol and opioids. The left panel depicts the plasma alfentanil concentrations versus blood propofol concentrations associated with a 50% probability of no response to intraabdominal surgical stimuli, illustrating substantial pharmacodynamic synergy between the two drug classes. The right panel is a computer simulation of the effect site propofol and alfentanil concentrations versus time during the first 40 minutes after termination of target-controlled infusions of the two drugs to levels associated with a 50% probability of no response to surgical stimuli; the bold line superimposed on the concentration decay curves represents the concentration at which 50% of subjects are predicted to regain consciousness. The bold line parabolic minimum is the concentration target pair that produces equivalent pharmacodynamic synergy but more rapid recovery. The right panel is thus a clinically useful integration of drug-interaction pharmacodynamic data with pharmacokinetic information, permitting the rational selection of propofol-alfentanil targets (i.e., hypnotic-opioid ratios); from Vuyk et al.(29, 35)

The left panel of Figure 4 shows the propofol and alfentanil concentrations necessary to prevent hemodynamic or movement response to intra-abdominal surgical stimuli in 50% of patients as reported by the pioneering work of Vuyk et al.(29) This graph is typical of all propofol-opioid pharmacodynamic interactions no matter which effect is being studied.(30) Low concentrations of alfentanil dramatically reduce the need for propofol, but even very high concentrations of alfentanil cannot completely eliminate the need for propofol to maintain adequate anesthesia. The relationship is highly non-linear, meaning that the dosage reduction of one drug produced by an increase in the other is not simply proportional, demonstrating the substantial pharmacodynamic synergy of the drug combination.(31) Experiments like these suggest that at high propofol concentrations, low dose alfentanil is contributing primarily an analgesic effect to the overall anesthetized state,

whereas at lower propofol concentrations, the higher alfentanil concentration required is also contributing importantly to the hypnotic effect.(29) Similar findings have been reported by Kern et al for propofol and remifentanil using surrogate drug effect measures in volunteers.(32)

EC_{50} reduction studies form the basis of our clinical understanding of the propofol-opioid interaction. The right panel of Figure 4 is a computer simulation of effect site propofol and alfentanil concentrations *versus* time during the first 40 minutes after termination of 300 minute computer controlled infusions targeted to concentrations designed to achieve a 50% probability of no response to surgical stimulation.(30) Based on response surface methodology, this simulation enables the rational selection of concentration target pairs for propofol and alfentanil (and other opioids as well). The bold line superimposed on the concentration decay curves represents the concentration at which 50% of subjects are predicted to regain consciousness. The bold line is a parabolic curve identifying the concentration pair that optimizes predicted recovery time. According to the simulation, the concentration targets for propofol and alfentanil to minimize the time to return of consciousness after a 300 minute infusion while maintaining a 50% probability of no response to surgical stimuli intraoperatively are 3.4 mcg/ml and 88.9 ng/ml respectively.(30) The appropriate targets can be computed for any opioid, for any length infusion and for any percentage probability of non-response. The clinical application of these drug interaction models through the use of computer simulation constitutes a revolutionary advance in our understanding of intravenous anesthetic clinical behavior.(31)

The profound pharmacodynamic synergy of the propofol-opioid interaction is perhaps best illustrated by considering the pharmacodynamics of propofol when administered as the sole anesthetic. In the absence of opioids, the blood propofol concentration that is associated with loss of consciousness in 50% of patients is approximately 3.5 mcg/ml,(33) whereas much higher concentrations (10-15 mcg/ml) are necessary to suppress responses to surgical stimuli such as skin incision or intraabdominal manipulation.(29, 34) In contrast, the lower limit of propofol's therapeutic window for adequate anesthesia in the presence of moderate concentrations of opioid adjuvants appears to be approximately 1 mcg/ml, which represents a dramatic reduction compared to the levels necessary when propofol is administered alone.(29) Depending on the dosage of opioid employed, the therapeutic range of propofol concentrations when using an opioid adjuvant is very large, necessitating a selection of the appropriate propofol-opioid ratio for any given anesthetic application.

The rational selection of the appropriate propofol-opioid ratio is in large part a function of opioid pharmacokinetics. Because the fentanyl congeners can be viewed as pharmacodynamic equals with important pharmacokinetic differences, the time to return of consciousness depends predominantly on the selected opioid (and also on the duration of infusion).(9, 35) For the longer acting fentanyl congeners (i.e., alfentanil, sufentanil and fentanyl), a lower opioid concentration target and a higher propofol concentration target is prudent because the opioid pharmacokinetics are the rate limiting step in the recovery process. When the short acting opioid remifentanil is combined with propofol, on the other hand, a lower propofol concentration is targeted because propofol's pharmacokinetic profile is the primary determinant of the time to regaining consciousness.(35)

Of course pharmacodynamic considerations also come into play when selecting the appropriate propofol-opioid ratio. In the hemodynamically compromised patient, for example, a higher opioid concentration target might help to promote hemodynamic stability. In patients prone to nausea and vomiting after receiving opioids, a higher propofol concentration target might be prudent.

PHARMACEUTICAL CONSIDERATIONS

Remifentanil: a Prototype Designer Drug

Remifentanil is a prototype example of how specific clinical goals can be achieved by designing molecules with specialized structure-activity (or structure-metabolism) relationships. The medicinal chemists responsible for the development of remifentanil sought to produce a potent opioid that would lose its *mu* agonist activity upon ester hydrolysis, thereby creating an intravenous opioid with a very short acting pharmacokinetic profile.(36) The perceived unmet need driving remifentanil's development was that the practice of anesthesia requires a degree of pharmacokinetic responsiveness unnecessary in most medical disciplines and that anesthetics (opioids included) therefore ought to be short acting so that they can be titrated up and down as necessary to meet the dynamic needs of the patient during the rapidly changing conditions of anesthesia and surgery.

Remifentanil's metabolic pathway is shown in Figure 5. Compared to the currently marketed fentanyl congeners, remifentanil's CSHT is short, on the order of about 5 minutes.(37) Pharmacodynamically, remifentanil exhibits a short latency to peak effect similar to alfentanil and a potency slightly less than fentanyl.(10)

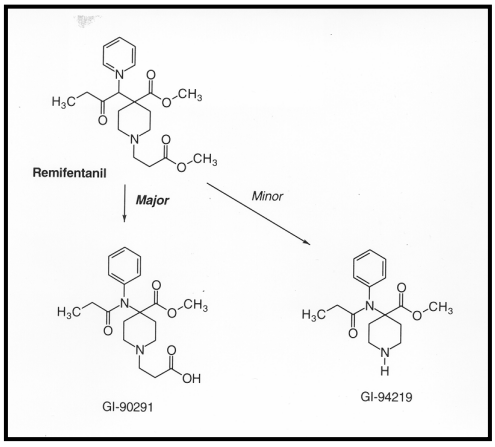

Figure 5. Remifentanil's metabolic pathway. De-esterification by nonspecific plasma and tissue esterases to form a carboxylic acid metabolite (GI90291) that has only 1/300th-1/1000th the potency of the parent compound is the primary metabolic pathway. N-dealkylation of remifentanil to GI94219 is a minor metabolic pathway; from Egan.(37)

Although remifentanil's role in modern anesthesia practice is still evolving, its unique pharmacokinetic profile certainly makes it possible to manipulate rapidly the degree of opioid effect in a way that could not be achieved with the previously marketed fentanyl congeners. Remifentanil is therefore perhaps best suited for cases where its responsive pharmacokinetic profile can be exploited to advantage (e.g., when rapid recovery is desirable, when the anesthetic requirement rapidly fluctuates, when opioid titration is unpredictable or difficult, when there is a substantial danger to opioid overdose, or when a "high dose" opioid technique is advantageous but the patient is not going to be mechanically ventilated postoperatively).(38)

The Importance of Formulation: Propofol as an Example

While perhaps not an issue to which most clinical anesthesiologists have devoted much thought, the formulation of a drug (and not just the active drug itself) can have an important influence on the drug's clinical behavior. Propofol is an important example of this pharmaceutical nuance.

The currently marketed propofol formulation has a number of undesirable properties that are in part a function of the lipid emulsion formulation. This lipid based formulation frequently produces pain on injection(39) and has also been associated with serious allergic reactions.(40, 41) In addition, because the lipid formulation supports rapid microbial growth,(42) inadvertent contamination of the formulation can be a cause of postoperative sepsis and death.(43) There is therefore substantial interest in the development of new formulations of propofol that are devoid of some or all of the undesirable features of the current formulation.

A number of investigational propofol formulations utilizing a wide variety of pharmaceutical technologies that make the delivery of poorly water soluble drugs possible are currently under development. These include an array of lipid based emulsions and non-lipid excipients.(44, 45, 46, 47, 48, 49)

A substantial challenge associated with the reformulation of propofol is that reformulation may alter propofol's pharmacokinetic and pharmacodynamic characteristics.(50, 51) Based on information from animal studies, it appears that at least some of propofol's rapid-onset, rapid-offset clinical pharmacologic profile is

dependent on the formulation.(52) Although it is too early to predict whether these new formulation technologies will come to fruition, we have learned from recent research that formulation plays a critical role in the behavior of propofol and perhaps other anesthetics and that this issue must be addressed when new formulations are developed.

TECHNOLOGICAL CONSIDERATIONS

Computerized Drug Delivery Methods

Until recently, the most sophisticated delivery device for the administration of opioids was the calculator pump, a device that enabled an accurate and precise delivery of fluid per unit of time. Used in both clinical and research settings, the physician operator of these devices simply specifies a delivery rate in terms of mg/hr or mcg/kg/min, etc. The patient controlled analgesia machine is a hybrid of the calculator pump that permits patient control of opioid administration within physician constrained parameters. The primary limitation of these calculator pumps is that they do not achieve the pharmacokinetic exactness possible with more advanced methods of administration.

Advances in pharmacologic modeling and infusion pump technology have now made it possible to administer injectable anesthetics *via* a computer controlled infusion pump.(53) By coding a pharmacokinetic model into a computer program and linking it to an electronic pump modified to accept computerized commands, delivery according to a drug's specific pharmacokinetic parameters can be achieved. The physician operating a target controlled infusion (TCI) system designates a target concentration to achieve rather than specifying an infusion rate. The TCI system then calculates the necessary infusion rates to achieve the targeted concentration.

Borrowing from inhalation anesthesia concepts, TCI pumps make progress toward the concept of a "vaporizer" for intravenous drugs because they address the fundamental limitation associated with delivering drugs directly into the circulation. Constant rate infusions result in continuous drug uptake. TCI systems, in contrast, gradually decrease the rate of infusion based on the drug's pharmacokinetics. Known in its general form as the BET method (i.e., bolus, elimination and transfer),(54) the dosing scheme determined by a TCI pump accounts for the initial concentration after a bolus dose and the subsequent drug distribution and clearance while an infusion is ongoing.

Delivery of drug via a TCI system requires a different knowledge base of the physician. Rather than setting an infusion rate based on clinical experience and literature recommendations, the physician using a TCI system designates a target concentration and the system calculates the infusion rates necessary to achieve the concentration over time. The TCI system changes the infusion rates at frequent intervals, sometimes as often as every 10 seconds. Successful use of a TCI pump thus requires knowledge of the therapeutic concentrations appropriate for the specific clinical application.(53)

Computer controlled drug delivery in the operating room is an exciting area with promising potential. (55) Pharmacokinetic model based patient controlled analgesia is also being developed with optimism. (56) This application of TCI technology requires the patient to specify whether pain relief is adequate or not. The TCI raises or lowers the target concentration accordingly.

Information Technology and Pharmacologic Models

Although PK-PD models can theoretically be used to predict the time course of drug concentration and effect for any conceivable dosage scheme (if the models are available…), the mathematical complexity of these models has precluded their practical introduction into the operating room in real time. Thus, PK-PD models characterizing anesthetic drug behavior have primarily been used as a computer simulation research tool to gain insight into how anesthetics can be rationally selected and administered.

Research is now being conducted to bring anesthetic pharmacology models to the operating room through automatic acquisition of the drug administration scheme and real time display of the predicted pharmacokinetics and pharmacodynamics. Based on high resolution PK-PD models, including a model of the PD synergy between opioids and propofol, this technology automatically acquires the drug doses administered by the clinician and shows the drug dosing history (bolus doses and infusion rates), the predicted drug concentrations at the site of action (past, present and future) and the predicted drug effects including sedation, analgesia and neuromuscular blockade.(57)

Although it is too early to predict what role this technology may play in determining a rational anesthetic dosage strategy, preliminary evidence suggests that it might be well received by clinicians. It is conceivable that in the future a real-time display of the predicted pharmacokinetics and pharmacodynamics of anesthetic drugs might be found alongside the traditional physiologic vital sign monitors.

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