

## ***Evolving Clinically Useful Predictors of Recovery from Intravenous Anesthetics***

The complex pharmacokinetics and pharmacodynamics of intravenous anesthetics precludes easily predicting the duration of anesthetic effect after drug administration, which we will subsequently call "predicting recovery." The terminal elimination half-life often is discussed as if it predicts recovery. In 1991, Shafer and Varvel demonstrated that the terminal elimination half-life can be misleading.<sup>1</sup> These authors introduced the "relevant effect-site decrement time,"\* the time required for the effect-site concentration to decrease from anesthetic concentrations to concentrations associated with recovery, as a function of infusion duration. Subsequently, Hughes *et al.* introduced the "context sensitive half-time," the time required for a 50% decrease in plasma concentration, also as a function of infusion duration.<sup>2</sup> An accompanying editorial used the example of the fictitious drug Duzitol to show how the context-sensitive half-time can provide clinical insight.<sup>3</sup> In this issue of ANESTHESIOLOGY, Bailey again explores predictors of recovery.<sup>4</sup> The result is a new predictor of recovery: the mean effect time. What does this new predictor mean clinically? How does it relate to the context-sensitive half-time and the relevant effect-site decrement time? We again turn to the imaginary Duzitol for answers to these questions.

Duzitol has a terminal half-life of 100 min in normal patients and 400 min in patients with hepatic failure.<sup>3</sup> Figure 1 shows the terminal half-life, the context-sensitive half-time, the relevant effect-site decrement time, and the mean effect time for normal patients and patients with hepatic failure, all as a function of infusion duration. Each predictor of recovery suggests a different clinical interpretation. The terminal half-life implies that Duzitol may be associated with slow recovery in patients with hepatic failure. The context-sensitive half-

time predicts the opposite: Duzitol may be associated with rapid recovery in hepatic failure, as was explored in the prior editorial.<sup>3</sup> The relevant effect-site decrement time predicts almost no difference in the time required for recovery. The mean effect time predicts that patients with hepatic failure will recover more rapidly than will normal patients after infusions lasting less than 8 h. For infusions longer than 8 h, recovery will be slower in patients with hepatic failure than in normal patients. We will reconcile these seemingly contradictory implications by exploring each panel in figure 1.

The terminal half-life, shown in the top panel of figure 1, is a pharmacokinetic parameter that is nearly independent of modeling assumptions. It sets an upper limit on the time required for the plasma concentrations to decrease by 50% after drug delivery. Because of the polyexponential pharmacokinetics of the intravenous anesthetics, the terminal half-life always overestimates the time for a 50% decrease in plasma concentration. Comparing the top panel of figure 1 to the subsequent three panels correctly suggests that the terminal half-life may be misleading as a predictor of recovery.<sup>1-3</sup>

The context-sensitive half-time, shown in the second panel of figure 1, is derived from the complete pharmacokinetic model. It describes the time for the plasma concentration to decrease by 50% as a function of the duration of drug administration. It is useful for comparing the pharmacokinetics of different drugs or of the same drug in two populations. The extent to which it predicts recovery depends on the extent to which recovery correlates with a 50% decrease in plasma concentration. A 50% decrease in concentration may be a greater or lesser decrease than necessary for recovery. Additionally, intravenous anesthetics exert their effect in the brain, not in the plasma.

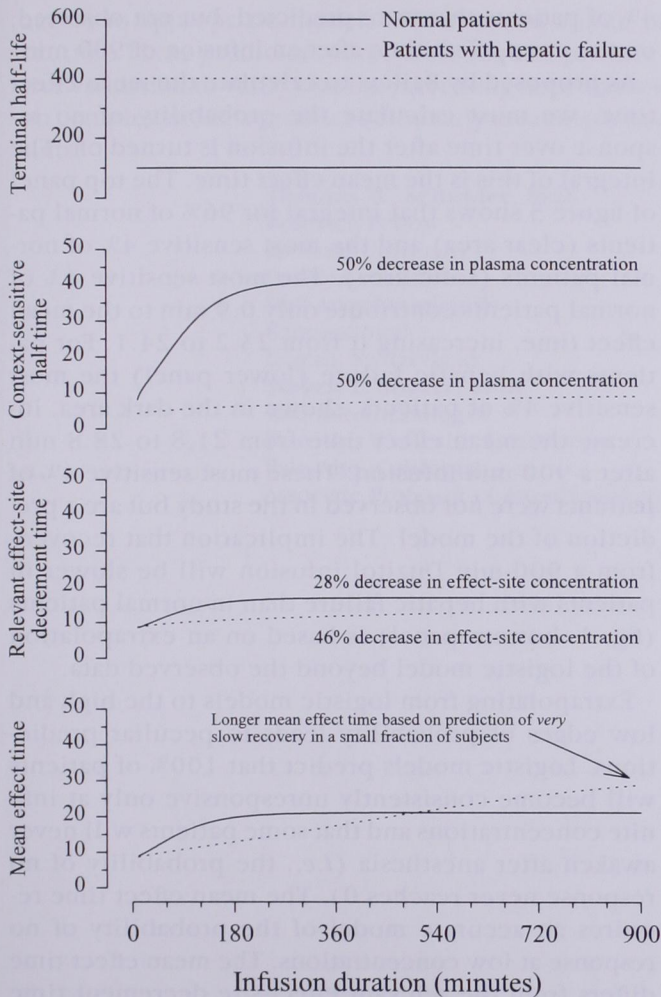
For these two reasons, the relevant effect-site decrement time, shown in the third panel of figure 1, may be a better predictor of recovery. The relevant effect-site decrement time is the time required for any specified decrement in effect-site concentration. It incorporates the effect-site model into the calculations, as

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\* Term used by Bailey<sup>4</sup> to refer to the concept that Shafer and Varvel called "recovery curves."<sup>1</sup>

EDITORIAL VIEWS



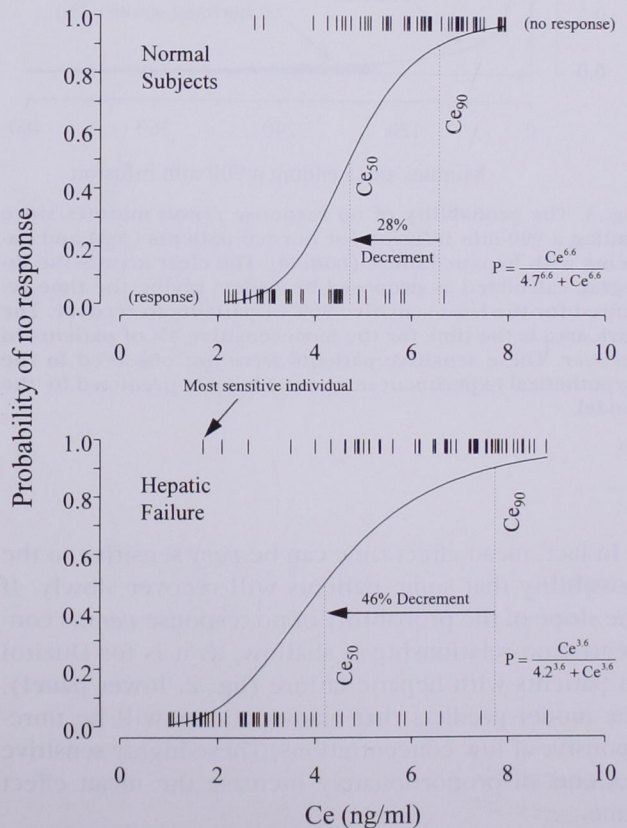
**Fig. 1.** Four predictors of recovery, graphed as functions of infusion duration. Only the terminal half-life is insensitive to the duration of drug administration. The other predictors of recovery use models to simulate the effects of drug accumulation in peripheral tissues over time.

well as an estimation of the decrement in effect-site concentration required for clinical recovery. The relevant effect-site decrement time is more dependent on modeling assumptions than either the context-sensitive half-time or the terminal half-life.

Figure 1 notes that the effect-site concentrations must decrease by 28% in normal patients but by 46% in patients with hepatic failure. These numbers come from a hypothetical experiment, shown in figure 2. In this experiment, the investigators related effect-site Duzitol concentration to assessments of response-no response (vertical bars) in normal patients (upper panel) and patients with hepatic failure (lower panel). Based on

logistic regression (inset equations), the Duzitol concentration must decrease by 28% in normal patients to make the transition from a 90% chance of no response to a 50% chance of no response (upper panel, horizontal arrow), and by 46% in patients with hepatic failure (lower panel, horizontal arrow).

The last panel of figure 1 shows the mean effect time, introduced in this issue of ANESTHESIOLOGY. The mean effect time is based on the full probabilistic model for response-no response (equations inset in fig. 2). Unlike the relevant effect-site decrement time, which is a predictor of the median time for recovery, the mean effect time is sensitive to the possibility that some patients will recover much more slowly than the median patient.



**Fig. 2.** Steady-state plasma concentration versus observations of response and no response (tick marks) and the probability of response versus no response as estimated with logistic regression. The transition from  $Ce_{90}$  to  $Ce_{50}$  requires a 28% decrease in effect-site concentration in normal patients (top, horizontal arrow) and a 46% decrease in effect-site concentration in hepatic failure (bottom, horizontal arrow). The most sensitive patient failed to respond at a concentration of 1.7 (arrow). The logistic equations are included for completeness.

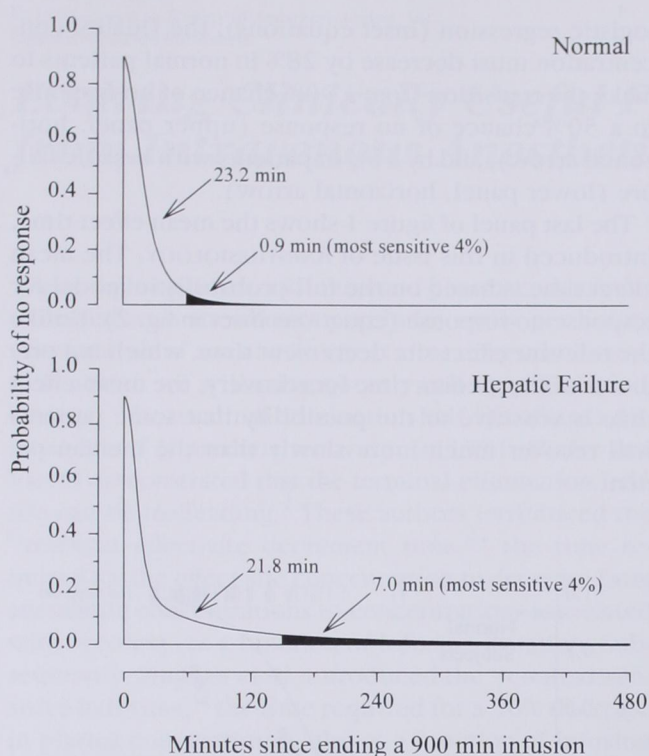


Fig. 3. The probability of no response *versus* minutes since ending a 900-min infusion for normal patients (*top*) and patients with hepatic failure (*bottom*). The clear area is the integral, calculated as proposed by Bailey, giving the time required for the least sensitive 96% of patients to recover. The dark area is the time for the most sensitive 4% of patients to recover. These sensitive patients were not observed in the hypothetical experiment in figure 2 but are predicted by the model.

In fact, mean effect time can be *very* sensitive to the possibility that some patients will recover slowly. If the slope of the probability of no response *versus* concentration relationship is shallow, as it is for Duzitol in patients with hepatic failure (fig. 2, lower panel), the model predicts that many patients will be unresponsive at low concentrations. These highly sensitive patients disproportionately increase the mean effect time.

Typically, there are few data about the most sensitive patients. In the hypothetical experiment shown in figure 2, no patient with hepatic failure was unresponsive at concentrations less than  $1.7 \text{ ng} \cdot \text{ml}^{-1}$  (arrow). Nevertheless, the logistic model predicts that 4% of the patients with hepatic failure will be unresponsive at this concentration. Figure 3 shows the influence of the

4% of patients that were predicted, but not observed, on the mean effect time after an infusion of 900 min.

As proposed by Bailey, to calculate the mean effect time, we must calculate the probability of no response over time after the infusion is turned off. The integral of this is the mean effect time. The top panel of figure 3 shows that integral for 96% of normal patients (clear area) and the most sensitive 4% of normal patients (solid area). The most sensitive 4% of normal patients contribute only 0.9 min to the mean effect time, increasing it from 23.2 to 24.1. For patients with hepatic failure (lower panel) the most sensitive 4% of patients, shown in the dark area, increase the mean effect time from 21.8 to 28.8 min after a 900-min infusion. These most sensitive 4% of patients were not observed in the study but are a prediction of the model. The implication that recovery from a 900-min Duzitol infusion will be slower in patients with hepatic failure than in normal patients (fig. 1, bottom panel) is based on an extrapolation of the logistic model beyond the observed data.

Extrapolating from logistic models to the high and low edges of probability leads to peculiar predictions. Logistic models predict that 100% of patients will become consistently unresponsive only at infinite concentrations and that some patients will never awaken after anesthesia (*i.e.*, the probability of no response never reaches 0). The mean effect time requires an accurate model of the probability of no response at low concentrations. The mean effect time differs from the relevant effect-site decrement time only when the logistic regression predicts that many patients remain unresponsive at low concentrations. If the logistic model is accurate at low concentrations, the mean effect time will contribute important clinical insight. If the logistic model is wrong, the difference between the mean effect time and the relevant effect-site decrement time may be an artifact of the logistic regression.

As predictors of recovery have evolved from terminal half-lives to mean effect time, we have turned to pharmacokinetic and pharmacodynamic models and computer simulations to predict the time required for recovery. This approach may give us predictors of recovery that reflect clinical use of intravenous anesthetics and clinically important measures of drug effect. As we have tried to demonstrate here, the increasing reliance on models may suggest conclusions that are not supported by data. We encourage investigators to calculate the mean effect time when they have

access to appropriate models. We also add a note of caution: These predictors of recovery require prospective validation to verify that the increasing dependence on complex models produces clinically meaningful results.

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