of drug concentrations. The authors developed one- and two-compartment mamillary models and then used nonlinear regression to characterize the blood marker dilution *versus* time, relative to the administered dose of intravenous fluid. The authors report that the volume of body fluid space expanded by the intravenous fluid was greatest for Ringers (change of 5.9 l), followed by dextran (change of 2.6 l), and was least with hypertonic saline (change of 1.2 l). The authors' data analysis approaches will require more rigorous evaluation; however, the fundamental concept that they suggest may provide a new clinical research tool to understand how intravenous fluids used in anesthetic practice affect the body. The concepts presented in this article could be used to provide better quantitation of the effects of different intravenous fluids in different patient populations or clinical situations and also allow for more rational design of intravenous fluid administration paradigms.

Donald R. Stanski, M.D.
Professor and Chair
Department of Anesthesia
Stanford University School of Medicine
Stanford, California 94305

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Propofol Requirements versus *Stimulus Intensity*

The study presented by Kazama *et al.* in this issue of ANESTHESIOLOGY makes a number of significant contributions to our understanding of general anesthesia produced by intravenously administered drugs. This study 1) illustrates the incorporation of fundamental pharmacologic principles into the design of the investigational protocol, 2) demonstrates substantial differences among different types of stimuli in regard to the amount of anesthetic required to suppress responses to them, 3) illustrates the usefulness of specific drugs to achieve specific effects in the overall spectrum of general anesthestic goals and the need for monitoring multiple physiologic variables to verify achievement of specific goals of anesthesia care, 4) characterizes the interactions of an opioid and hypnotic, and 5) suggests a strategy for achieving and maintaining adequacy of anesthesia while allowing for an appropriately rapid recovery.

The experimental design used by Kazama *et al.* incorporated measurements of drug effects with stable drug concentrations in plasma after adequate time for equilibration of concentrations in plasma with those at effector sites, and measurements of drug effect at different drug concentrations allowing expression of the concentration *versus* effect relationships. The high degree of variability in dose *versus* response relationships is substantially reduced by relating the drug effect to stable drug concentrations in plasma. The latter condition of verifying stable drug concentrations in plasma is comparable with the measurement of inhalational anesthetic effects while maintaining stable concentrations in end-tidal gases.

The study by Kazama *et al.* confirms for propofol, an intravenous hypnotic, what has been demonstrated for opioids[1] and inhalational anesthetics.[2] Skin incision is not the most intense type of stimulation, and different types of noxious stimuli require different concentrations of anesthetic agent to suppress somatic, autonomic, and hemodynamic responses. Suppression of sympathetically mediated hemodynamic responses does not guarantee suppression of somatic responses and *vice versa*. The study also suggests a strategy for administration of combinations of hypnotics and opioids to produce general anesthesia: first administer a hypnotic drug and verify loss of consciousness (*e.g.*, pressure applied to the styloid bone to produce grimacing without awakening to verbal command before administration of a muscle relaxant) and then administering an opioid as necessary to suppress sympathetic signs to further noxious stimulation. This strategy would likely reduce the risks of arousal and awareness in the paralyzed patient.

Kazama *et al.* also demonstrated that a single hypnotic (propofol) is similar to a single inhalational anesthetic[2] because, used alone, neither type of drug is fully efficacious in subduing hemodynamic responses to noxious stimulation even when there is marked, dose-dependent depression of blood pressure by the hypnotic or volatile anesthetic. The addition of relatively low (analgesic)

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concentrations of an opioid does not markedly reduce the amount of the hypnotic or volatile anesthetic required to render the patient unconscious, but the opioid produces a marked, dose-dependent reduction of somatic, sympathetic, and hemodynamic responses to intense noxious stimulation. These observations call attention to specific, discrete pharmacologic effects of different drugs used in combination to achieve the overall spectrum of effects that may be desired during general anesthesia. Moreover, attention is drawn to the need to monitor individually the specific goals of general anesthesia.

The importance of the interactions of hypnotics and opioids is evident in this study. Given the existing knowledge of the concentrations of propofol and fentanyl alone that are required to suppress responses to noxious stimulation and to maintain unconsciousness (not consistently possible with an opioid alone) makes it highly likely that the interaction is a synergistic one. This means that relatively low doses of each drug can be used in combination to limit their individual side effects and accumulation in the body. It is important to note that relatively low concentrations of fentanyl, clearly within the analgesic range (fentanyl 1–3 ng/ml of plasma), reduced the requirement for propofol just as it does for inhalational agents by 30–50%.[3] Huge opioid doses are not needed to achieve satisfactory anesthetic conditions when the opioid is used in combination with hypnotic or volatile anesthetic.

Finally, the findings of this study are particularly relevant in this era of "fast tracking." To achieve rapid recovery from anesthesia, there is a growing tendency to limit the doses of hypnotic and analgesic drugs administered intraoperatively. This tendency may increase the risk of inadequate anesthesia, especially arousal in response to noxious stimulation, which may go undetected in the paralyzed patient. Given the widespread practice of administering amnesic drugs, the lack of recall of intraoperative events is no guarantee that the patient has not experienced pain or fear intraoperatively. In my opinion, amnesia does not fulfill the implied conditions of the contract that is established when the patient and anesthesiologist agree on general anesthesia. Again, the strategy of achieving unconsciousness with a hypnotic before administration of a muscle relaxant, maintenance of that level of hypnotic concentration, and supplementation with an opioid as needed to suppress sympathetic and hemodynamic signs of responsiveness to noxious stimulation goes a long way to achieving satisfactory fulfillment of the general anesthesia contract.

Carl C. Hug, Jr., M.D., Ph.D.
Professor of Anesthesiology and Pharmacology
Emory University School of Medicine
Department of Anesthesiology
Emory University Hospital
1364 Clifton Road, NE
Atlanta, GA 30322-1104
Electronic mail: chug@emory.org

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Keep the Blood Red . . . The Right Way

All currently volatile anesthetics are degraded by carbon dioxide absorbents to compounds that are toxic. Desflurane, enflurane, and isoflurane are degraded to carbon monoxide (CO), which is neurotoxic and cardiotoxic. A 1-h exposure to 1,000 ppm CO will produce approximately 25% carboxyhemoglobin, sufficient to cause severe neuropsychiatric impairment, whereas 67% carboxyhemoglobin causes death.[1] The current Environmental Protection Agency limit for a 1-h exposure is 35 ppm. Signs and symptoms of CO toxicity are

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Key words: Baralyme, calcium hydroxide, carbon dioxide, carbon monoxide, carboxyhemoglobin, complications, desflurane, hemoglobin, intraoperative monitoring, isoflurane, soda lime, sodium hydroxyide.