Pharmacokinetic and Pharmacodynamic Concepts Underpinning Total Intravenous Anesthesia

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VOLATILE ANESTHETICS often are combined with intravenous (IV) opioids and other IV anesthetics. Strictly speaking, total intravenous anesthesia (TIVA) refers to the exclusive use of IV anesthetics. Although many anesthesiologists use TIVA to mean anesthesia with propofol; other hypnotics such as midazolam could be used for TIVA as well. Propofol is popular because of its nonhypnotic properties.[1] Although the pharmacokinetic profile with regard to speed of onset and offset of drug effect is good compared with other IV hypnotics, recovery can be slow after long infusions of propofol. In clinical practice, the concentration of propofol, in contrast to volatile anesthetics, cannot be measured during anesthesia. If volumetric or syringe pumps are used, setting an infusion rate is different from targeting an end-tidal concentration of volatile agent.

With target-controlled infusion (TCI) systems, the predicted concentration can be used similar to an end-tidal concentration for better titration. However, this option is not universally available. Anesthesiologists, who give TIVA, empirically develop some appreciation of the input-to-effect relationship of IV anesthetics that is adequate for many situations. For optimal and rational dosing, an understanding of some basic pharmacokinetic principles is very helpful, independent of whether a TCI system or continuous infusion is being used.

PHARMACODYNAMICS

Every anesthesiologist is familiar with the minimal alveolar concentration (MAC) concept for volatile anesthetics,[2] which describes the relationship between the concentration of the anesthetic and its effect. The shape of the curve that shows the probability that a patient will move in response to skin incision is sigmoidal. The relationship is time independent, and only at steady state does the concentration relate unequivocally to the effect. There is a time delay between the time course of the inspiratory concentration, end-tidal concentration, and concentration at the effect site. The concept of MAC also is useful because dosing of different volatile anesthetics can be based on fractions (percentage) of the MAC value. The concentration can be measured in exhaled air, and it usually is displayed on anesthesia machines as absolute concentration and the MAC equivalent.

When administering IV anesthetics, many anesthesiologists are not as used to titrating based on concentrations as they are with volatile anesthetics. Although the plasma or effect site concentration of propofol at which 50% of patients are awake (Cp_{50}) has been compared with the MAC_{awake} of, for example, desflurane,[3] anesthetics uncommonly are dosed in terms of a fraction of some Cp_{50}. For example, the relative potency of alfentanil, fentanyl, and remifentanil for respiratory depression is 1:1:40,[4,5] which is about the same for analgesic endpoints.

With TCI systems, it is possible to titrate IV anesthetics to a target concentration; dosing is similar to choosing an end-tidal concentration of a volatile anesthetic. Anesthesiologists who do not have access to these TCI systems should be particularly aware that, as described subsequently, infusion rate correlates well with concentration only in steady-state conditions.

PHARMACOKINETICS

Correlation Between Infusion Rate and Concentration

IV anesthetics classically are given either by bolus (eg, 100 μg fentanyl) or as a constant infusion (eg, 6 mg/kg/h propofol). With a constant infusion, the drug concentration of propofol increases and asymptotically approaches the steady-state concentration. It takes about 15 minutes for propofol to reach 80% of the steady-state concentration. If propofol is titrated by changing the infusion rate frequently, the correlation between the "set-point" and the concentration at the effect site is poor (Fig 1). To achieve a constant concentration of propofol rapidly, specific infusion schemes are recommended.[6] With the combination of bolus (or high infusion rates) and decreasing infusion rates, a relatively stable concentration can be achieved. When titrating to an effect by changing the infusion rate, it takes considerable time until the new effect level correlates with the new infusion rate. However, if infusing remifentanil, the steady-state concentration is approached rapidly because of its pharmacokinetic properties, although for clinical purposes this is still too slow if a sudden painful stimulus has to be controlled. With an effect site TCI system, a new effect site concentration can be reached as fast as is pharmacokinetically possible. If TCI systems are unavailable,

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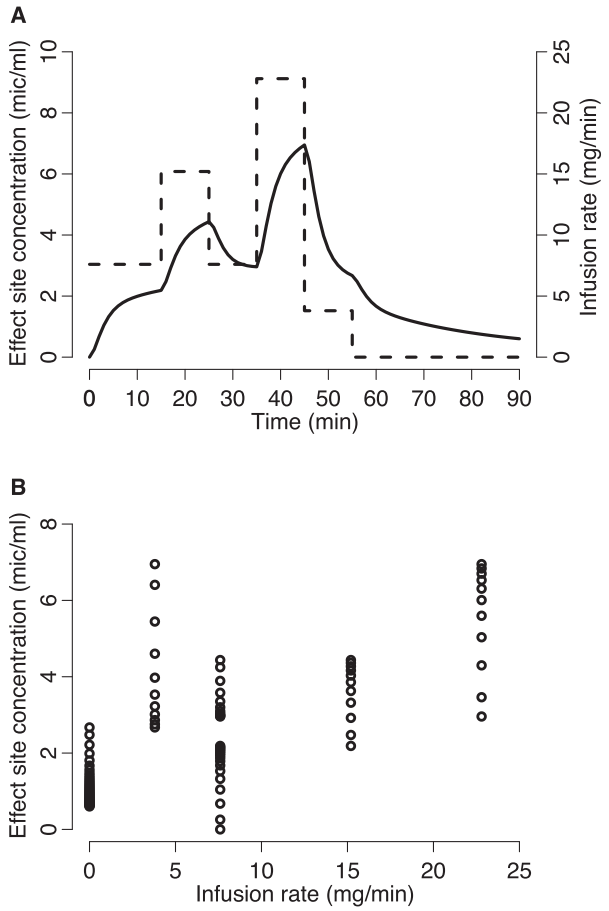

Fig 1. (A) The time course of the effect site concentration when the infusion rate (dotted line) changes at 15, 25, 35, 45, and 55 minutes. Within these time intervals of constant infusion rate, the concentration is increasing and decreasing, approaching the steady-state concentration. (B) Correlation between the infusion rate and the effect site concentration for the simulated scenario. Each circle represents the predicted effect site concentration sampled every minute for each infusion rate. The concentration is correlated with the infusion rate only at steady state; the correlation is poor if the infusion rate changes frequently.

an initial brief fast infusion (or bolus) hastens the onset of the drug effect.

Onset of Drug Effect

After a bolus dose, the concentration at the effect site increases because of the concentration gradient between the plasma and the effect site concentration. The bigger the dose, the faster the onset of the effect site concentration. Anesthesiologists make clinical use of this fact, particularly with muscle relaxants (eg, the recommended dose for rapid-sequence induction of rocuronium is double the dose for normal induction). Despite a faster onset with bigger doses, the time to the peak effect site concentration (t_{peak}) is drug specific and dose independent.[7] With a higher dose and higher peak concentration (although t_{peak} is unchanged), drug effects would be prolonged, contributing to a potentially greater drug effect and possibly more side effects (eg, hemodynamic side effects). When comparing the "speed of onset" of 2 drugs, it would not make sense to compare the onset times of 2 drugs given in doses that are not equipotent because the onset times are dose dependent.

The pharmacokinetic model–based description of the transfer of drug from the plasma to the effect site involves the transfer constant "ke0." It often is argued that a drug with a higher ke0 (ie, a shorter $t_{½}$ke0) will have a more rapid onset than a drug with a lower ke0, but this is guaranteed to be true only if the plasma pharmacokinetic profiles are identical. The overall pharmacokinetic profile (plasma kinetics and plasma effect site transfer), not only $t_{½}$ke0, is responsible for the time course of the effect site concentration. Shafer and Varvel[8] demonstrated with computer simulations that single parameters such as $t_{½}$ or ke0 are insufficient descriptors of the pharmacokinetic profile of anesthetics. They calculated the time to peak effect site concentration for fentanyl, alfentanil, and sufentanil as 3.6 minutes, 1.4 minutes, and 5.6 minutes. The time to peak effect site concentration of remifentanil is age dependent (1.22 minutes for a 20-year-old and 2.26 minutes for an 80-year-old).[9]

Recovery From Drug Effect

The half-life ($t_{½}$) of a drug is still a popular parameter. Volume of distribution and clearance also can be estimated with basic pharmacokinetic analysis, and $t_{½}$ can be calculated from these 2 parameters. In anesthesia, in contrast to other medical specialties, the initial distribution of the drug is also of interest. Knowing that the terminal $t_{½}$ for fentanyl is several hours is not very clinically useful. For all drugs given intravenously, it has been observed that time to the first 50% decrease of drug concentration is less than the time for the next 50%. This difference is due to the distribution of the drug into the different body compartments. The pharmacokinetic abstraction of this distribution is a multicompartmental model.

Nevertheless, it takes a defined time for the concentration to decrease by a defined percentage (ie, 50%, 60%, or 70%). Instead of defining the decrease of the concentration by multiples of the half-life (eg, $2 \times t_{½} = 75\%$, $3 \times t_{½} = 87.5\%$), determining decrement times is more meaningful. For many drugs, what is primarily reported is the terminal $t_{½}$. Although there is some redistribution after the cessation of administration of a drug, the terminal $t_{½}$ can have some significance outside of anesthesia (and intensive care).

During an infusion, drug is accumulated in the peripheral compartments, and the initial decrease of the concentration after the infusion has been stopped becomes less with time. When the duration of an infusion increases (the context), it takes longer for the concentration to decrease by 50%. This idea was formalized by Shafer and Varvel,[8] and Hughes et al[10] subsequently coined the term "context-sensitive half-time."

The clinically relevant decrease in concentration is not necessarily a 50% decrease. The difference between the concentration for adequate effect and the concentration for adequate recovery is clinically more meaningful. This difference between the 2 concentrations depends on the steepness of the slope of the concentration to effect relationship. Shafer and Varvel[8] showed families of recovery curves, and the concept was explored further later as the "relevant effect site concentration decrement time"[11,12] based on the fictitious drug "Duzitol."