Reviewers receiving corporate sponsorship will continue as reviewers (unless it is discovered that they have failed to disclose their conflicts), but the editor-in-chief will consider their potential biases before any editorial decisions are made. The present editor-in-chief will also make every effort to avoid any personal form of corporate involvement that might influence (or appear to influence) his judgment.

This journal does not wish to discourage the working relationship between researchers and manufacturers. Both play an indispensable role in bringing new drugs and devices into practice. Neither can function without the other. However, great mischief can result from the relationship.[10] The "rules" just noted cannot solve all of our problems and obviously cannot prevent authors or sponsors from intentionally concealing important relationships (although we will try to remain vigilant). But we believe that editors, reviewers, and, most importantly, our readers have a right to know about the relationships that may influence the conduct or interpretation of important research. ANESTHESIOLOGY will do its best to provide this information. From that point forward, it is up to our readers to critically evaluate what they read and to draw their own conclusions.

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The Pharmacokinetics of Intravenous Fluids

This original research publication presents a new and innovative application of pharmacokinetic data analysis, usually applied to drug disposition, to the physiologic effects of parenteral intravenous fluid administration. In classical pharmacokinetic data analysis, a drug is administered, blood is sampled, and drug concentrations are measured over time. Pharmacokinetic models, usually mamillary with first-order kinetics, are fit to the measured drug concentrations using nonlinear least-squares regression. The data analysis estimates drug volumes and clearances that characterize the extent of drug distribution into body tissues and the rate of drug movement between tissues and removal from the body. Drs. Svensen and Hahn have examined the pharmacokinetics of the intravenous administration of Ringer's acetate, 6% dextran, and 7.5% NaCl using the dilution of three markers in blood, blood hemoglobin, blood water, and plasma albumin, analogous to the measurement

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Key words: dextrans, fluid therapy, hemodilution, pharmacokinetics, saline solution–hypertonic, serum albumin, water/blood.

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.

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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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Key words: intravenous anesthetics, fentanyl, propofol, anesthetic techniques, tetanic stimulation, tracheal intubation, anesthetic potency, hemodynamics, motor reaction.