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PHARMACODYNAMIC MODELING OF ANESTHETIC EEG DRUG EFFECTS

Donald R. Stanski

Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305, and Palo Alto Veterans Administration Medical Center, Palo Alto, California 94304

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INTRODUCTION

The integration of pharmacokinetics and pharmacodynamics using pharmacodynamic modeling concepts has been advanced by investigative efforts with anesthetic drugs. By simultaneously measuring the drug plasma concentration and the drug effect, it becomes possible to dissect the dose vs response relationship into its pharmacokinetic and pharmacodynamic components (Figure 1). There are several reasons why anesthetic drugs are ideal compounds for understanding integration of pharmacokinetics and pharmacodynamics. These include the common use of intravenous (IV) or pulmonary administration, the relatively rapid blood:biophase equilibration that is necessary for an anesthetic drug to be clinically useful, the rapid dissipation of drug effect from a combination of redistribution and elimination mechanisms, and finally the relatively profound degree of drug effect that anesthetic drugs create. Drug effect that is relatively intense makes pharmacodynamic measurement and quantitation an easier task. Finally, it has been possible to develop "surrogate" measures of drug effect with many anesthetic drugs. Surrogate drug effects are secondary drug-induced measurable changes of body physi-

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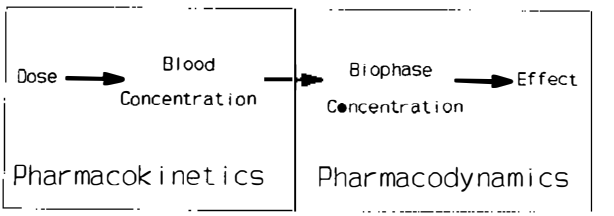

Figure 1 The dose vs drug response relationship divided into the pharmacokinetic and pharmacodynamic components.

ology. Surrogate drug effects become very useful if the primary drug effect is difficult to measure. The clinical meaning or interpretation of the surrogate drug effect relative to clinically relevant measures of drug effect may not be completely established.

The main clinical focus of anesthetic practice is to produce adequate central nervous system depression (CNS) to allow surgical procedures. Clinical measurement of anesthetic depth has not been established to the same degree of sophistication that exists for measurement of respiratory or cardiovascular function (1). The utility of the electroencephalogram (EEG) as a "surrogate measure" of CNS drug effect is developed in this article. The EEG is a continuous, noninvasive measure of cerebral physiology that is markedly altered by anesthetic drugs (1, 2). The EEG has been developed as a useful surrogate measure of CNS drug effect given that anesthetic depth or degree of CNS depression is extremely difficult to measure clinically. In humans pharmacodynamic modeling of EEG drug effects has elucidated many aspects of the clinical pharmacology of anesthetic drugs that are therapeutically relevant and clinically important. In animal research, specifically in the chronically instrumented rodent, the use of the EEG has significantly advanced our understanding of the mechanistic pharmacological relationships between in vivo and in vitro pharmacology.

PHARMACODYNAMIC MODELING OF HUMAN EEG ANESTHETIC DRUG EFFECTS

Anesthetic Drug Raw EEG Effects

Pharmacodynamic modeling of the EEG as a measure of CNS drug effect has been performed with three classes of intravenously administered anesthetic drugs: intravenous hypnotics that are used to induce anesthesia (i.e. thiopental, propofol); opiates that are used for analgesia and anesthesia (i.e. fentanyl, sufentanil, alfentanil); and benzodiazepines that are used for sedative and amnestic effects (i.e. midazolam, diazepam). The changes in EEG morphology are profound and also different for each class of drug. For intravenous

anesthetics like thiopental (Figure 2), the EEG changes from the awake, low-voltage, high-frequency signal to an initial activation with an increase in frequency and voltage (3, 4). At this EEG state, loss of consciousness occurs. With increasing doses, the EEG progressively slows with a further decrease of EEG voltage. Finally, at deep barbiturate anesthesia, bursts of EEG occur between periods of electrical silence, (burst-suppression). A completely isoelectric signal can be achieved. The opiates, as represented by fentanyl (Figure 2), cause progressive slowing in the EEG frequency with an increase in the EEG voltage (5). The maximal EEG change one can achieve is a low-frequency, high-voltage δ (0.5 to 4 Hz) wave pattern. The clinical opiate effects occur progressively with the EEG changes: initially analgesia with early EEG slowing, then respiratory depression, and finally profound narcosis, complete respiratory depression and clinical unconsciousness when the EEG δ wave state occurs. The benzodiazepines, as represented by midazolam (Figure 3), cause an increase in the EEG voltage with a specific activation of the EEG in the high frequency, β range (14 to 20 Hz) (6, 7). Clinically, sedation progresses to unconsciousness with these EEG changes.

The EEG changes displayed in Figures 2 and 3 are relatively consistent within each drug class but different between drug classes. The three different drug classes cause CNS depression by pharmacological mechanisms that differ greatly, ranging from specific opiate μ receptors to the GABA-benzodiazepine receptor complex for the benzodiazepines. It has not been possible to identify a unifying EEG pattern or morphology that represents the

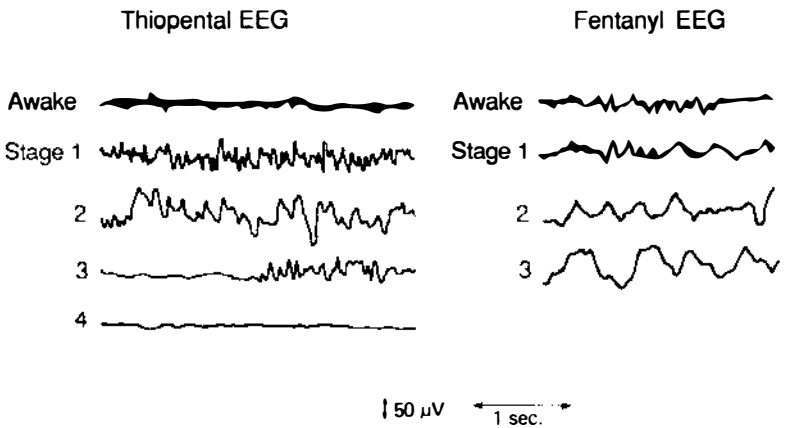

Figure 2 The progressive changes in the EEG with increasing plasma concentrations of thiopental and fentanyl. In stage 1, the frequency and amplitude of waveforms increase for thiopental. In stage 2, both drugs produce a decrease in frequency and an increase in amplitude. In stage 3, thiopental produced burst-suppression and finally an isoelectric stage 4. Fentanyl has its maximal EEG effect in stage 3 with the creation of large, slow δ waves. (Reproduced from Ref. 1.)

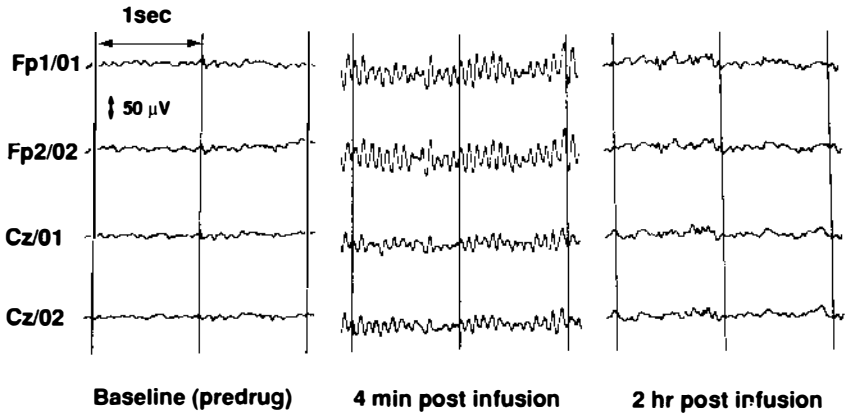

Figure 3 The effect of midazolam on four channels of the EEG. The first panel shows the baseline EEG. In the center panel intravenous administration of midazolam 15 mg over 5 min has increased the EEG amplitude and frequency to a maximum. The third panel shows the nearly complete return of EEG effect to baseline. (Reproduced from Ref. 6.)

"anesthetic state" in a generic sense, possibly because the clinical anesthetic state can occur from very diverse pharmacological mechanisms. For the benzodiazepines it has been possible to demonstrate clear relationships between benzodiazepine receptor pharmacological activity and the measured EEG response. This data is presented later. The correlation of the EEG signal to traditional measures of anesthetic depth are limited in part because of our inability to accurately define and measure clinical depth of anesthesia in humans.

Quantitating EEG Drug Effects

Having presented the anesthetic-induced changes in the raw EEG signal it becomes necessary to use waveform analysis to quantitate a pharmacological response. Figure 4 displays two waveform analysis techniques that have been applied to the anesthetic drugs. Fast Fourier transform (FFT) analysis takes digitized 3- to 5-second epochs of EEG signal and breaks the the EEG signal down into the fundamental frequency and amplitude data. FFT is used to quantitate the degree of voltage in defined frequency bins, usually at 0.5 Hz intervals from 0.5 to 30 Hz (8). The histogram of frequency vs voltage is used to generate a power spectrum for each digitized epoch from which univariate, summary descriptors are chosen. Parameters like the spectral edge (frequency below which 95th percentile of the EEG power exists) or the median frequency (50th percentile of EEG power) have been described as univariate measures of the EEG drug effect.

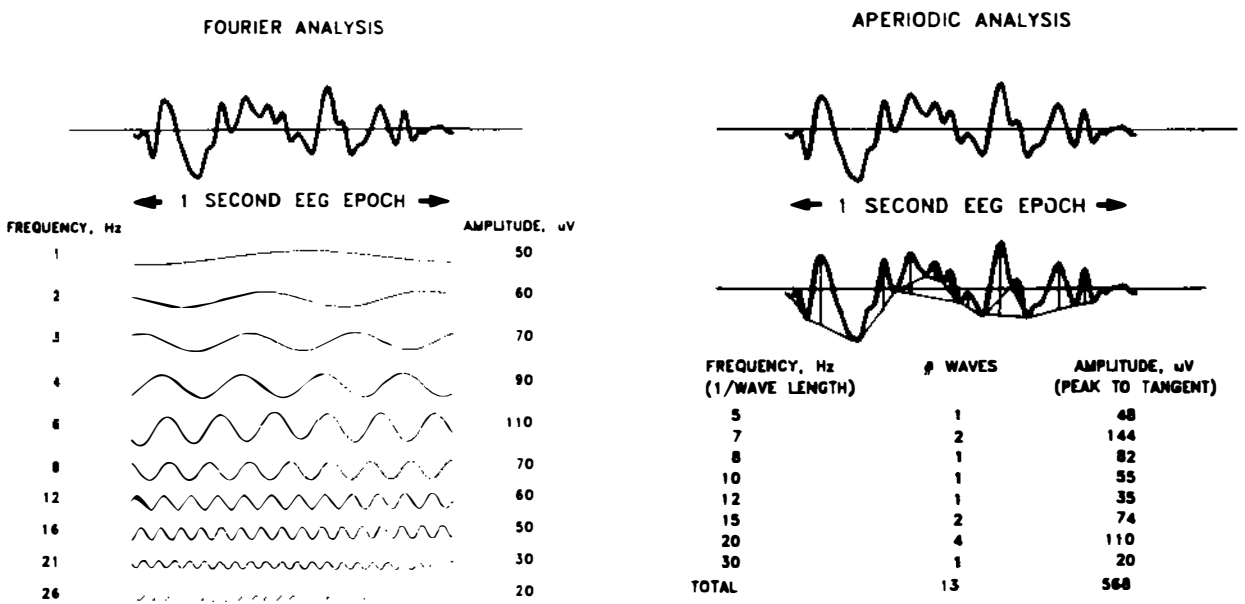

Figure 4 Schematic comparison of two different methods of analyzing EEG waveforms. The fast Fourier transform takes EEG epochs and quantitates the EEG amplitude in defined frequency ranges. The aperiodic analysis takes each "wave" or electrical event and characterizes the frequency and amplitude. Each frequency range has an associated number of waves and EEG amplitudes. (Reproduced from Ref. 6.)

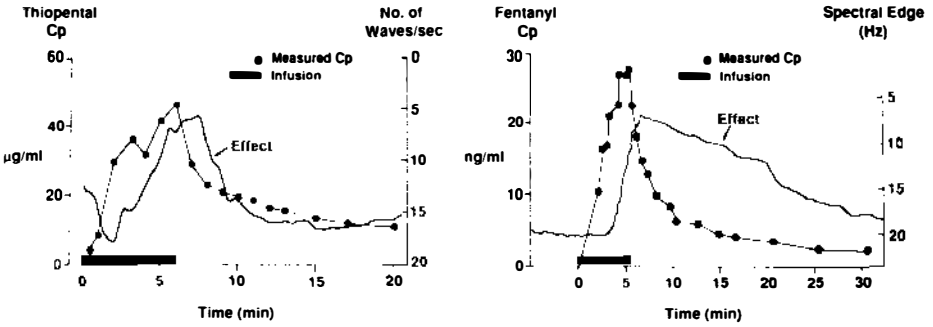

Figure 5 The relationship between thiopental and fentanyl plasma concentration and EEG response. Aperiodic waveform analysis was used to estimate the number of waves/sec for thiopental and the FFT analysis was used to estimate the spectral edge (frequency at which 95% of the EEG power exists) for fentanyl. The drug infusion time is indicated with the solid bar. Note the biphasic effect of thiopental on the EEG and the lag or hysteresis between drug plasma concentration and EEG effect for each drug. (Reproduced from Ref. 1.)

Aperiodic waveform analysis is a stochastic technique that first digitizes the EEG signal and then uses software algorithms to characterize each EEG wave or electrical event (9). Each electrical event is first assigned a frequency and voltage. For each digitized epoch an array of frequency bins with associated number of waves and wave voltages is generated. Thus, like FFT analysis, aperiodic analysis characterizes the EEG with a frequency spectrum. The aperiodic waveform analysis is especially robust when isoelectric EEG signal occurs. Fast Fourier transform analysis is unable to accurately characterize isoelectric EEG. To date, the choice of EEG waveform analysis and parameterization have been empirical processes geared toward deriving a continuous EEG effect vs time relationship that is appropriate as a measure of pharmacological effect.

Figure 5 displays the time course of thiopental and fentanyl drug plasma concentration and of the EEG effect parameter for the raw EEG effects displayed in Figure 2. In each case the anesthetic drug was infused for 3 to 10 min until a defined maximal EEG effect was seen. Arterial plasma concentrations were measured during and after the drug infusion while the EEG was being recorded. The study paradigm is one of achieving the maximal drug effect in a short period of time (5 to 10 min) then allowing redistribution and elimination of the drug to cause the drug effect to return to the awake, baseline state. Thus, one captures the drug concentration vs drug effect relationship, albeit under nonsteady-state conditions where drug plasma concentration and drug effect are constantly changing. This study paradigm is used for the pharmacodynamic modeling to be presented later. Performing a

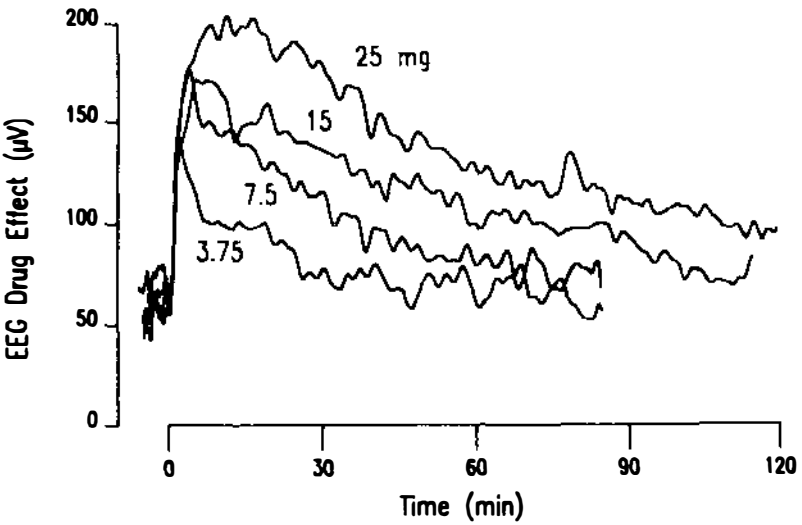

Figure 6 The time vs EEG effect curve for midazolam using the total voltage from 0 to 30 Hz. as obtained by aperiodic waveform analysis. Four different doses of midazolam were given to the same subject on four different occasions. Time zero represents the start of the infusion which was 5 mg/min in each study. Peak effects for midazolam doses of 7.5 to 25 mg were achieved and recovery of drug effect was proportional to the administered dose. (Reproduced from Ref. 6.)

true steady-state experiment in which constant plasma concentrations are achieved with a constant drug effect is frequently clinically impossible given the relatively slow elimination kinetics of most drugs.

For thiopental and midazolam, aperiodic waveform analysis was used to estimate the number of waves/second and the total voltage/second, respectively. For fentanyl FFT analysis was used to estimate the spectral edge. In each case the EEG drug-effect parameter behaves in an expected manner, with increasing drug effect occurring with increasing drug-plasma concentrations. For thiopental, a biphasic EEG drug effect is present with an initial increase of the number of waves/second with the EEG activation then progressive slowing of the number of waves. A distinct lag or disequilibrium (hysteresis) between drug concentration and drug effect is visible for each drug. For midazolam, plasma concentrations are not displayed in Figure 6, rather the EEG response to increasing doses of midazolam to the same individual on separate occasions is indicated. This demonstrates that the time to recovery is proportional to dose, yet the rate of recovery is constant and independent of dose. The peak effect is proportional to the administered dose with a plateau of drug effect occurring at increasing doses. This data demonstrates that the

EEG amplitude as obtained from aperiodic analysis is a useful measure of midazolam EEG drug effect.

Pharmacodynamic Modeling Concepts

When the anesthetic drug plasma concentration and EEG drug effect are known, pharmacodynamic modeling techniques can be applied to characterize the equilibration delay between the plasma concentration and drug effect and predict the steady-state drug concentration vs drug-effect relationship. These concepts have previously been reviewed in detail and are thus only briefly reviewed here (10). Figure 7 displays the two modeling approaches that have been used for anesthetic drug pharmacodynamics. Figure 7A indicates the parametric modeling approach that defines a separate effect compartment or biophase that is characterized by a first order rate constant called K_{eo} (11). The biophase concentrations are then related to the drug effect using an appropriate pharmacodynamic model that characterized the underlying biophase concentration vs effect relationship. This could be a linear, log linear, E_{max}, or a sigmoid E_{max} mathematical relationship. The parametric pharmacodynamic modeling requires definition of the effect compartment and the pharmacodynamic model prior to the data characterization.

If the pharmacodynamic model is not correctly specified, error can occur in the pharmacodynamic parameter estimates. A more robust approach is the semiparametric pharmacodynamic modeling indicated in Figure 7B; 12,13). This concept allows one to remove the disequilibrium between the plasma concentration and drug effect using an effect compartment and a first order rate constant (K_{eo}) to characterize the plasma concentration vs drug effect equilibration. A mathematical technique using numerical convolution estimates the rate constant of drug-effect equilibration (12). After the rate constant of equilibration is estimated, the predicted biophase drug concentration vs drug effect can be plotted. The biophase concentrations would predict the steady-state plasma concentration vs drug effect relationship from data gathered under nonsteady-state conditions. The appropriate pharmacodynamic model can then be chosen to characterize the concentration vs response relationship. The semiparametric modeling concept of Figure 7B appears to be a more robust approach with a decreased risk of pharmacodynamic model misspecification confounding the results.

Pharmacodynamic modeling of a sigmoid E_{max} and the effect compartment concept allows estimation of the following parameters: The half-time of equilibration of the plasma concentration and drug effect ($T_{1/2}$ K_{eo}), the maximal drug effect (E_{max}), the steady-state plasma concentration that results in 50% of the maximal drug effect (CP_{50}) and the slope of the plasma concentration vs drug effect relationship. The $T_{1/2}$ K_{eo} will be governed by the perfusion to the site of drug action, the diffusion into the biophase, the

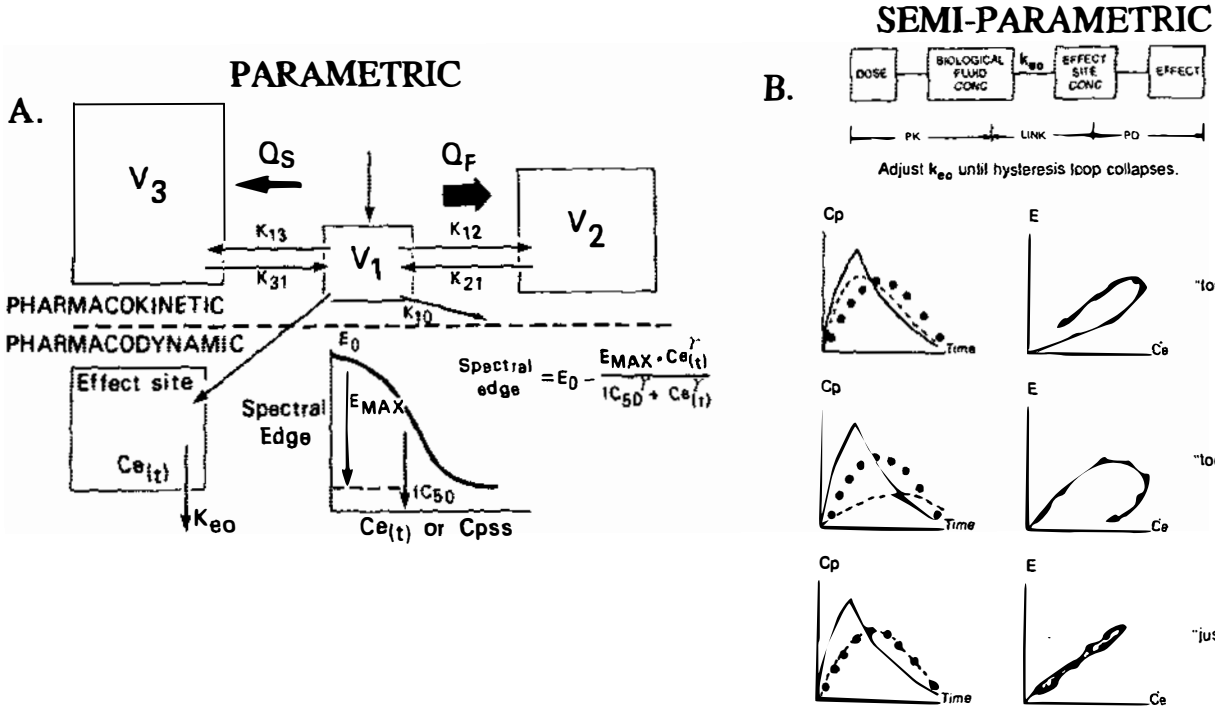

Figure 7 Two conceptual approaches to pharmacodynamic modeling. The parametric approach is a combined pharmacokinetic and pharmacodynamic model. The effect compartment is linked to the central compartment with a first order rate constant, K_{eo}. The drug effect (spectral edge) is related to the effect compartment concentrations using a sigmoid E_{max} pharmacodynamic model. The semiparametric approach does not assume a pharmacokinetic or pharmacodynamic model. An interactive algorithm is used to estimate a K_{eo} rate constant that removes the hysteresis between drug plasma concentration and drug effect. In panel B, the solid line is the measured plasma concentration, the solid dots the measured drug effect and the dashed line the predicted biophase concentrations (Ce) estimated from a K_{eo} value. (Reproduced from Ref. 7, 14.)

partitioning of drug at the site of action, the time necessary to interact with receptors/proteins to create the drug effect, and finally the time necessary to transduce receptor events into a measurable drug effect. The CP_{50} is a pharmacodynamic measure of organ sensitivity to the drug when the pharmacokinetic considerations present in an ED_{50} or dose that results in 50% of the drug effect are removed.

Application to IV Anesthetics, Opiates and Benzodiazepines

The development of continuous, noninvasive EEG methods to measure anesthetic drug effects has enabled this methodology to be used to examine relevant clinical pharmacology issues. Examples for each of the anesthetic drug classes are presented.

INTRAVENOUS ANESTHETICS With increasing age the dose of thiopental needed for induction of anesthesia decreases. Homer & Stanski quantitated the mechanism of this age-related change of pharmacological requirement by the use of EEG waveform analysis (14). Thiopental was infused at a rate of 75 to 100 mg/min in young and old surgical patients until 1–3 seconds of isoelectric EEG was present and the thiopental dose requirement could therefore be calculated. Arterial plasma concentrations were obtained to measure thiopental plasma concentrations and the EEG was recorded and processed with waveform analysis as described previously. Figure 8A displays the thiopental dose requirement in young and elderly patients. The thiopental dose requirement decreased approximately 70% from age 20 years to 80 years. Pharmacodynamic modeling allowed estimation of the thiopental CP_{50} or steady-state thiopental plasma concentration that resulted in 50% of the EEG slowing, a measure of CNS sensitivity to thiopental. Figure 8B demonstrates that CNS sensitivity to thiopental does not change with increasing age. Pharmacokinetic analysis demonstrated that the rate of thiopental distribution to tissues decreases with age such that the same dose given to an elderly patient results in higher thiopental plasma concentrations relative to a younger patient (15). An age-related decline of cardiac output and altered regional blood flow may explain this pharmacokinetic finding. Similar pharmacokinetic mechanisms that alter distribution phase disposition with increasing age have been obtained with propofol and etomidate (16, 17). These findings were unexpected since CNS sensitivity to the potent inhalational anesthetics increases with increasing age (18), which suggests an age-related pharmacodynamic mechanism for inhalational anesthetics.

Pharmacokinetic and pharmacodynamic modeling has been used to demonstrate that heavy alcohol intake does not appear to increase thiopental anesthetic requirement (19) and that acute tolerance to thiopental's EEG effects does not occur (3). Hung and colleagues have characterized the relation-

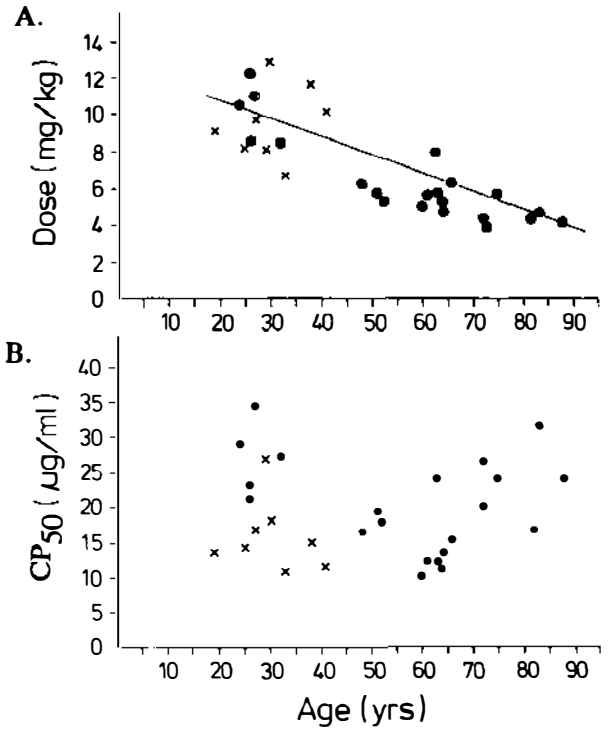

Figure 8 The effect of age on thiopental EEG dose requirement (panel A) and brain sensitivity or CP_{50}, thiopental plasma concentration that is needed to achieve 50% of the decrease in EEG frequency (panel B). With increasing age, thiopental dose requirement decreases but there is no change in brain responsiveness. Circles present surgical patients while the X represent volunteer subjects. (Reproduced from Ref. 14.)

ship between thiopental clinical depth of anesthesia and EEG changes (20). Loss of consciousness occurs at the peak of EEG activation (15–20 EEG waves/sec) whereas an isoelectric EEG (1–3 waves/sec) is required to prevent movement response to endotracheal intubation.

OPIATES Pharmacodynamic modeling of the EEG response has been important in understanding the comparative clinical pharmacology of three commonly used opiates in clinical practice: fentanyl, alfentanil, and sufentanil. Clinical studies have suggested that alfentanil has a more rapid onset and dissipation of effect relative to fentanyl. The shorter duration of effect was initially attributed to the shorter terminal elimination half-life (1.6 vs 5.9 hr). Scott and colleagues characterized the fentanyl/alfentanil plasma concentration/spectral edge relationship (5). Fentanyl and alfentanil were infused into unpremedicated surgical patients until maximal EEG changes (δ waves)

were seen. Arterial plasma concentrations were measured and the EEG signal analyzed with FFT to generate the spectral edge vs time relationship. Figure 9A displays the plasma concentration and spectral edge vs time relationship for these opiates. A lag between fentanyl plasma concentration and spectral edge is clearly evident. The onset of EEG effect is delayed 3–5 min and the peak EEG effect is separated from the peak of the plasma concentration by a similar amount of time. Figure 9B displays similar data from a patient receiving an infusion of alfentanil. The spectral edge clearly tracks the plasma concentration more closely than fentanyl. Peak plasma concentration is associated with the peak EEG effect. Pharmacodynamic modeling demonstrated that the $T_{1/2}K_{eo}$ for fentanyl was 5 to 7 min while the value for alfentanil was only 1 to 2 min. The more rapid onset of alfentanil's effect was due to more rapid blood:brain equilibration. Bjorkman et al demonstrated that alfentanil has a 22-fold lower solubility in the rodent CNS, explaining the more rapid onset of opiate effect (21). Ebling et al (22) used computer simulations of the fentanyl and alfentanil dose/plasma concentration/spectral edge relationship to demonstrate that, after single intravenous bolus dosing, alfentanil recovery of opiate effect is more rapid due to the shorter blood:brain equilibration. Plasma concentration decay is similar for fentanyl and alfentanil while the biophase washout is distinctly more rapid for alfentanil relative to fentanyl.

Scott et al examined the comparative EEG pharmacodynamics of fentanyl and sufentanil. Sufentanil was introduced into clinical practice as an opiate approximately three times more potent than fentanyl and with a more rapid onset of drug effect. These investigators (23) found that the half-time of blood:brain equilibration time of sufentanil was identical to that of fentanyl (6.2 ± 2.8 vs 6.6 ± 1.7 min) and the onset of EEG opiate effect identical when equipotent doses are given. Pharmacodynamic modeling demonstrated that by examining the CP_{50} values, sufentanil was approximately 10 to 12 times more potent than fentanyl. The previously reported rapid onset of sufentanil relative to fentanyl arose from clinical research in which equipotent opiate doses were not used. By assuming only a threefold greater potency, effective overdosing with sufentanil occurred such that a more rapid onset of drug effect was seen relative to fentanyl. Traditional clinical measures of opiate effects (i.e. analgesia, respiratory depression) lack the resolution to accurately estimate onset of drug effect or the comparative potency.

BENZODIAZEPINES In 1987, midazolam was introduced into the United States as a water soluble benzodiazepine with more desirable clinical properties than diazepam when used intravenously for sedation. Midazolam had a shorter terminal elimination half-life of 2 to 3 hr vs 30 to 50 hr for diazepam. Midazolam was considered twice as potent as diazepam and produced a more

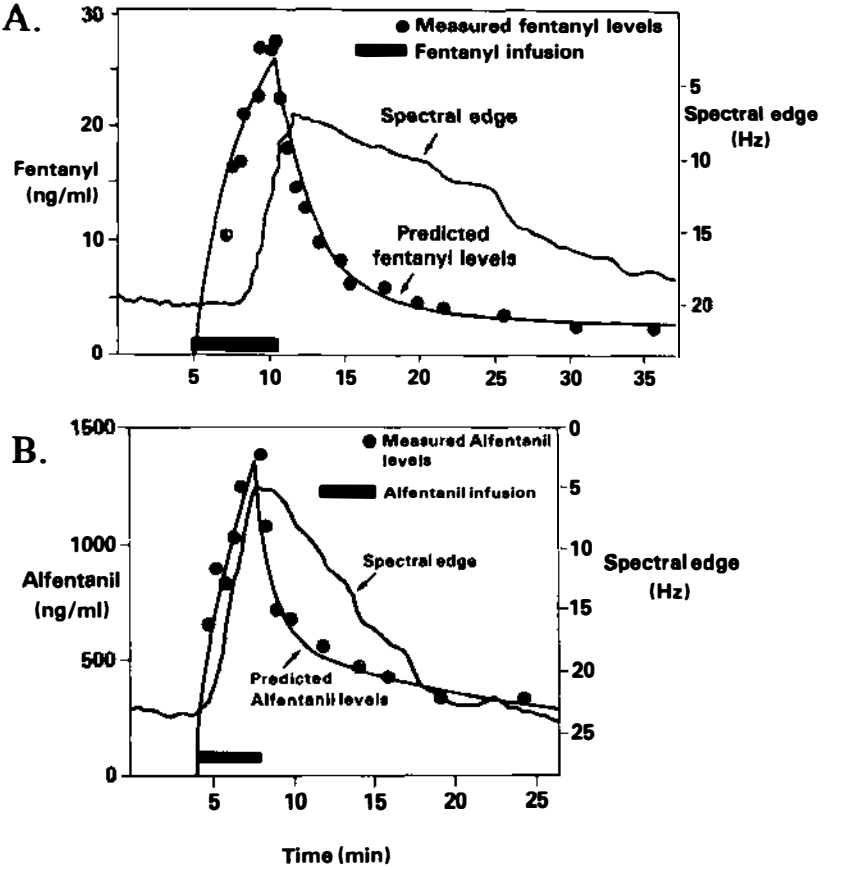

Figure 9 The fentanyl (panel A) and alfentanil (panel B) plasma concentration and EEG effect (spectral edge) vs time in two subjects during and after a brief infusion of each drug. Note the difference in equilibration between drug concentration and drug effect for the two opiates. (Reproduced from Ref. 5.)

rapid onset of sedation and shorter duration compared to diazepam. Soon after its release, instances of cardiac and respiratory arrests associated with the clinical use of midazolam were reported to the Food and Drug Administration department that monitors adverse drug reactions. Over 70 episodes of significant midazolam overdosage with major clinical consequences were reported (24).

After midazolam was approved by the FDA, Bührer et al determined its pharmacological effect by using aperiodic waveform analysis (See Figure 6). Comparative studies with diazepam and midazolam using the EEG as a measure of drug effect and pharmacokinetic/dynamic modeling demonstrated

that the CP_{50} of midazolam for EEG effects was approximately fivefold lower than diazepam and that the blood:brain equilibration was actually slower than diazepam (7). Figure 10 displays the predicted biophase concentrations of midazolam and diazepam vs the EEG drug effect in the same subject who received three different doses of each benzodiazepine. The semiparametric pharmacodynamic modeling approach was used to relate benzodiazepine plasma concentration to EEG drug effect. The maximal EEG effects are similar. However, midazolam is approximately 5 times more potent than diazepam when the CP_{50} values are examined. Greenblatt et al confirmed the fivefold difference in intrinsic potency of midazolam relative to diazepam by using a different EEG measure of benzodiazepine drug effect (25). Analogous to the sufentanil example raised earlier, traditional clinical investigations had failed to accurately characterize midazolam's clinical pharmacology.

The twofold greater midazolam dose potency relative to diazepam was a significant underestimation of the true pharmacological potency. Also, the slightly slower blood:brain equilibration time requires that one must wait longer to achieve midazolam's peak drug effect before additional drug is

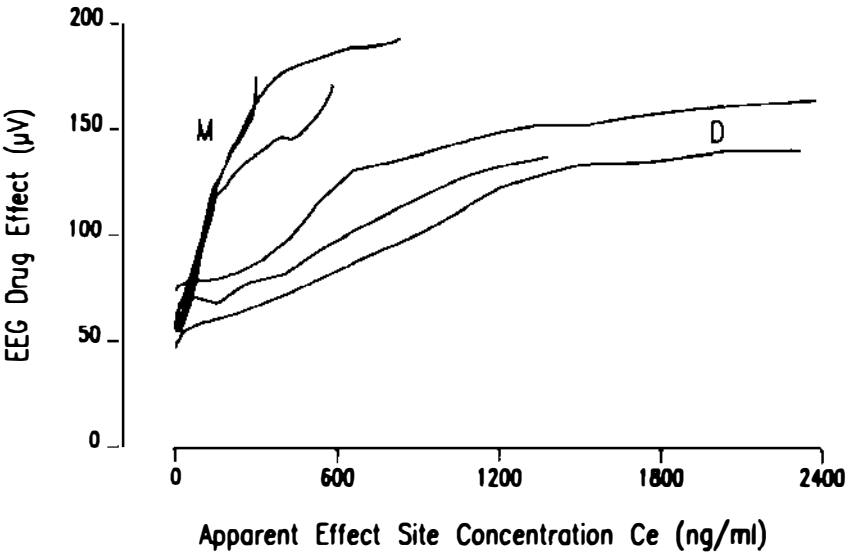

Figure 10 The EEG effect (total voltage from aperiodic waveform analysis) vs apparent effect site concentrations for three different doses of midazolam (M) and diazepam (D) in a single subject. Semiparametric pharmacodynamic modeling was used to remove the hysteresis between benzodiazepine plasma concentration and EEG effect allowing the prediction of the effect site concentrations. Maximal EEG effects were similar with the two drugs, but half of the maximal effect is markedly different, with fivefold lower concentrations needed for midazolam. (CP_{50} = 200 ng/ml) vs diazepam ($CP_{50} \cong$ 1000 ng/ml). (Reproduced from Ref. 7.)

given. When midazolam was released to United States physicians, less than optimal dosing guidelines and incomplete clinical pharmacological characterization of the drug resulted initially in a significant patient morbidity and mortality. Traditional study design and measurement of drug effect had failed to accurately characterize the onset characteristics of midazolam and the comparative potency relative to diazepam.

PHARMACODYNAMIC MODELING OF RODENT ANESTHETIC EEG DRUG EFFECTS

A chronically instrumented rodent model has been developed to examine anesthetic plasma concentration:EEG drug effect relationships. The rodent has chronically implanted electrodes for recording of the EEG, a chronically implanted venous catheter for drug administration, and a chronic arterial catheter for blood sampling to measure drug concentrations (26, 27). The chronic instrumentation allows awake, baseline control physiological data to be gathered after which anesthetic drugs can be administered to defined EEG endpoints. The ability to measure the awake, baseline EEG effect is an essential component of this research approach. The arterial catheter allows monitoring of hemodynamics and acid/base status via arterial blood gases. The significant parallelism between the human and rodent methodology should allow comparative humans-to-rodent pharmacology. Investigative efforts with this rodent model have been limited to the intravenous anesthetics and benzodiazepines.

Intravenous Anesthetics

Ebling et al examined the thiopental plasma concentration/EEG effect relationship by using aperiodic waveform analysis to derive the EEG parameter number of waves/sec (26). Thiopental was infused rapidly into the rodent to a defined EEG endpoint of 5 sec of isoelectric EEG. Arterial blood samples were collected for measurement of thiopental plasma concentrations and the EEG recorded. Semiparametric pharmacodynamic modeling was used to remove the disequilibrium between the plasma concentration and EEG effect. The $T_{1/2}K_{eo}$ was found to be 1.3 min, a similar value to that found in humans (14, 15). Figure 11B displays the thiopental effect compartment concentration vs EEG number of waves found in the rodent. A distinct biphasic concentration vs response relationship was found.

For comparison, Figure 11A displays the thiopental effect site concentrations vs the EEG response for pharmacodynamic data obtained in humans (28). The human and rodent pharmacodynamics are surprisingly similar, both in the biphasic nature and the predicted biphasc thiopental concentrations that result in a given degree of EEG drug effect. This animal/human simi-

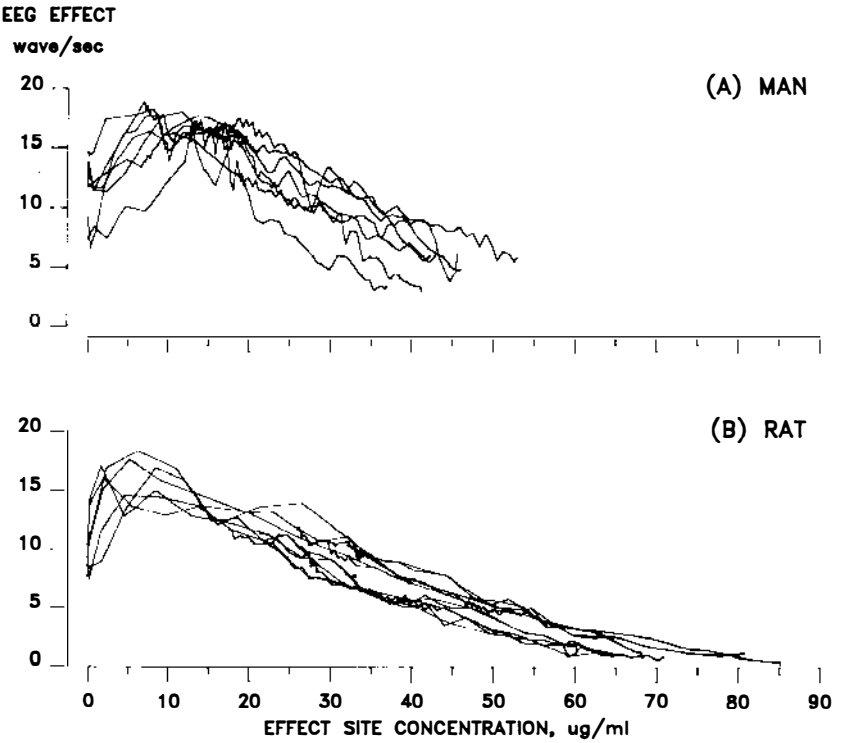

Figure 11 The apparent effect site concentration vs EEG effect (number of waves/sec from aperiodic waveform analysis) in the seven rodents (panel B) and seven human subjects (panel A). The semiparametric pharmacodynamic modeling was used to remove the hysteresis between thiopental plasma concentration and EEG effect allowing prediction of the effect site concentrations. Note how similarity of the EEG pharmacodynamics of the rodent and human. (Reproduced from Ref. 26.)

larity of pharmacodynamic responses using the EEG as a measure of CNS drug effect suggests further pharmacological utility of the EEG. Mandema et al have gathered similar data using another barbiturate, heptabarbital (27). These investigators proposed several alternative EEG parameters that appear useful and other pharmacodynamic modeling approaches for the biphasic drug effect.

Benzodiazepines

Danhof and colleagues have used the chronically instrumented rodent model to provide new and important information on how whole-animal pharmacological measures of EEG drug effect correlate with mediated receptor-mediated pharmacological events. Mandema et al (29) have correlated the

EEG effects of benzodiazepines in the rodent to the receptor binding and anticonvulsant activity. Figure 12 displays the plasma concentration and EEG effect (amplitude in the 11.5–30 Hz frequency range as determined by aperiodic analysis) vs time for flunitrazepam, midazolam, oxazepam, and clobazam. No hysteresis was noted between the plasma concentrations and EEG effects for the four drugs such that concentration could be directly related to the EEG effect (Figure 13).

A sigmoid E_{max}pharmacodynamic model was used to characterize the concentration vs response relationship after adjusting for the plasma protein binding. Table 1 presents the pharmacodynamic parameters obtained from the EEG analysis and the degree of receptor affinity as measured by displacement of [^{3}H] flumazenil. The average EEG E_{max} for flunitrazepam was significantly higher than midazolam, oxazepam or clobazam. This would suggest that the latter three benzodiazepines are partial agonists relative to flunitrazepam.

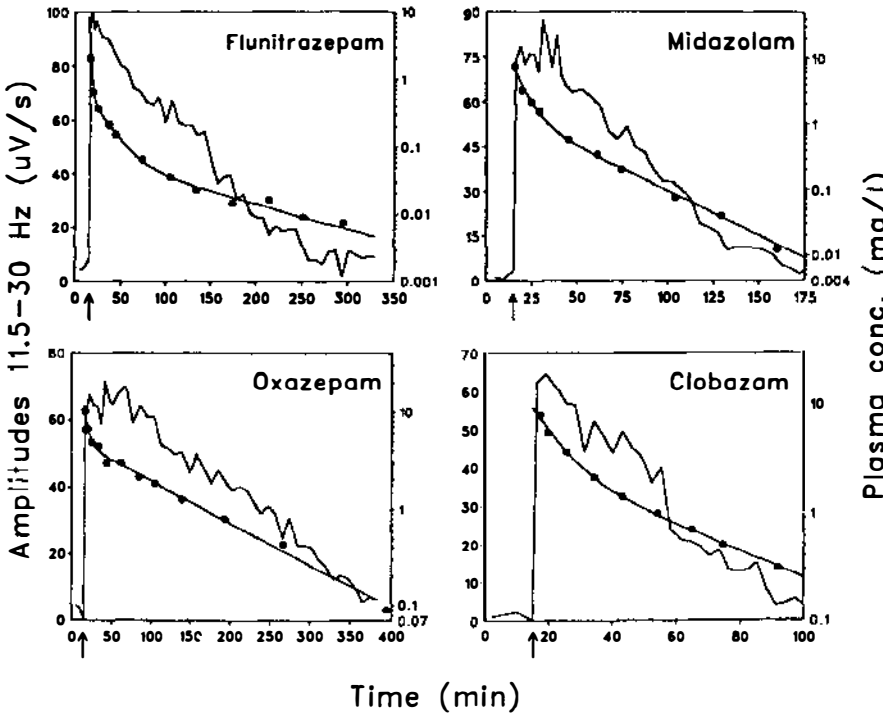

Figure 12 The plasma concentration (solid dots with fitted pharmacokinetic function) and EEG effect (solid line) vs time profiles for four representative rats after IV bolus doses (arrow) of flunitrazepam (2.5 mg/kg), midazolam (5 mg/kg), oxazepam (10 mg/kg), and clobazam (20 mg/kg). The amplitude/sec in the 11.5 to 30 Hz range as obtained from aperiodic waveform analysis was used as the measure of EEG drug effect. (Reproduced from Ref. 29.)

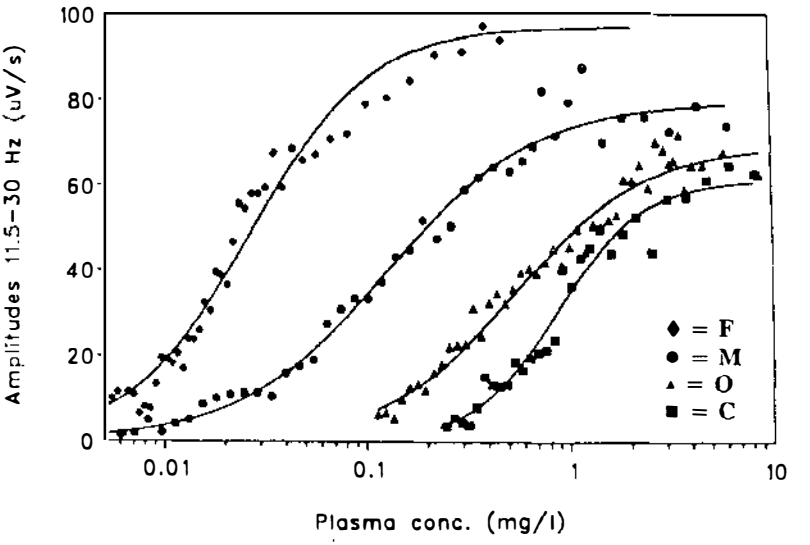

Figure 13 The plasma concentration vs EEG effect relationship of the data indicted in Figure 12 of representative rodents receiving flunitrazepam (F), midazolam (M). oxazepam (O), or clobazam (C). The solid line is the fitted function to a sigmoidal E_{max} pharmacodynamic model. (Reproduced from Ref. 29.)

The CP_{50} for unbound flunitrazepam and midazolam were not different, although oxazepam and clobazam were significantly less potent with higher CP_{50} values. The K_i values for the four drugs are presented in Table 1. The affinity to the benzodiazepine receptors was highest for midazolam and flunitrazepam, whereas oxazepam and clobazam showed much lower receptor affinity. There was a close correlation between the potency of the four benzodiazepines in the EEG model, as judged by the CP_{50} values, and their affinity for the receptor, as reflected by the constant ratio of the unbound CP_{50} and K_i. Similar findings were obtained when the EC_{50} and E_{max} values from a pentylenetetrazol-induced seizure model were compared to the EEG pharmacodynamic data (Table 2). The CP_{50} values obtained from the EEG model paralleled the PTZ antiepileptic potency of the four benzodiazepines. Flunitrazepam had the greatest intrinsic effect as measured by maximal EEG and PTZ effects. This study indicated that the changes in the amplitudes of the EEG in the 11.5–30 Hz frequency range is an appropriate surrogate pharmacodynamic measure of benzodiazepines and reflects their interaction with and efficacy at the central gamma-aminobutyric acid-(GABA) benzodiazepine receptor complex.

Mandema et al (30) extended the evaluation of the EEG as a surrogate measure of benzodiazepine pharmacological response by examining the concentration vs EEG response relationships and receptor-binding characteristics

Table 1 Comparison of EEG activity and benzodiazepine receptor affinity

	Emax (uv/sec)	Total drug CP_{50}	Unbound CP_{50}	k_i ng/ml	Ratio $\frac{CP_{50}}{k_i}$
Flunitrazepam	90 ± 5	26 ± 3	4.2 ± 0.7	7.0 ± 0.8	0.60
Midazolam	73 ± 2	105 ± 10	3.7 ± 0.5	4.9 ± 0.5	0.76
Oxazepam	65 ± 6	559 ± 37	49 ± 4	86 ± 15	0.57
Clobazam	63 ± 8	859 ± 98	277 ± 34	350 ± 61	0.79

Mean ± SE—Adapted from Tables 1 and 2 of Ref. 29 (with permission)

of a benzodiazepine agonist (midazolam), a partial agonist (bretazenil Ro 16-6028), an antagonist (flumazenil), and an inverse agonist (Ro-19-4603). Figure 14A displays the average changes in EEG amplitude (11.5–30 Hz) over time from these benzodiazepines. Midazolam produced the largest increase in EEG amplitude, bretazenil produced a much smaller increase, whereas Ro-19-4603 produced a small but significant decrease in the EEG amplitude. Flumazenil produced an initial increase in the EEG effect that lasted for only 3 min, after which no significant differences from the baseline were seen. No hysteresis was observed between the plasma concentration and EEG effect for the benzodiazepines.

Figure 14B displays the average plasma concentration vs EEG effects for the four drugs as characterized by a sigmoid E_{max} pharmacodynamic model. The pharmacodynamic parameters and receptor binding data are indicated in

Table 2 Comparison of pharmacodynamic parameters derived from the EEG model and a PTZ threshold model of seizure

	CP_{50} (ng/ml)[a]		Emax[b]	
	PTZ	EEG	PTZ	EEG
Flunitrazepam	51 ± 18	26 ± 3	1	1
Midazolam	158 ± 35	105 ± 10	0.74	0.81
Oxazepam	708 ± 133	559 ± 37	0.68	0.72
Clobazam	1113 ± 240	859 ± 98	0.69	0.70

[a] Values reported as mean ± SE
[b] The maximal effects are normalized to flunitrazepam
Adapted from Table 3 of Ref. 29 (with permission)

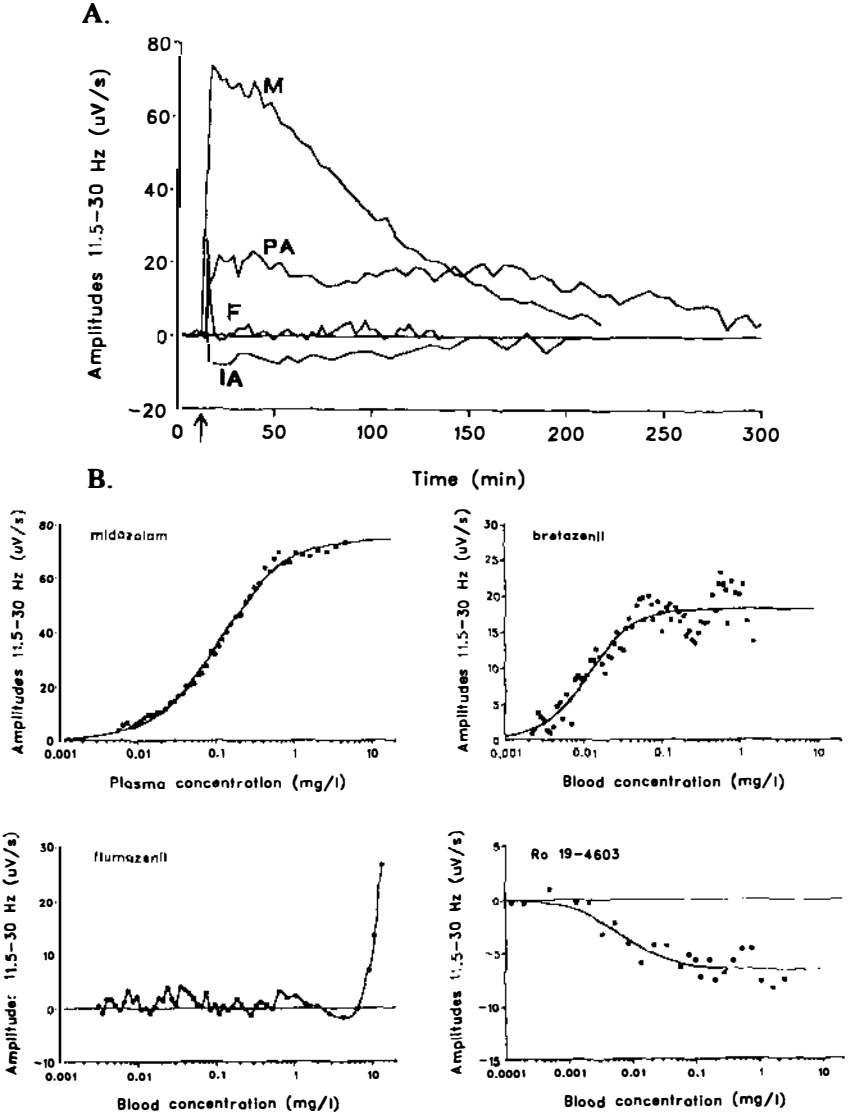

Figure 14 Panel A The averaged EEG effect vs time profiles for representative rodents who received an IV bolus dose (arrow) of midazolam (M) 5 mg/kg, flumazenil (F) 10 mg/kg, bretazenil (PA or partial agonist) 2.5 mg/kg or Ro-19-4603 (IA or inverse agonist). Panel B The averaged blood concentration vs EEG effect relationship of the data indicted in panel A. A sigmoidal E_{max} pharmacodynamic model was fitted to the midazolam, bretazenil, and Ro-19-4603 data. Note the different scales of the y-axis. (Reproduced from Ref. 30.)

Table 3. The maximal EEG effect reflects intrinsic drug efficacy. A close correlation was found between the CP_{50} values, based upon CSF drug concentrations and receptor affinity as determined by displacement of [^{3}H] flumazenil in washed brain homogenates. This study demonstrated that EEG response is a relevant measure of the benzodiazepine pharmacological effect that reflects the affinity and intrinsic efficacy of the benzodiazepines at the central GABA-benzodiazepine receptor complex.

The continuous nature of the EEG has allowed an estimation of the interaction of benzodiazepine agonists, antagonists, partial agonists and inverse agonists. Mandema et al (31) have pharmacodynamically modeled these relationships using a competitive interaction model that could describe and predict the time course of EEG effect after administration of several combinations of these drugs. In a first study, they characterized the interaction of the benzodiazepine agonist, midazolam, and its antagonist, flumazenil, initially under conditions where either the midazolam or flumazenil plasma concentrations were kept at steady-state and the other drug given as a nonsteady-state rapid infusion for pharmacodynamic modeling purposes. Steady-state plasma concentrations of flumazenil were shown in the chronically instrumented rodent model to cause a systematic and proportional parallel shift in the midazolam concentration-EEG effect relationship. Figure 15 displays this shift. Mandema et al (31) demonstrated that flumazenil, if given during a steady-state infusion of midazolam, can completely inhibit the midazolam-induced increase in EEG drug effect. If an agonist-antagonist interaction pharmacodynamic model was used to characterize the steady-state data described above, together with a pharmacokinetic model for midazolam and flumazenil, the time course of EEG effect after a nonsteady-state administration of a combination of midazolam and flumazenil could be successfully predicted. Figure 16A displays the average midazolam and flumazenil plasma concentrations when midazolam 10 mg/kg was given over a 15 min interval,

Table 3 A comparison of EEG pharmacodynamic parameters of benzodiazepine agonist, partial agonist and inverse agonist

	E_{MAX} (uv/sec)	Total Drug CP_{50} (ng/ml)	CSF CP_{50} (ng/ml)	K_i (ng/ml)
Midazolam	73 ± 2	85 ± 8	4.3 ± 0.8	4.9 ± 0.5
Bretazenil	19 ± 1	12 ± 3	1.4 ± 0.4	1.2 ± 0.2
Ro-19-4603	−6.5 ± 0.4	6.2 ± 1.9	1.7 ± 0.5	1.5 ± 0.5

Adapted from Table 3 of Ref. 30 (with permission)

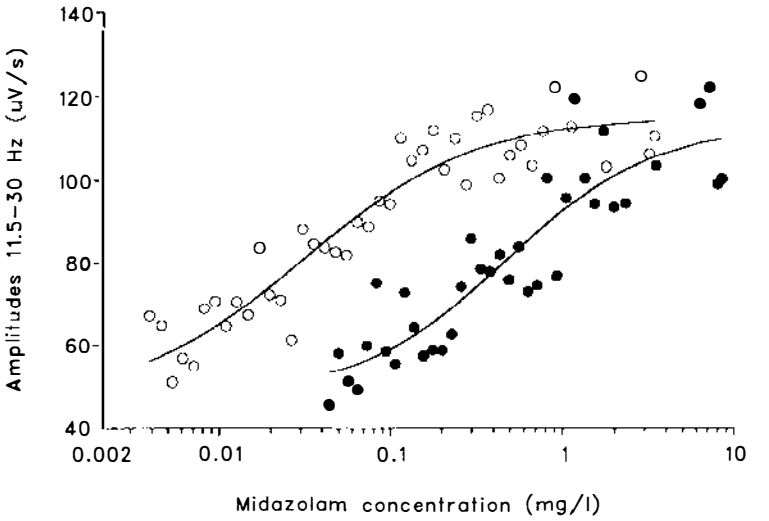

Figure 15 The midazolam plasma concentration vs EEG effect relationship of two representative rodents receiving a continuous infusion of placebo (open circles) or flumazenil (solid circles) at a rate of 1 mg/kg together with a 20 mg/kg infusion of midazolam over 15 min. Note the right shift of the concentration vs response curve with flumazenil. Open symbols are from a rodent receiving midazolam 10 mg/kg over 15 min. The closed symbols represent a rodent receiving a continuous infusion of flumazenil at a rate of 1 mg/kg/hr together with 20 mg/kg of midazolam over 15 min. (Reproduced from Ref. 31.)

followed 30 min later by an intravenous infusion of flumazenil 2 mg/kg in 5 min. Figure 16B displays the EEG drug effect vs time from the above experiment. It can be seen that the predictions from the model are nearly identical to what was actually measured.

In a second study, Mandema et al (32) demonstrated similar results to the midazolam/flumazenil interaction by examining the interactions of midazolam, the partial agonist bretazenil, and the inverse agonist Ro 19-4603. Both bretazenil and Ro 19-4603 markedly antagonized the midazolam-induced increase of EEG effect to the extent of their own intrinsic maximal effects. These interactions could be described by a competitive interaction model. The findings of steady-state experiments were validated after a single intravenous administration of these drugs. The studies presented above by Danhof and colleagues have demonstrated that the EEG measure of drug effect, when linked with pharmacokinetic and pharmacodynamic methodology, can be a powerful investigative tool to understand in vivo and in vitro relationships for the benzodiazepines.

In summary, this review article has presented the current applications of pharmacokinetic and pharmacodynamic modeling with anesthetic drugs. The

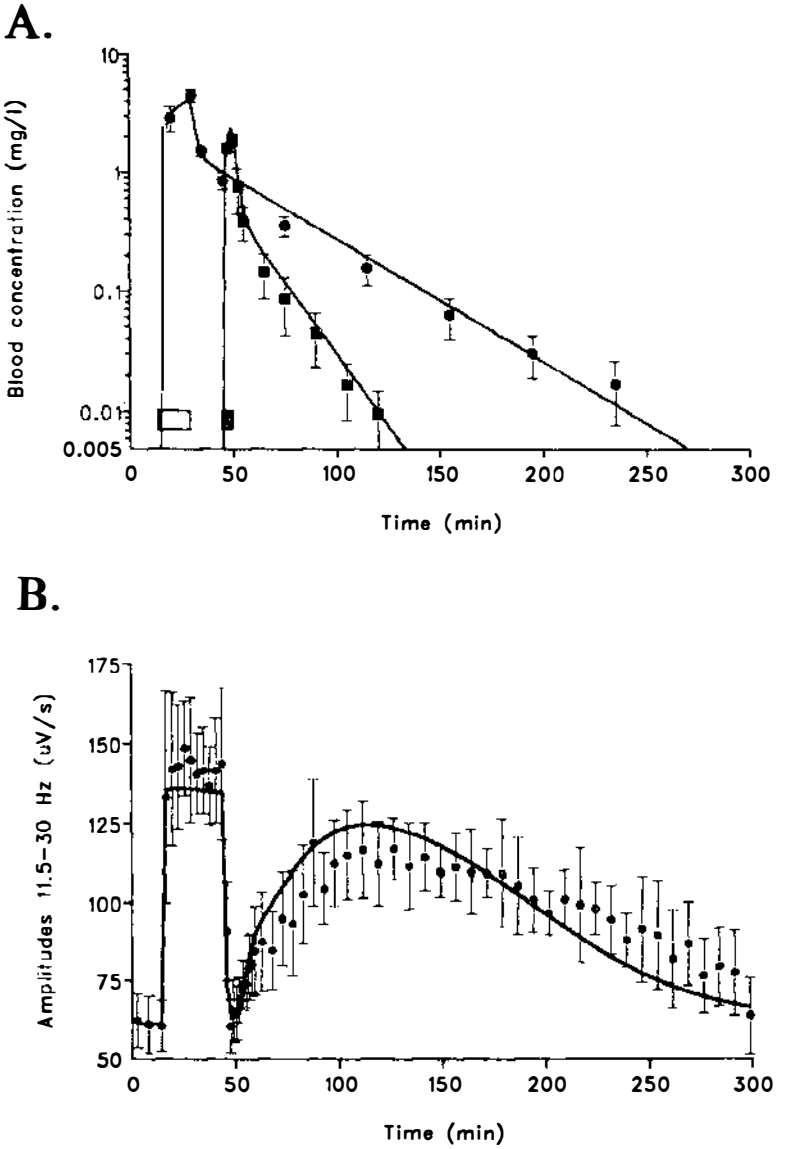

Figure 16 Panel A shows the average blood concentrations (mean 95% confidence interval) of midazolam (solid circles) and flumazenil (solid squares) measured after a nonsteady-state administration. The solid line is the predicted blood concentration obtained from a pharmacokinetic model. The open bar represents the midazolam infusion and the solid bar the flumazenil infusion. Panel B shows the time profile of the average EEG effects in six rodents that had received the midazolam and flumazenil dosing indicated in panel A. The solid line represents the predicted EEG effect according to a pharmacokinetic-dynamic interaction model derived from steady-state dosing. The solid lines present the predicted plasma concentration and EEG effect vs time profile from the pharmacokinetic and pharmacodynamic model along with the actual measured data. (Reproduced from Ref. 31.)

EEG has served as a powerful measure of CNS drug effect. Human studies have allowed the discovery of important components of the clinical pharmacology of anesthetic drugs that could not have been detected with conventional measurement of anesthetic drug effects. The parallel development of a chronically instrumented rodent model for pharmacokinetic and pharmacodynamic studies has allowed the pharmacological utility of the EEG to be examined in animals. Invasive, mechanistic studies can be performed in the rodent model relative to human research. Together, the human and rodent application of the EEG as a measure of anesthetic drug effect, coupled with pharmacokinetic and pharmacodynamic modeling, have provided new information and expanded clinical understanding.

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