Using simulations in the design of an anesthesia system

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The authors are developing a closed-loop system for intravenous anesthesia in human. Using published pharmacokinetic data for the intravenous anesthetic agent, propofol, they have generated a population of "virtual patients" and simulated their response to induction and maintenance of intravenous anesthesia using a feedback system based on an electroencephalogram derivative. Their simulations suggested that the proposed system would accommodate patients with widely varying pharmacokinetic characteristics. The system was subsequently tested in human, and successfully induced and maintained anesthesia in 7 volunteers.

KEYWORDS: *anesthesia*; *bispectral index*; *closed loop system*; *computer controlled anesthesia*; *EEG; modeling*; *pharmacokinetics*; *pharmacodynamics*; *simulation*; *virtual patients*.

In contrast to fields such as aviation, anesthesia currently enjoys low levels of automation (Glen, 1998; Sharma, Griffith, & Roy, 1993). When an intravenous drug is used to induce and maintain anesthesia, the doctor administering anesthesia must estimate the initial dose and subsequently make an appropriate adjustment to the drug infusion rate to reflect the gradual accumulation of the drug within the body. Recently, the introduction of Target Controlled Infusion (TCI) has made it easier to achieve relatively stable blood concentrations but the anesthetist must still decide whether the patient's level of anesthesia is sufficient and make adjustments as necessary (Glen, 1998). Electronic monitoring of the electroencephalogram (EEG) offers a selection of processed EEG derivatives that may reflect the patient's underlying state of anesthesia. We are developing a closed-loop system for computer controlled anesthesia in human using an EEG derivative, the Bispectral Index (BIS), as a feed back signal. Our work so far has involved extensive computer simulations using "virtual patients" and successful tests on volunteers after ethical approval.

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Feedback Signal

The BIS is a commercially developed EEG derivative optimized to produce a linear, monotonic index of hypnosis (depth of sleep/anesthesia) (Doi, Gajraj, Mantzaridis, & Kenny, 1997; Leslie, Sessler, Schroeder, & Walters, 1995). The BIS is a real-time EEG derivative generated by a proprietary algorithm developed by Aspect Medical Systems, Inc., and is a composite, numerical index ranging from 0 to 100 showing hypnotic states/sedation levels.

Before the calculation of BIS, the EEG segments with artifacts and suppressed EEG are identified and rejected; thereafter, the index is calculated by combining the EEG features selected from a set of candidate bispectral and power spectral variables. While conventional spectrum analysis represents the power of frequency components of the EEG waveform, the bispectral analysis quantifies the interfrequency relationship. The BIS provides a measure of the effects of anesthetics and other pharmacological agents on the hypnotic state of the brain. It was reported that the BIS both correlated well with the level of responsiveness and provided an excellent prediction of the loss of consciousness, and that BIS is linearly correlated with the blood concentration of propofol and the magnitude of the cerebral metabolic reduction caused by propofol and isoflurane anesthesia (Doi et al., 1997; Leslie et al., 1995). This suggests that a physiologic link exists between the EEG and cerebral metabolism during anesthesia that is mathematically quantifiable. The BIS has been prospectively validated with a large clinical database (Doi et al., 1997; Leslie et al., 1995).

We have developed a closed-loop system in which raw EEG is collected from the patient, processed to produce the derivative BIS, which is then fed to an anesthesia control system, which incorporates a Proportional Integral Derivative (PID) controller with additional rules, which calculates an appropriate target drug concentration for the patient and adjusts the rate of infusion of the anesthetic agent by controlling a clinical infusion pump. We have used published data on the distribution within the body and brain response to a commonly used anesthetic agent, propofol, and simulated a large population of "virtual patients" (Gepts, Camu, Cockshott, & Douglas, 1987; Leslie et al., 1995). This has allowed us to evaluate how our closed-loop system might perform when deployed on a range of individual patients.

Methods

Pharmacokinetics and Pharmacodynamics

In modern medical practice, anesthesia is usually induced by an intravenous injection of an anesthetic agent (hypnotic). It may then be maintained by a continuous infusion of the same drug. The rise and fall in blood concentration of a commonly used anesthetic agent, propofol, following a single dose is illustrated in Figure 1. The decline in blood anesthetic concentration following a single dose may be described as some other series of exponentials (see Equation 1) (Egan, 1996).

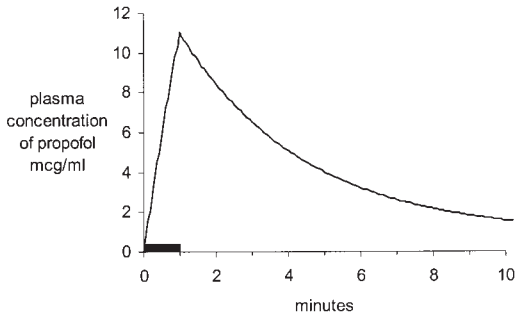

FIGURE 1: Changes in Plasma Concentration of an Intravenous Anesthetic Drug, Propofol, Which Is Infused for a Period of 1 Minute (black bar)

NOTE: The concentration of the drug rapidly reaches a peak and then gradually decays in a poly-exponential manner.

$$D_p(t) = \sum_{i=1}^{n} A_i e^{-\lambda_i t}$$

$$Cp_{CALC}(t) = I(t) * D_p(t) \quad (1)$$

where D_p(t) is the disposition function of the drug in the body after a bolus infusion, exponents $_i$ are the inverse of the half-lives (half-life = 0.693 / λ), coefficients A_i are the relative contributions of each half-life to overall drug disposition, and the integer n is the number of exponentials. If the infusion rate over time is $I(t)$, then the plasma drug concentration over time is $Cp_{CALC}(t)$. The operator * denotes the convolution algorithm.

These equations may be used to describe the body in terms of a series of connecting compartments between which the drug (initially administered into the blood) equilibrates by a series of micro rate-constants. (see Figure 2).

In medical anesthetic practice, it is common experience that there is a delay between the administration of drug and the peak effect. This may be confirmed by electronic monitoring of the EEG. When blood concentration and brain effect are simultaneously measured, this latency of drug action may be clearly seen (see Figure 3). When drug concentration and EEG measured brain effect are plotted against each other, a hysteresis loop is demonstrated (see Figure 4) and the mathematical model of drug distribution may be extended to include an additional compartment known as the effect site, which reflects the latency between peak blood concentration and drug action (Holford & Sheiner, 1981; Levy, 1998).

TCI

A clinical application of pharmacokinetic models such as Equation 1 has been developed by solving the equations necessary to calculate the changing quantities of drug that must be administered across time to achieve stable blood concentrations. The

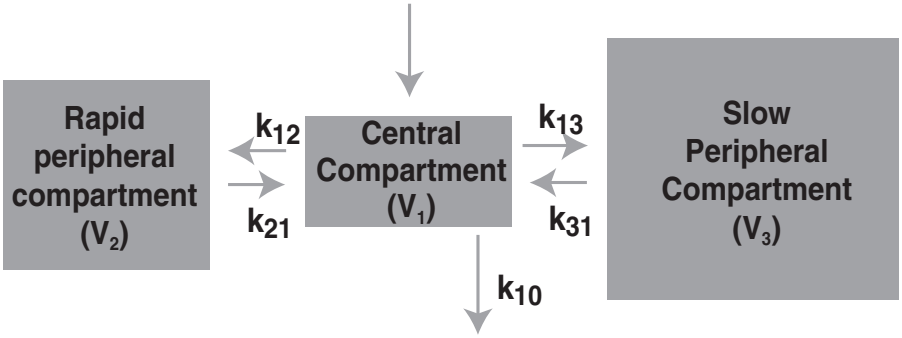

FIGURE 2: A Three Compartment Mathematical Model Describing the Distribution and Elimination of the Anesthetic Drug, Propofol

NOTE: The drug is administered to a central compartment V_1, which equilibrates with two other compartments V_2 and V_3. The transfer of drug between compartments is described by micro rate-constants k_{12} and so on. The drug is eliminated from the central compartment at a rate determined by k_{10}.

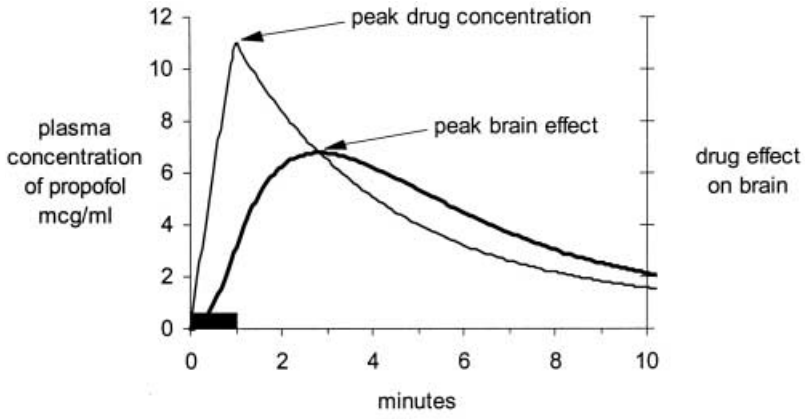

FIGURE 3: Following a Single Dose of the Human Anesthetic Agent, Propofol, There Is a Delay Between Peak Concentration of the Drug in the Blood and the Peak Effect on the Brain

NOTE: Blood concentration of the intravenous anesthetic agent, propofol, following a single dose is illustrated by the thin line. An electroencephalogram-derived measured brain effect is indicated by the heavy line. Note the delay between the two peaks.

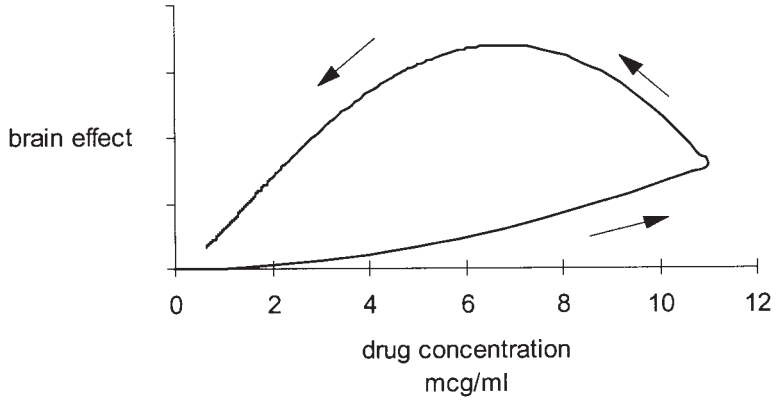

FIGURE 4: The Plasma Concentration and Brain Effect Data From Figure 3 Can Be Plotted Against Each Other to Form a Hysteresis Loop

NOTE: The passage of time is indicated by arrows. Note that concentration initially arises rapidly and well in advance of the onset of drug action.

initial bolus injection and subsequent changes in infusion rate necessary to achieve and maintain a stable clinical concentration of the anesthetic drug, propofol, are illustrated in Figure 5.

Simulations such as these have advanced our understanding of drug distribution and effect, however, they reflect the average response of a population of patients and do not accommodate inter-patient variability. Figure 6 illustrates the simulated response of 9 patients with slightly different pharmacokinetic characteristics to whom a standard scheme of drug infusion has been applied. We see that application of this standard infusion scheme results in different drug concentration/time profiles in each patient and this variability must be considered if we are to use an automatic system to induce and maintain clinical anesthesia.

Closed-Loop Anesthesia

In a closed-loop anesthesia system, an indication of the individual patient's "depth of anesthesia" is derived from the EEG, and an EEG derivative such as the BIS is fed to a central controller. The controller may control the drug infusion directly or, alternatively, use a process of pharmacokinetic (drug distribution) or pharmacodynamic (drug effect) modeling as described above to improve the system's control of drug infusion to the patient. We have implemented closed-loop intravenous anesthesia using a standard control theory with a PID controller that quantifies the error between the measured BIS and a preset target. This, with the addition of some additional rules, is used to adjust the target concentration of drug to the individual patient to which is then implemented using a modified target controlled drug infusion system.

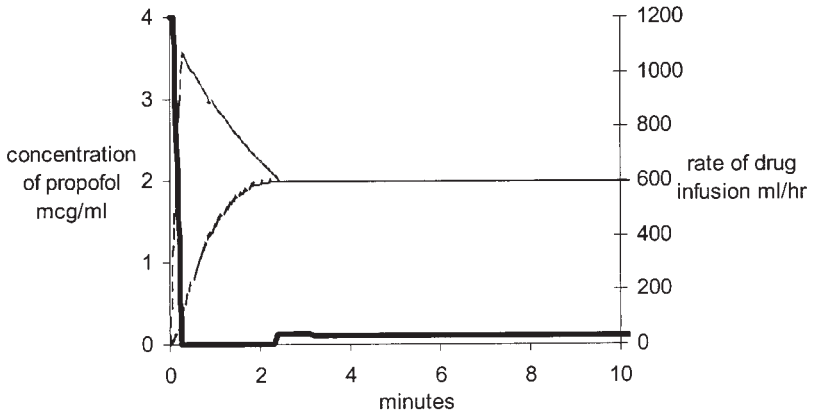

FIGURE 5: Implementation of a Complex Infusion Scheme Designed to Achieve a Stable Drug Effect In Man

NOTE: To achieve the desired drug effect (lower thin line), the rate of drug infusion is changed every few seconds (thick line). Note that the rate of drug infusion is initially very rapid, that is, a bolus of the drug is given; the pump then switches off and restarts 2 minutes later at a much lower rate. This infusion scheme gives a high initial concentration of drug in the plasma (upper thin line), which produces an increasing brain effect (lower thin line). A stable brain effect is achieved within 2.5 minutes.

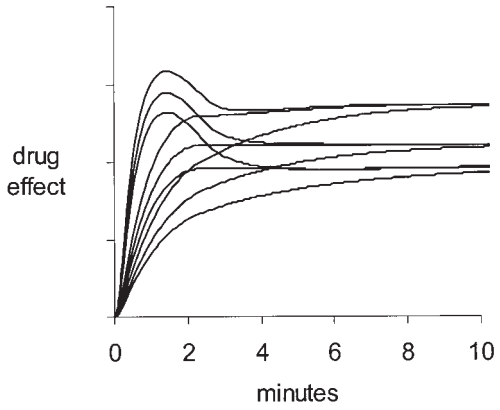

FIGURE 6: Illustration of Interpatient Variability

NOTE: The infusion scheme developed in Figure 5 has been implemented in 9 virtual patients with different pharmacokinetic characteristics. Notice that the same infusion scheme produces differing drug effect/time profiles in individual patients.

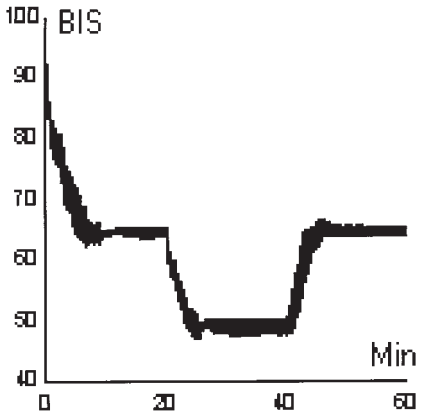

FIGURE 7: The Traces Are the Simulated Response of 3,125 Individual Virtual Patients Anesthetized by a Closed Loop Anesthesia System

NOTE: The system is set to depress the Bispectral Index (BIS), a measure of consciousness from a baseline (conscious) level of 100 to a lightly anesthetized level of 65 from 0 to 20 minutes, to a deeper level of 50 between 20 and 40 minutes, back to 65 between 40 and 60 minutes when anesthesia is discontinued and the virtual patient allowed to recover. Note that there is some initial instability; however, the responses of the virtual patients are tightly grouped, suggesting that if the system has been correctly modeled, there is a low risk of excessive responses or gross instability in man.

Design Consideration and Constraints

The control system was designed and optimized based on the published pharmacokinetic/dynamic data that were obtained from a certain range of patients (Gepts et al., 1987; Vuyk, Engbers, Burm, Vletter, & Bovill, 1995), outside this population it would result in a larger induction overshoot or a longer time to achieve stable level of anesthesia. The basic assumption of the control system is that the pharmacokinetics and pharmacodynamics are linear.

Choice of Control Strategy

A control strategy combining a PID controller with a reference model is used in the simulation. Usually, PID control is effective for a process containing some unknown dynamics like the one under investigation, and can give satisfactory results. The reference model provides a general guide for the PID control, especially for the size of the induction bolus. The use of a reference model will reduce the risk of a large and sudden increase in infusion rate (this will be spread over a period of time if the physical limit on maximum infusion rate applies) as the adjustment from the PID controller is only an

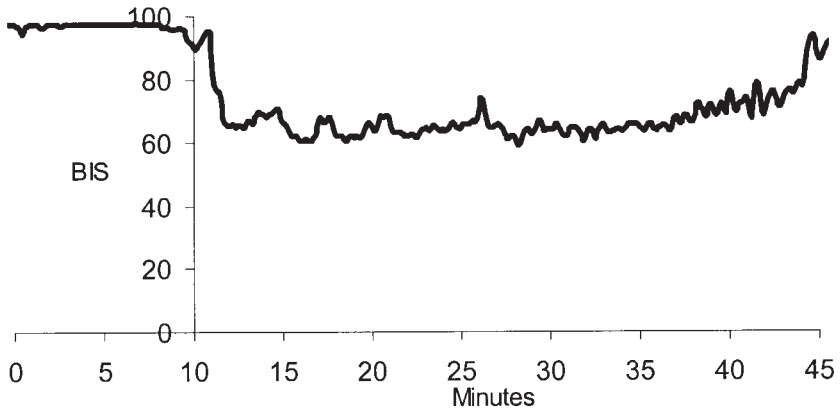

FIGURE 8: Anesthesia of a Single Human Volunteer Using a Bispectral Index (BIS) Derivative of the Electroencephalogram and a Proportional Integral Derivative Controller With Additional Rules

NOTE: The system has successfully induced and maintained light anesthesia between the 10th and 45th minutes with a target BIS of 65.

offset to the guess from the reference model, and the adjustment is therefore small and safe to the patients. If the feedback signal is absent or other emergent events occurred, the reference model can automatically take over the control to force the system to run in TCI mode until everything returns to the normal status. Finally, referring to the literature this control strategy has not been investigated.

Validation of the Underlying Model

The PID controller has achieved huge success in industrial process control and the reference model has also been successfully used in TCI (Glen, 1998). The use of the reference model will provide safer control on drug infusion while PID controller gives the infusion system ability to dynamically respond to the real time measurement of anesthetic depth of patients.

Simulation

Before implementing closed-loop anesthesia in practice, we simulated the individual components of our proposed system and tested its response to a population of "virtual" patients with different pharmacokinetic and pharmacodynamic characteristics. Figure 7 illustrates the sequential changes in the BIS that might be programmed for a particular patient and illustrates how our population of virtual patients might respond when anesthetized.

Clinical Testing of Closed-Loop Anesthesia

We have subsequently used our closed-loop system to anesthetize human volunteers and this is illustrated in Figure 8.

Conclusion

Mathematical modeling of blood concentrations and EEG derivatives after drug administration to human permit the elaboration of mathematical models. Implementation of these models has allowed the clinical development of Target Controlled Anesthesia, which is now commercially available. We have developed this technique further by using standard industrial control theory to adjust drug administration in response to an EEG derivative, the BIS measured from each individual patient. Because the characteristics of individual patients are variable, we simulated the response of our system to a wide range of individual patients prior to successful testing of the closed-loop system in human.

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