THE PRINCIPLES OF TOTAL INTRAVENOUS ANESTHESIA (TIVA)

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This review will provide the reader with a rational basis for the administration of intravenous anesthetics. This will be based on our increasing understanding of the pharmacological processes that provide anesthesia. The goal of any anesthetic drug is to rapidly render the patient unconscious, maintain adequate anesthesia (irrespective of any surgical intervention), and then allow a rapid recovery to the awake state. To achieve this the drug needs to provide a rapid onset/offset and have a delivery system that can readily alter the effective concentration of the drug. Over the past 30 years we have gained a greater appreciation of the pharmacokinetic principles that determine onset and offset of intravenous drugs. Classically, intravenous anesthetics have been given either as a large single dose or by multiple smaller intermittent doses for induction and maintenance of anesthesia. Recent studies indicate that intravenous anesthetics given by variable rate continuous infusions provide several advantages over intermittent bolus administration. These include: a) greater hemodynamic stability; b) fewer incidences of hemodynamic breakthrough and other signs of patient responsiveness; c) reduced need for supplemental anesthetics or vasoactive drugs; d) more rapid awakening; e) decreased incidence of requirements for naloxone or need for post-operative ventilatory support; f) decreased incidence of side effects; and g) lower total dose of drug given (1). In addition to the introduction of intravenous anesthetic drugs that meet the criteria for rapid onset/offset and are thus ideal for administration by continuous infusion, there have been technological advances that will make intravenous drug delivery as convenient as the administration of volatile anesthetics.

When administering an intravenous anesthetic, the physician is aiming to obtain a predetermined therapeutic goal, i.e., anesthesia. The physician will administer a set dose which is expected to provide the desired response. The dose is based on the pharmacokinetics of the drug such that a therapeutic level of the agent is obtained. This set dose will provide, in any particular patient, a certain measured response, which, when compared to the anticipated response, will influence the physician as to what further dosing scheme may be necessary to provide the therapeutic goal. Thus, the therapeutic process involves the interaction of pharmacokinetics, i.e., what the body does to the drug, and the pharmacodynamics, what the drug does to the body. An understanding of each of these modalities is important in providing intravenous anesthesia.

**PHARMACOKINETICS**

The importance of pharmacokinetics is the ability to make use of mathematical descriptions of the disposition process to predict the resultant drug concentration within the plasma. For a two-compartment model, the plasma concentration at time T, can be calculated from the formula $CP(t) = Ae^{-at} + Be^{-bt}$. Alternatively one can make use of compartment models to calculate the plasma concentration resulting from an infusion regime. The exact solution required to calculate drug concentration using compartment models is complex. An understanding of the process involved in drug disposition, as illustrated by compartment modeling (Figure 1), does allow the clinician to provide a more rational approach to intravenous dosing regimens. The drug concentration in plasma/blood resulting from a single bolus dose of a drug administered intravenously is illustrated in figure 1.

Drug is introduced into the central compartment (blood) at a specified rate ($K_{0-1}$). This central compartment has a specified volume $V_1$. As the drug dilutes in this central compartment, it will result in a concentration dependent on the rate of drug administration/dose ($K_{0-1}$) and the volume of the central compartment ($V_1$). As drug begins to dilute within the central compartment, drug also leaves the central compartment and enters into peripheral compartment (e.g., muscle/fat) at rates specific for the drug (i.e., redistribution $K_{1-2}, K_{1-3}$). Obviously,