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Lipid Solubility, Pharmacokinetics, and the EEG: Are You Better Off Today Than You Were Four Years Ago?

THERE ARE SEVERAL QUESTIONS raised by the study, "EEG Quantitation of Narcotic Effect: The Comparative Pharmacodynamics of Fentanyl and Alfentanil," published in this issue by Scott, Ponganis, and Stanski[1]: 1) Of what importance is hysteresis between drug concentrations in plasma and intensity of drug effect to the anesthesiologist? 2) Should the potency (and efficacy) of a drug be expressed in terms of dose or plasma concentration? 3) Is the electroencephalogram (EEG) a useful monitor of narcotic anesthetic depth in paralyzed patients?

An understanding of the importance of hysteresis between the rise and decline of drug concentrations in plasma and the increase and decrease of drug action requires a brief consideration of basic pharmacology. The overall relationship between dose and effect is dependent on two distinct sets of variables. Pharmacokinetic variables determine the relationship between dose and the drug concentrations achieved at the site(s) of drug action. Pharmacodynamic variables affect the relationship between drug concentration at a site of action and the intensity of the effect produced. It is not feasible to measure the concentration of a drug at its site of action. Under steady state conditions, the drug concentration at a site of action is proportional to its concentration in plasma. Under other conditions, drug concentrations at sites of action will tend to change in the same direction as the concentrations in plasma. The closeness of the correlation between plasma and tissue concentrations of drugs depends on the rate of equilibration of the free, un-ionized drug concentrations across membranes and among "binding" sites in plasma (protein, blood cells) and in tissue (proteins, lipids, receptors) (Fig. 1). Since ionization equillibria and most protein-binding reactions occur almost instantaneously, the rate of establishing an overall equilibrium (steady state) is dependent mainly on two factors: 1) the rate of drug penetration of membranes, and 2) the rate of drug delivery to the tissue relative to the capacity of the tissue to take up the drug.

In the case of the central nervous system, with its relatively high blood flow, the primary factor determining the rate of equilibration of drug concentrations and the rate of onset of drug action has been assumed to be the drug's lipid solubility. The more lipid soluble the drug, the more rapidly it penetrates membranes, the more rapid its onset of action, and presumably the closer the relationships 1) between plasma concentrations and brain concentrations,[2] and 2) between plasma concentrations and the intensity of drug effects.[3]

There are some subtle but important physiocochemical and pharmacokinetic differences between fentanyl and alfentanil. In terms of lipid solubility (expressed as the octanol–water partition coefficient) and other factors affecting the ability of drugs to enter the central nervous system (CNS), fentanyl would be expected to enter the CNS more rapidly and to have a faster onset of action than alfentanil (table 1). But Scott *et al.* have focused attention on another implication of lipid solubility. A drug with a very high lipid solubility probably is taken up in large quantities by lipids in the CNS. This partitioning into lipids limits the rate of rise of the free drug concentration in brain water and in equilibrium with narcotic receptor sites. In other words, there is a larger brain distribution volume* for fentanyl than for alfen-

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* A large brain distribution volume will be reflected in the brain–plasma partition coefficient, which is approximately 3 for fentanyl and 0.13 for alfentanil in rats.[2] (Michiels M, Hendriks R, Michielsen L, Heykants J, Lenaerts F: Plasma levels and tissue distribution of alfentanil (R39 209) in the male Wistar rat after a single intravenous dose of 0.16 mg/kg. Janssen Pharmaceutica, Preclinical Research Report R39 209/13, January 1981.)

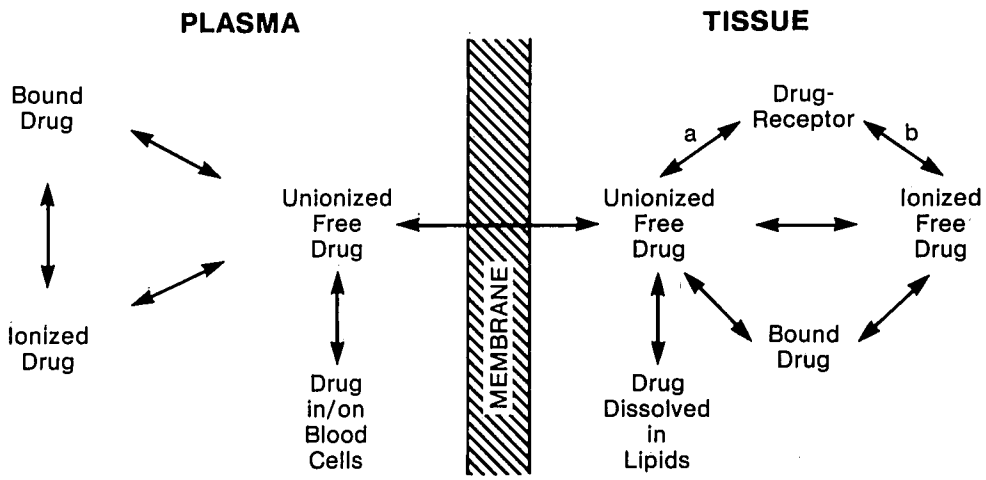

FIG. 1. Reversible processes affecting the total amount of drug on each side of a biological membrane permeable only to the un-ionized free form of a drug. Some binding of both the un-ionized and ionized forms may occur, but depending on the specific drug, one form usually predominates (the un-ionized form is preferentially bound in the case of narcotic analgesics). Similarly, at active receptor sites, one form of the drug usually is effective and the other is not (a or b). A very high affinity of the drug for pharmacologically inactive binding sites in tissues or a large partitioning of a lipophillic drug into lipids creates a sink for drug accumulation in tissue and limits the free drug concentration, which determines the number of drug-receptor complexes formed and the intensity of drug action. Extensive binding and partitioning in tissue creates a large tissue distribution volume.

tanil, which is less lipid soluble. Given equivalent delivery of both drugs in plasma to the CNS, it is going to take more time to deliver enough fentanyl to fill up its larger CNS distribution volume and to establish an adequate concentration of fentanyl at its receptor sites. The rate of drug delivery by plasma to the CNS becomes the rate-limiting step; both drugs have sufficient lipid solubility to enter the CNS rapidly.[5]

The hysteresis or delay in equilibration of drug concentrations (and effects) will be most apparent when there is a rapid change in plasma concentrations of a large magnitude relative to the concentration at the site of action. Such circumstances exist 1) immediately after a rapidly injected intravenous dose, 2) at the start of a rapid intravenous infusion, and 3) at the termination of a brief infusion. The latter two circumstances characterize the experimental protocol of Scott *et al.* (see fig. 3 in their article).

TABLE 1. Physiochemical Factors Affecting the Ability of Narcotic Analgesics to Enter the CNS[4,5]

Factor	Fentanyl	Alfentanil
pK_a	8.43	6.50
Percent unionized at *p*H 7.4	9.3	88.8
Octanol: water partition coefficients		
Un-ionized base	9,550	145
Ionized as salt	0.5	0.07
Apparent at *p*H 7.4	816	128
Free fraction (unbound drug) in plasma (%)	15.6	7.9
Relative potential to enter CNS (partition coefficient at *p*H 7.4 multiplied by the free fraction in plasma)	127	10

As expected, drug concentrations in plasma decreased rapidly after discontinuation of the infusion in the case of both fentanyl and alfentanil. Although a brief lag in the decrease of their effects would be anticipated, the apparent differences between alfentanil and fentanyl are not explained easily (see fig. 3 and 4 in Scott *et al.*). One would expect the concentration of lipid-soluble drugs readily able to exit the CNS to decrease simultaneously in plasma and brain water. If there were rapid dissociation of fentanyl and alfentanil from the opioid receptor sites, the intensity of effect also would be expected to decrease in parallel with the decrease in plasma concentrations. In fact, a close relationship between decreasing fentanyl concentrations in plasma and recovery from ventilatory depression has been reported.[3,6,7] The lack of parallelism at any time between recovery in the EEG (progressive increase in spectral edge frequency) and the decrease of either fentanyl or alfentanil concentrations in plasma is not expected. Are these discrepancies more apparent than real because of the use of an arithmetic rather than logarithmic scale for drug concentrations? The concentration *versus* effect relationships for most drugs, including the narcotic analgesics, are expressed most appropriately using a logarithmic scale for concentration.[3] Does the CNS lipid reservoir of the narcotics serve to maintain their con-

centrations in brain water at receptor sites, analgous to the persistence of drug levels in plasma maintained by their reuptake from fat?[2,8] A relatively low blood flow to fat explains the slow washout of drugs from fat. Is there a slow circulation (or redistribution) within the brain to explain a slow washout of the narcotics? Is there a difference between fentanyl and alfentanil in terms of the rates of their dissociation from opioid receptors? Leysen *et al.* could not quantitate the extremely rapid rate for alfentanil; fentanyl also had a very short dissociation half-time when compared with other narcotics.[9]

There are practical implications of these observations by Scott *et al.*, even though they cannot be understood or explained completely. First of all, it is possible to produce a more rapid onset of fentanyl effects by giving a larger intravenous dose. A larger dose produces a higher concentration of fentanyl in plasma; the quantity of fentanyl delivered per unit time to the CNS is increased; the CNS distribution volume is filled more rapidly. In fact, loss of consciousness was induced within 30 s following a 50 μg/kg intravenous dose administered within 20 s.[10] This dose is much larger than that required to produce unconsciousness if one is willing to wait until the peak effect occurs.

Secondly, as pointed out by Scott *et al.*, the peak effects of a small supplemental dose of fentanyl will occur later than after a comparable dose of alfentanil. As a result, it is necessary to give the supplemental dose of fentanyl earlier in anticipation of increased noxious stimulation or to use a larger dose (relative overdose leading to greater accumulation and more prolonged recovery) to prevent responses to stimulation. This also may mean that it will be more difficult with fentanyl to control sympathetic and hemodynamic responses to noxious stimulation once they occur.[11] All of this suggests that it may be easier to titrate the dose of alfentanil to the desired degree of effect, thereby minimizing its accumulation and the duration of its recovery phase.[12–14]

Third, the existence of hysteresis further complicates attempts to correlate drug concentrations in plasma with the intensity of drug effects, and it makes the comparison of investigations based on single or intermittent intravenous injections more difficult, if not virtually impossible. Is it not time to demand that the same experimental criteria be applied to intravenous anesthetics as are applied to studies of the inhalational anesthetics? In the case of the latter, acceptance of the results of the study necessitates that the investigator demonstrate either 1) the continuous administration of a constant inspired concentration of the anesthetic for a period of time sufficient to create a relatively steady vapor tension in the blood and brain, or, preferably, 2) the measurement of a stable concentration (partial pressure) of the vapor in end-tidal (alveolar) gas or in blood during the periods of measurements of anesthetic actions. Infusion schemes based on average pharmacokinetic values can produce a relatively stable drug concentration in plasma during periods of measurements, although the investigator may not be able to verify the stability and the actual drug concentrations until after the experiment.[15]

Fourth, hysteresis has to be taken into account in the interpretation of "acute tolerance," based on observations of recovery at higher plasma levels of the drug than those measured at the onset of the effect.[16] The degree of tolerance may be underestimated.

Should the potency of intravenous anesthetics be expressed in terms of dose or plasma concentration? It is now customary to express the potency of an inhalational anesthetic in terms of MAC, the minimum alveolar concentration, which in reality represents the effective concentration in 50% of the subjects tested (EC50).[17] The pharmacokinetic principles and behavior of drugs administered by inhalation and by intravenous infusion are the same, and the brain uptake curves of lipid-soluble intravenous and inhalation drugs are very similar during their continuous administration at a constant dose-rate. The use of MAC has greatly improved the accuracy and precision of comparisons of inhalational anesthetics. Why not specify the potency of intravenous drugs in terms of their EC_{50}, the median effect concentration in plasma that produces the intended effect in one-half of the subjects tested?[4]

Certainly it is desirable to know the EC50 or EC95 for purposes of designing drug administration schemes.[15,18] Certainly it is better to study and to compare drugs at stable concentrations (*vide supra*).[15] Certainly it is easier to distinguish between kinetic and dynamic factors as causes of variability in the response to a given drug dose if the drug concentrations in plasma are known. All of these are desirable benefits of pursuing clinical and basic investigations on this basis, and I think that we in anesthesia inevitably are headed in this direction.

But for now there are some problems to be solved before it is reasonable to insist on plasma concentration data for all studies of intravenous anesthetics and other drugs. First and foremost, it is not yet possible to measure plasma concentrations of intravenous drugs on line in a manner equivalent to end-tidal gas monitoring of inhalation anesthetics by infrared or mass spectrometry. There is a realistic possibility of developing rapid assays to be performed intermittently in the operating

† The median effective concentration for a population of subjects, EC50, is to be distinguished from the concentration that produces one-half the maximal response in a single individual (*e.g.*, IC_{50} as defined by Scott *et al.*).

room anesthesia laboratory.[19] A second hurdle for many drugs is distinguishing between the total drug in plasma or blood and the pharmacologically active form of the drug that is free and in equilibrium across membranes and with drug receptors. This is particularly important under clinical conditions in which drug binding to plasma proteins is subject to sudden and substantial changes. For example, the initiation of extracorporeal circulation during a constant infusion of alfentanil immediately results in a 50% reduction in the total plasma concentration of alfentanil, but the level of the free drug remains virtually unchanged.‡ Many other factors routinely altered by anesthetic and surgical conditions affect drug binding to plasma protein.[20] Finally, there are the questions of cost-effectiveness and whether or not computer simulations based on limited fundamental pharmacokinetic data reliably can serve to produce stable and predictably adjustable drug concentrations within the desired range.[21],§ The answers to these questions will come with further experience, based on the actual measurement of drug concentrations and their correlation with pharmacodynamics, analogous to the study by Scott *et al.*

The potential usefulness of the EEG as a monitor of anesthetic depth, especially for narcotic anesthesia in paralyzed patients, is demonstrated in the study by Scott *et al.* It clearly filled their need for a continuous measure of narcotic action in order to demonstrate the phenomenon of hysteresis. But can the EEG serve as a guide to anesthetic dosage and to detect awareness in the patient during surgical operations? The potential problems of awareness recently were considered in this journal.[22,23] The following must be emphasized: 1) amnesia is not equivalent to unconsciousness and does not prevent the consequences of awareness and anxiety during operations[22]; 2) the absence of sympathetic and hemodynamic signs of light anesthesia does *not* mean that the patient is asleep or unconscious[13,14]; muscular paralysis removes the somatic signs of arousal and consciousness, the only reliable signs available to date. In fact, by limiting the use of muscle relaxants to specific indications and administering the minimum doses required only for as long as the indication exists during the operation, we routinely observe patients who have received more than the usually recommended doses of narcotic, hypnotic, and premedicant drugs open their eyes in response to verbal commands or to noxious stimulation at times when there is no other indication of light or inadequate anesthesia.¶

In the study by Scott *et al.*, the subjects were not premedicated, and sleep occurred before the shift of the frequency spectral edge had reached the end-point set by the investigators. This is suggestive of a correlation between the EEG frequency slowing and the induction of sleep, but the correlation has not yet been made. And there are reasons to hold reservations about the reliability of the EEG as a gauge of anesthetic depth under surgical conditions in which the anesthesiologist attempts to match the dose of the narcotic anesthetic to the intensity of the noxious stimulation.

First, the average doses of fentanyl (8.5 μg/kg) and of alfentanil (85 μg/kg) were lower than those usually reported for the induction of anesthesia and the suppression of responses to tracheal intubation. In the case of alfentanil, the ED_{50} for induction of anesthesia in unpremedicated healthy adults averaged 111–119 μg/kg.[24] It should be noted that larger rather than smaller doses would be expected to be required with the constant infusion administered over 4–6 min by Scott *et al.*, when compared with the intravenous bolus doses administered in 10 s by the other investigators. Fentanyl doses between 20 and 50 μg/kg have been recommended for induction of anesthesia, but these may be larger than necessary in order to speed the onset of unconsciousness (*vide supra*). It is also interesting to note that sufentanil doses much lower than those recommended for the induction of anesthesia produced EEG slowing.[25]

Second, the concentrations of fentanyl (6.9 ± 1.5 SD ng/ml) associated with EEG slowing in the unpremedicated healthy patients of Scott *et al.* were considerably lower than those required to maintain hemodynamic stability and unconsciousness in heavily premedicated cardiac surgical patients before and after cardiopulmonary bypass (>18 ng/ml).[18,26] The argument that Scott's patients were not subjected to noxious stimulation (which increases narcotic anesthetic requirements[14] is countered to some extent by the observations of Sebel *et al.* in surgical patients given a single intravenous dose of fentanyl (30–70 μg/kg).[27] The EEG slowing produced by these doses showed little or no recovery over time, even though the plasma concentrations of fentanyl declined progressively to less than 10 ng/ml and despite the superimposition of intermittent noxious stimulation

‡ Hug CC Jr, Burm AGL, de Lange S, Hermans G: Alfentanil pharmacokinetics and protein binding before and after cardiopulmonary bypass (CPB). Abstracts, 5th Annual Meeting Society of Cardiovascular Anesthesiologists, San Diego, California, April 24–27, 1983, pp 76–77.

§ Alvis JM, Reves JG, Govier AV, Menkhaus PG, Henling CE, Spain JA, Bradley E: Computer assisted continuous infusions of fentanyl during cardiac anesthesia: Comparison with a manual model. Submitted for publication.

¶ Hug CC Jr, Moldenhauer CC, unpublished observations).

of the surgical operation.[27,28] Fentanyl concentrations of less than 10 ng/ml of plasma are associated with patient responsiveness to commands, even after substantial premedication.[18]

In the case of alfentanil, the EC50 for EEG slowing was 520 ± 163 SD ng/ml of plasma. This slightly exceeds the alfentanil concentrations required to supplement 66% nitrous oxide in order to maintain adequate anesthesia in healthy young women undergoing abdominal surgery,[14] but it is substantially lower than the concentrations of alfentanil alone (after lorazepam premedication) required to maintain hemodynamic stability and unconsciousness during cardiac surgery.[29] In the unpremedicated dog, maximal EEG changes and suppression of somatosensory evoked responses were produced by alfentanil concentrations of approximately 100 ng/ml of plasma; concentrations exceeding 1000 ng/ml produced no further modification of the EEG.**

All of this is intended to sound a note of caution in accepting the EEG during narcotic-induced anesthesia as a reliable guide to the adequacy of anesthetic depth and as assurance of the production and maintenance of unconsciousness. The real demonstration necessary to remove these reservations remains to be done. It is important to do so, because the practicing anesthesiologist needs a reliable guide to the adequacy of anesthetic depth and unconsciousness in the paralyzed patient.[22,23]

It often is said that a very good scientific study proves or disproves a hypothesis and at the same time raises new questions to be answered as it extends our understanding. The study by Scott *et al.* qualifies as a very good one because 1) it demonstrates the existence of hysteresis, 2) it suggests its importance in clinical practice, 3) it raises important questions to be answered, and 4) it provides insight into the means of answering them.

CARL C. HUG, JR., M.D., PH.D.
Professor of Anesthesiology and Pharmacology
Director of Cardiothoracic Anesthesia
Department of Anesthesiology
Emory University and Clinic
Atlanta, Georgia 30322

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The Health of Operating Room Personnel

BECAUSE OF DISAGREEMENT among knowledgeable investigators regarding the validity and interpretation of published reports, the American Society of Anesthesiologists (ASA) commissioned Dr. Theodore Colton to head a group of epidemiologists–biostatisticians (Epistat Associates) to evaluate the epidemiologic surveys that had examined the putative health hazards attributed to exposure to waste anesthetic gases in the operating room. The Special Article, which appears in this issue, entitled "Health Experiences of Operating Room Personnel," by Buring *et al.*[1] is the abridged version of the group's report,* the full version of which was submitted to the ASA in 1982. Although the effect of operating room employment on worker's health is less of a burning issue today than in was in the 1970s, it is still the subject of much interest and controversy. Publication of this article makes the conclusions of Colton, Buring and associates readily available to anesthesiologists and other interested parties.

Buring *et al.*[1] used the measurement of relative risk to describe the strength of the association between operating room work and various disease outcomes. Relative risk is defined as the ratio of the rate of disease among an exposed group compared with a control population. Results from each study are treated as individual data points that, after weighting in proportion to their sample size, are pooled. Summary relative risks and 95% confidence limits then are calculated. When the range of the 95% confidence limits does not include 1.0, the relative risk is significantly different at the $P < 0.05$ level.

Based on this analysis, the authors concluded that the adverse health outcome for which the evidence was most extensive and reasonably consistent was spontaneous abortion for pregnant physicians and nurses working in the operating room. The relative risk for this condition was 1.3, representing a 30% increase in risk when compared with the control population. Data for the other reproductive outcome they examined, congenital anomalies, were less conclusive. The overall relative risk for this condition was 1.2, with the difference statistically significant for women physicians but not for nurses. Among nonreproductive outcomes, there was an increase in relative risk of liver disease (men, 1.6; women, 1.5), kidney disease among women (1.3), and cervical cancer (2.8).

Having pointed out what appear to be significant health hazards, Buring *et al.*[1] emphasize the many limitations of their conclusions. Of the 17 articles that they considered relevant to the issue, they rejected nine because of deficiencies in study design, such as the use of noncomparable control groups. Two additional studies of dentists and their chairside assistants were eliminated because work practices and waste anesthetic gas exposure of these populations was markedly different than that of operating room personnel. Thus, Buring *et al.*[1] were left with only six studies to analyze.[2–7] Even these, they noted, had significant limitations:

> ". . . including low response rates among potential study subjects and inadequate information on non-respondents; lack of details on amount, duration and nature of exposure; lack of confirmation and verification of reported adverse outcomes; lack of information on many possible confounding variables; the possibility of response bias both through the nature of the questionnaires or the respondents' prior beliefs regarding adverse effects; and the possibility of biased recall of events and exposures which occurred in years past."

Several of these shortcomings deserve additional discussion. Perhaps the most serious deficiency, present in all but one of the studies[2] examined, was the absence of verification of the medical outcomes reported in the questionnaires. It is well known among epidemiologists[3]

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* Colton T: Evaluation of the epidemiologic evidence for occupational hazards of anesthetic gases. American Society of Anesthesiologists, Park Ridge, Illinois 60068, January 21, 1982.