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Quantifying Anesthetic Drug Interaction: Implications for Drug Dosing

Stanski, Donald R. MD; Shafer, Steven L. MD

Author Information

Donald R. Stanski, M.D., Professor and Chair, Department of Anesthesia, Stanford University School of Medicine.

Steven L. Shafer, M.D., Associate Professor, Department of Anesthesia, Stanford University School of Medicine, Stanford, California, Staff Anesthesiologist, Palo Alto Department of Veterans Affairs Medical Center, 3801 Miranda Avenue, Palo Alto, California 94304.

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In this issue of ANESTHESIOLOGY, Vuyk and colleagues ^[1] present a state-of-the-art quantitation of the pharmacodynamic interaction of propofol and alfentanil for induction and maintenance of anesthesia in surgical patients. Recent data suggest that our understanding of depth of anesthesia will advance only when there is more scientific information available on the interaction of two or more clinically relevant anesthetic drugs. What is the link between depth of anesthesia and anesthetic drug interactions?

In 1937 Guedel published his classic description of the clinical signs of ether anesthesia. ^[2] Clear physical signs involving somatic muscle tone, respiratory patterns, and ocular signs were used to define stages of ether anesthesia. Judging clinical depth of anesthesia and adjusting dosing with ether was relatively straightforward in those earlier days of singleinhalational-agent anesthesia. With the advent of muscle relaxants in 1942 and then more modern anesthetic drugs (potent inhalational anesthetics, opioids, and hypnotics), our discipline entered a 5-decade period in which defining and understanding anesthetic depth was difficult and controversial and generally failed to advance. ^[3].

Although the minimum alveolar concentration (MAC) concept, developed by Eger and colleagues in 1965, ^[4,5] has been a powerful scientific and clinical tool to understand inhalational anesthetic depth of anesthesia, recent studies by Zbinden and colleagues have

raised fundamental questions. ^[6,7] Zbinden et al. have shown that when isoflurane is given as the sole anesthetic and both movement and hemodynamic responses are examined for defined noxious stimuli, increasing isoflurane concentrations can prevent purposeful movement but cannot prevent significant hemodynamic responses (hypertension or tachycardia), even at high end-tidal isoflurane concentrations. Hemodynamic control seen with high isoflurane concentrations occurs from a decrease of the prestimulation baseline hemodynamics.

Thus, although hemodynamic responses are the most commonly used clinical measures to judge inhalational anesthetic depth of anesthesia and adjust dosage, the scientific basis for this approach is less than clear. In clinical practice opioids are added to inhalational anesthetics to obtain hemodynamic control at clinically acceptable inhalational anesthetic concentrations. Several investigators have now quantitated the profound decrease of inhalational anesthetic MAC with increasing opioid concentrations. ^[8,9] For example, isoflurane MAC decreases 39% at a steady-state plasma fentanyl concentration of 1 ng/ml and 63% at a steady-state plasma fentanyl concentration of 3 ng/ml. The plasma fentanyl concentration range of 1-3 ng/ml represents the analgesic therapeutic window for fentanyl in conscious patients.

Similar concepts can be presented when opioid depth of anesthesia is considered. Murphy and Hug ^[10] and Hall and colleagues ^[11,12] have shown in a series of animal studies that opioids are not complete anesthetics when given alone. Numerous investigators have demonstrated this finding in humans also. ^[13-15] In clinical practice a second anesthetic drug (nitrous oxide, potent inhalational anesthetic, or hypnotic) must be added to the opioid to obtain a clinically adequate anesthetic state. For alfentanil, when used with oxygen only, steady-state concentrations in plasma of 1,500-2,000 ng/ml cannot consistently obtain hemodynamic control in patients undergoing cardiac surgery. ^[16] The addition of 70% nitrous oxide can create an adequate hemodynamic state during noxious surgical stimuli, decreasing the plasma alfentanil concentrations needed to approximately 200-300 ng/ml. ^[17].

From the above examples, it emerges that achieving adequate general anesthesia with the currently available anesthetic drugs usually requires a minimum of two different classes of anesthetic drugs. Adequate general anesthesia can be defined as prevention of both purposeful movement and autonomic signs of inadequate anesthesia (lacrimation, flushing, or tearing), achieved with hemodynamic control, during noxious surgical or anesthesia stimuli. In a recent editorial, Kissin grapples with the concepts of anesthetic drugs can be used to create the general anesthetic state, including analgesia; anxiolysis; amnesia; unconsciousness; and suppression of somatic motor, cardiovascular, and hormonal responses to the stimulation of surgery. This spectrum of effects that constitutes the state of general anesthetic action; rather, it represents separate pharmacologic actions, even if the

anesthesia is produced by one drug. With the drugs currently available in anesthetic practice, the clinician usually uses at least two anesthetic drugs to achieve the clinical goals of adequate anesthesia.

Vuyk and colleagues have quantitatively examined the interaction of propofol and alfentanil for the induction and maintenance of general anesthesia. ^[1] Most previous investigations of intravenous hypnotic drugs have focused on the induction of anesthesia. Vuyk's group used established, clinically relevant end points of anesthetic depth, optimal drug delivery, correct study design, frequent drug concentration measurement, and sophisticated pharmacokinetic and pharmacodynamic data analysis. The methods and concepts used by Vuyk et al. draw from a decade of clinical pharmacology research in anesthesia. Both propofol and alfentanil have rapid blood-brain equilibration, ^[19],* and thus it is realistic to relate the measured arterial concentration of drug in plasma to the resulting drug effect. Ausems and colleagues provided the fundamental method of assessing depth of anesthesia, originally developed with an anesthetic technique of continuous alfentanil infusion and nitrous oxide inhalation. ^[17] The concept of the computer-driven infusion pump in anesthesia was developed by Schwilden and colleagues to achieve stable concentrations in plasma, ^[20] and this technique has become the state-of-the-art approach to quantitating concentration-response relations.

Several findings in this study deserve close attention. The pharmacodynamic interaction between propofol and alfentanil is very nonlinear. What does this mean? As plasma propofol concentrations increase, the decrease of alfentanil requirement is not proportional to the change in plasma propofol concentration because of the synergistic interaction of propofol and alfentanil. This relation is particularly evident in Figure 6 of the article by Vuyk et al., ^[1] which plots the steady-state plasma propofol concentration against the concentration of alfentanil associated with a 50% chance of no response. At a plasma propofol concentration of 2 micro gram/ml, the plasma alfentanil concentration associated with a 50% chance of no response to abdominal surgery is 209 ng/ml, but an 8-fold increase in propofol concentration of alfentanil.

How can we use the information on drug interactions to help us administer drugs more rationally? Vuyk and colleagues ^[1] offer an example of the power of such models. In Figure 9, the authors examine the time course of propofol and alfentanil concentrations after an infusion of 180 min. This simulation is based on an assumption that alfentanil and propofol are being given by computer-controlled infusion pump to maintain the combined drug effect at 50% likelihood of no response to intraabdominal surgery. At time 0 (the floor of Figure 9) we see the same curve for drug interaction as shown in Figure 6. Attached to this floor are the propofol and alfentanil trajectories when the infusion is turned off. The authors identify on each trajectory the time at which the patient has a 50% chance of awakening, as shown by the meandering solid line on the time versus concentration surface. This line suggests that the most rapid emergence will occur if the propofol and alfentanil concentrations are maintained at concentrations of 3.5 micro gram/ml and 85 ng/ml, respectively, for an

anesthetic of 180 min.

We can ask a more general question: for the clinician who is not running computercontrolled infusions of propofol and alfentanil and whose patients receive anesthetics lasting more or less than 180 min, how can the drugs be given to result in the most rapid possible emergence? To answer this question, we developed an Excel spreadsheet (Microsoft, Redmond, WA) that combines the interaction models for propofol and alfentanil reported by Vuyk and colleagues ^[1] for intubation, maintenance of anesthesia during intraabdominal surgery, and emergence. We linked these models to pharmacokinetic models for propofol and alfentanil. We did not use the Gepts et al. ^[21] and Maitre et al. ^[22] models of propofol and alfentanil used by Vuyk and colleagues because of the bias that they observed in those models. Instead, we used the propofol pharmacokinetics reported by Tackley et al. ^[23] and the alfentanil pharmacokinetics reported by Scott and Stanski, ^[24] because both of these have been found to be unbiased in prospective trials. ^[25,26] We also examined effect-site concentrations rather than concentrations in plasma. The rate constant, keo, for plasmaeffect site equilibrium in the model was 0.77 min sup -1 for alfentanil and 0.81 min sup -1 for propofol.

The spreadsheet calculates the initial bolus dose of propofol and alfentanil to achieve 50% likelihood of response to intubation and then the maintenance infusion rates for propofol and alfentanil to maintain 50% likelihood of response to intraabdominal surgery. Because anesthesiologists frequently do not know how long the operation will last, we simulated ending the infusions at 10, 30, 60, 90, 120, 180, 240, 300, 360, 420, 480, and 600 min and calculated how long it would take for the propofol and alfentanil concentrations to decrease to the point at which the interaction model predicted a 50% probability of emergence. The Solver function in Excel was used to find the initial bolus and maintenance infusion rates over time for propofol and alfentanil that resulted in the fastest overall recovery.**

The simulation suggests that the initial boluses of propofol and alfentanil to provide anesthesia for intubation should be given as follows: 0.7 mg/kg of propofol administered 2.3 min before intubation and 30 micro gram/kg of alfentanil administered 1.4 min before intubation. If the propofol dose sounds too modest (and who wants to see 50% of patients respond to intubation?) the initial propofol dose can be increased to 1 mg/kg given 2.3 min before intubation with a net increase of only 1 min in the time required for recovery.

The maintenance infusion rates for propofol and alfentanil appear in Figure 1(A). After intubation (at time 0) the propofol infusion starts at 180 micro gram *symbol* kg sup -1 *symbol* min sup -1 for 10 min, decreases to 140 micro gram *symbol* kg sup -1 *symbol* min sup -1 from 10-30 min, and then decreases to approximately 100 micro gram *symbol* kg sup -1 *symbol* min sup -1 for the next 9.5 h. The alfentanil infusion is not turned on until 10 min after intubation. The alfentanil infusion rate for the 1st h is approximately 350 ng *symbol* kg sup -1 *symbol* min sup -1, is decreased to 275 ng *symbol* kg sup -1 *symbol* min sup -1 for the 2nd h, and is then decreased to 240 ng *symbol* kg sup -1

symbol min sup -1 for the next 8 h.



Figure 1

(Figure 1(B and C)) show the propofol and alfentanil concentrations, respectively, during maintenance (solid lines) and upon emergence after termination of the infusion (dashed lines) for anesthetics of 10-600 min duration, using the dosing guidelines from Figure 1(A). The interaction models of Vuyk et al., ^[1] when combined with the pharmacokinetic models for propofol and alfentanil, favor providing a high effect-site alfentanil concentration (344 ng/ml) and a more modest propofol concentration (1.44 micro gram/ml) for the noxious stimulation of intubation. After intubation, the propofol concentration is increased to 3-3.5 micro gram/ml, while the alfentanil concentration is immediately decreased to 85-100 ng/ml. There is close agreement between these maintenance concentrations and the optimal propofol and alfentanil concentrations of 3.5 micro gram/ml and 85 ng/ml, respectively, for a 180-min computer-controlled anesthetic regimen as suggested by Vuyk and colleagues in Figure 9 of their report. The dashed lines in Figure 1(B and C) show the predicted concentration when the patients awaken as a function of infusion duration. The time required for this decrease of propofol/alfentanil drug concentration is shown in Figure 1(D). For example, if the infusion regimen shown in Figure 1(A) is terminated at 120 min, the propofol concentration will be 3.2 micro gram/ml (Figure 1(B), solid line). Its concentration must decrease to 1.6 micro gram/ml (Figure 1(B), dashed line) for the patient to awaken, which occurs in 15 min (Figure 1(D)).

(Figure 1(D)) shows the number of minutes from the end of the infusion to awakening as a function of the duration of drug administration. This relation suggests that when carefully constructed dosing guidelines are used, the typical patient will awaken from a total intravenous anesthetic with propofol and alfentanil within 15 min of termination of the infusions for anesthetics of less than 2 h duration and within 20 min of termination of the infusions for anesthetics of 2-10 h duration.

(Figure 1(E)) shows the percentage decrease in propofol and alfentanil concentration required for emergence at the conclusion of the "optimal" anesthetic developed from the interaction models. It is interesting that the propofol concentration must decrease almost exactly by 50%. This finding supports the use of the "context-sensitive half-times" as a clinically relevant estimator of recovery from propofol, as proposed by Hughes and colleagues. ^[27] The context-sensitive half-time assumes a computer-controlled continuous

infusion to maintain a constant concentration in plasma. Figure 1(B) suggests that the "optimal" propofol infusion regimen developed from the model is a close approximation of the pseudo-steady-state infusion assumed by the context-sensitive half-time. With the proposed regimen, the alfentanil concentration need decrease only by 25-30% at the conclusion of the anesthetic. This result is consistent with our previous observation that propofol has a more rapid offset than alfentanil ^[28] and that decrements other than the 50% decrease may be clinically important in some settings. ^[29].

Thus, the interaction models reported by Vuyk and colleagues ^[1] can be used to develop dosing guidelines that are nearly optimal, in the sense that they will give the most rapid recovery when the duration of surgery and anesthesia is not known a priori. The optimum applicability in this analysis is limited to (1) the typical person, (2) the population of healthy patients and volunteers from which the models were developed, (3) maintenance of the concentration with a 50% probability of responding (which would be, by definition, a clinically rocky anesthetic course!), and (4) the discrete time intervals used in the simulations. However, these simulations illustrate how carefully constructed models of drug interaction, as reported by Vuyk et al., ^[1] can be used to understand how to administer intravenous anesthetics more rationally.

Donald R. Stanski, M.D., Professor and Chair, Department of Anesthesia, Stanford University School of Medicine.

Steven L. Shafer, M.D., Associate Professor, Department of Anesthesia, Stanford University School of Medicine, Stanford, California, Staff Anesthesiologist, Palo Alto Department of Veterans Affairs Medical Center, 3801 Miranda Avenue, Palo Alto, California 94304.

* Schuttler J, Schwilden H, Stoeckel H. Pharmacokinetic-dynamic modeling of Diprivan (abstract). ANESTHESIOLOGY 65:A549, 1986.

**The Excel spreadsheet is available by anonymous FTP from pkpd.icon@paloalto.med.va.gov in directory /public/vuyk.dir.

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