Intravenous Anesthesia: Techniques and New Drugs

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While the topic of this refresher course is "Techniques and New Drugs" there is only one new drug to discuss: PROPOFOL. Propofol (DIPRIVAN®, Stuart Pharmaceuticals, Wilmington, Del.) was approved by the FDA for use in the United States in October, 1989 and has been available to anesthesiologists since November, 1989. Prior to the US release, it had been used extensively in many other countries.

Propofol, 2,6,-diisopropylphenol, has been in use in the Unites States since November, 1989. Propofol is a low molecular weight (178D) molecule that is virtually insoluble in water and is highly soluble in fat. Propofol is marketed as Diprivan® by Stuart Pharmaceuticals. Diprivan® is 1% propofol mixed in an emulsion of soybean oil, glycerol and purified egg lecithin (Intralipid®). The handling of Diprivan® should be the same as the handling of Intralipid®: always use strict aseptic technique.[1] The fat in Diprivan® provides one calorie per ml.

Propofol Pharmacokinetics

Propofol has a unique pharmacokinetic profile relative to the other intravenous anesthetics. The table to the right compares the pharmacokinetics of propofol and thiopental using propofol data generated in the authors' laboratory (unpublished) and recently published pharmacokinetics for thiopental.[2]

	Propofol	Thiopental
Initial Volume (l)	6.3	12.7
Steady-State Volume (l)	530	120
Metabolic Clearance (l/min)	1.7	0.2
Rapid Dist. Clearance (l/min)	1.7	2.6
Slow Dist. Clearance (l/min)	2.1	0.6
Total Clearance (l/min)	5.5	3.4
Elimination Half-Life (hr)	6.3	12.7

The metabolic clearance of propofol is ten times as fast as the metabolic clearance of thiopental. In fact, the metabolic clearance of propofol exceeds hepatic blood flow, suggesting that propofol has extrahepatic sites of metabolism and elimination. This rapid metabolic clearance is one of the most important characteristics that makes propofol clinically and pharmacokinetically different from thiopental. The distribution clearance of an intravenous anesthetic drug is a measure of the movement of drug from the central compartment (the instantaneously equilibrating tissues including the blood and highly perfused vessel rich tissues) into tissues with lower blood flow. The total distribution clearance of propofol and thiopental ranges from 3 to 4 liters·minute^{-1}·70 kg^{-1}, a value that is approximately 60 to 80% of the cardiac output. This suggests that propofol and thiopental distribution to body tissues will be governed by cardiac output and regional blood flow. The large steady state volumes of distribution for propofol and thiopental suggest extensive partitioning into muscle and fat tissue. The long (and clinical irrelevant) elimination half-lives of propofol and thiopental result from the slow elimination of drug from the large stores in fat and muscle.

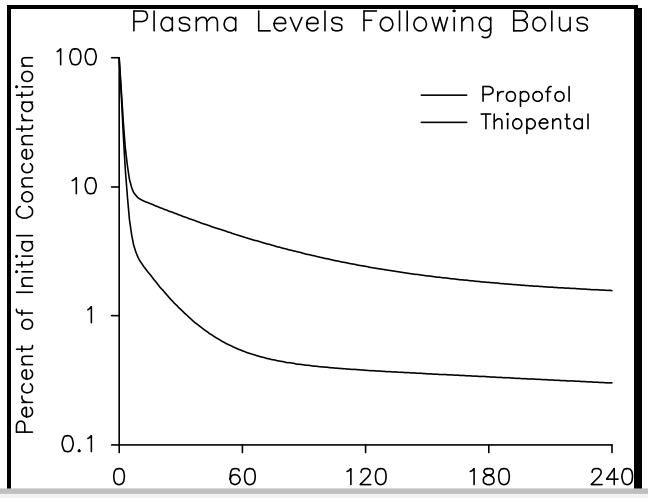

Figure 1 shows simulated declines in blood thiopental and propofol concentration as a percentage of the initial peak concentration following an intravenous bolus. This simulation is based on the pharmacokinetic parameters shown in the table on page 1. Plasma concentrations decline rapidly for both drugs in the first few minutes. The similar shapes of the curves over the first few minutes reflect the similar distribution clearances of propofol and thiopental. However, after the first few minutes the propofol concentration

relative to thiopental.

Figure 2 shows a simulation of the time required for the plasma concentration of thiopental and propofol to decline by 50% following discontinuation of a continuous infusion. This quantitates the increasing time required for recovery with increasing infusion duration. When the infusion is terminated, the propofol concentration decreases by 50% far more rapidly than the thiopental concentration. Moreover, the time required for a 50% decline once the infusion is stopped increases far more with infusion duration for a thiopental infusion than for a propofol infusion. This is consistent with clinical experience that when thiopental is used for maintenance of anesthesia, recovery may be unacceptably slow. By contrast, even after a 6 hour infusion of propofol, only 15 minutes are required for a 50% decrease in drug concentration. This finding has been confirmed in clinical studies using propofol as a sedative in intensive care units.[3]

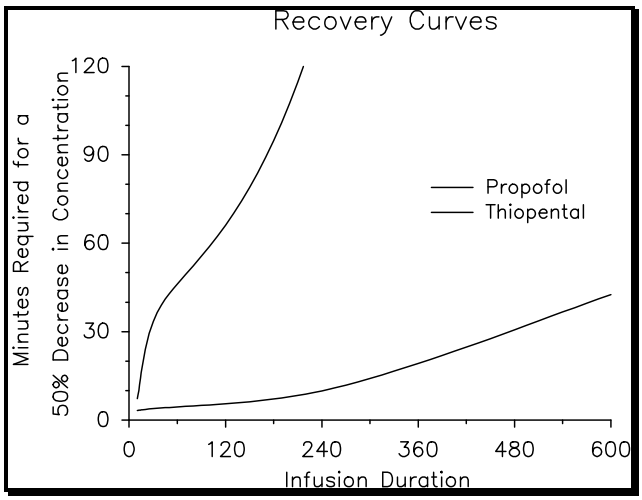

Figure 2: Curves showing time required for 50% decrease in propofol and thiopental concentration following discontinuation of a continuous infusion.

Figure 3 on the following page compares the relationship between infusion duration and recovery time for propofol (as also shown in figure 2) with alfentanil and sufentanil, based on the published pharmacokinetics of alfentanil[4] and sufentanil.[5] Even though alfentanil has more rapid half-lives than sufentanil, for infusions of less than 8 hours the plasma alfentanil concentrations may not decline as rapidly the plasma sufentanil concentrations when the infusion is terminated. This concept is more fully presented in a recent manuscript.[6]

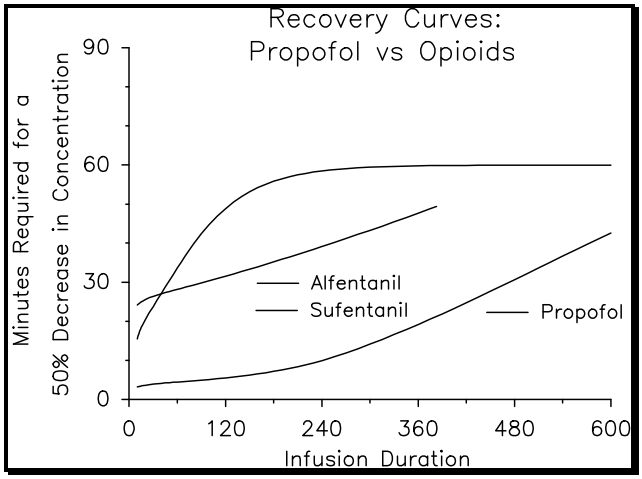

Figure 3: Curves showing time required for 50% decrease in propofol, alfentanil, and sufentanil concentration following discontinuation of a continuous infusion.

Propofol infusions are often combined with opioid infusions during anesthesia. Since the decline in propofol concentration is several fold faster than the decline in opioid concentration, it makes pharmacokinetic sense to titrate the propofol while maintaining a constant opioid concentration. Thus, if a drug overdose occurs, it will be with the drug most quickly eliminated from the blood. Clinically, it is our impression that titration of propofol produces the desired increase or decrease in anesthetic depth more quickly and reliably than titration of the opioid. The clinical dosing guidelines contain a recommendation for combining sufentanil with propofol to achieve "total intravenous anesthesia." Sufentanil was selected because its pharmacokinetic properties suggest that after infusions of less than 6 hours, patients will awaken more quickly from a sufentanil infusion than from an alfentanil infusion, as shown in figure 3.

In summary, propofol's pharmacokinetic characteristics of extremely rapid metabolism and large distribution clearances relative to distribution volumes result in a unique disposition that is well suited to both induction and maintenance of anesthesia.

Induction of anesthesia

The induction dose of propofol ranges from 1-2.5 mg/kg, administered as several divided doses (2-3 cc per dose). Elderly patients and patients receiving opioids prior to induction should receive doses closer to 1 mg/kg. Following the induction dose, patients will lose consciousness in approximately 1 minute. The blood pressure usually falls by 20-40%, while the heart rate remains stable. Intubation should be attempted 60-90 seconds following the induction dose. The blood pressure usually returns to within 10-20% of the baseline blood pressure following intubation. The heart rate tends

responds to 5-10 mg of ephedrine, and is a sign of relative hypovolemia. Fluid administration will usually resolve the hypotension. Patients in hypovolemic shock should not be induced with propofol.

Premedication with opioids decreases the propofol dose necessary for induction of anesthesia, decreases the hemodynamic response to noxious stimuli such as laryngoscopy and intubation, and increases the likelihood of hypotension following induction. Some practice is required to find the correct doses of opioid and propofol that offer smooth hemodynamics for different categories of patients.

Maintenance of Anesthesia

Appended to this syllabus is our dosing guideline for maintenance of anesthesia with a continuous infusion of propofol. This is the handout which we give residents at Stanford.

Intermittent boluses of propofol produce oscillations in propofol concentration and anesthetic depth. Therefore, the dosing guidelines assume that propofol will be given by continuous infusion during the maintenance of the anesthetic. The guidelines are intended to serve as a starting point, beyond which the anesthesiologist must titrate the maintenance infusion rate to the desired degree of CNS depression. To maintain reasonably constant propofol blood concentrations, the maintenance infusion rate should be decreased during the operation. The guidelines recommend downward adjustments at ten minutes and at two hours.

When propofol is used without N_2O or a potent vapor, there is the possibility of intraoperative awareness. Although intraoperative awareness can also occur when using a N_2O/opioid anesthetic technique, N_2O is a sufficiently potent analgesic that intraoperative awareness of pain almost never occurs during when using N_2O with an opioid. This is not the case with propofol. Intraoperative awareness during a propofol/opioid technique (e.g. during total intravenous anesthesia) *may include awareness of intraoperative pain.* To prevent awareness:

1. ***Remain vigilant for signs of light anesthesia.*** A **rapid** change in heart rate, even if only from 60 to 70 BPM, may signal impending awareness. If the patient is not fully paralyzed, nonspecific movements may occur virtually simultaneously with the change in heart rate.

2. Treat light anesthesia with a 1-2 cc bolus of propofol. One major advantage of an intravenous hypnotic over an inhaled hypnotic is the ability to administer an intravenous bolus. When signs of light anesthesia develop, this is the time to take advantage of the rapid deepening of anesthetic state that is possible with an intravenously administered drug. For this reason, we recommend keeping the propofol syringe attached to the I.V. line during the entire anesthetic.

3. Note that several minutes of light anesthesia are usually required before the patient is sufficiently aware that recall is possible. In each case of intraoperative awareness with which we are familiar, the patient was allowed to remain light for a substantial period of time. Even if patients clearly demonstrate purposeful movement, prompt treatment with a bolus of propofol will prevent postoperative recall.

4. At the end of the case, turn off the infusion several minutes prior to the desired time of emergence. However, remain vigilant for signs of light anesthesia during placement of the last sutures, etc. If signs of light anesthesia develop prior to the desired time of emergence, administer one or more small boluses (1-2 cc) of propofol. This will prolong the anesthetic without causing excessive sedation.

Propofol boluses are much more suitable for briefly extending an anesthetic by a few minutes than thiopental boluses. It is our experience that patients wake up slowly, and are quite sedated, if a small bolus of thiopental is used to extend an anesthetic. For this reason, we suggest having a syringe of propofol, not thiopental, ready to extend the anesthetic by a few minutes when necessary at the end of the case.

Cardiovascular, Respiratory and Cerebrovascular Effects

Propofol causes a decrease in mean arterial blood pressure. The decrease is usually greater than seen following induction with thiopental. The primary mechanism appears to be venous and arterial vasodilation. There is controversy about the direct cardiovascular depressant effects of propofol. However, it appears to be a mildly negative inotrope. Propofol usually causes a mild decrease in heart rate. With the exception of the effect on heart rate, the cardiovascular effects of propofol are very similar to the cardiovascular effects of isoflurane. Patients who respond with excessive decrease in blood pressure following propofol administration should be treated with volume administration.

Propofol causes apnea in hypnotic doses. The respiratory depression is enhanced by concurrent administration of opioids. Spontaneously breathing patients who receive propofol should be constantly monitored to assure the adequacy of ventilation. Equipment for controlling ventilation is essential whenever propofol is used. As seen with other intravenous hypnotics, even small doses of propofol may cause apnea in sensitive individuals.

The effects of propofol on the CNS are similar to the effects of thiopental. Propofol decreases cerebral blood flow, increases cerebral vascular resistance and decreases cerebral metabolic oxygen consumption. The EEG initially activates during propofol administration. Consciousness is lost at the time of peak activation. The EEG then slows until burst suppression is reached. Further administration of propofol causes isoelectricity. Clinical experience in patients with raised intracranial pressure is limited, and propofol is currently not approved for use in patients with raised intracranial pressure.

Clinical Dosing Guidelines

Figure 4 shows the "therapeutic ranges" of propofol concentrations needed to achieve varying degrees of CNS depression, based upon propofol concentrations presented in several recent manuscripts.[7-12] Very high propofol concentrations may be required when propofol is used as a sole anesthetic drug because propofol lacks intrinsic analgesic properties. Much lower propofol concentrations suffice when propofol is combined with drugs that provide analgesia, such as nitrous oxide or opioids. When combined with opioids, increasing the plasma opioid concentration reduces the amount of propofol needed to provide adequate clinical anesthesia.

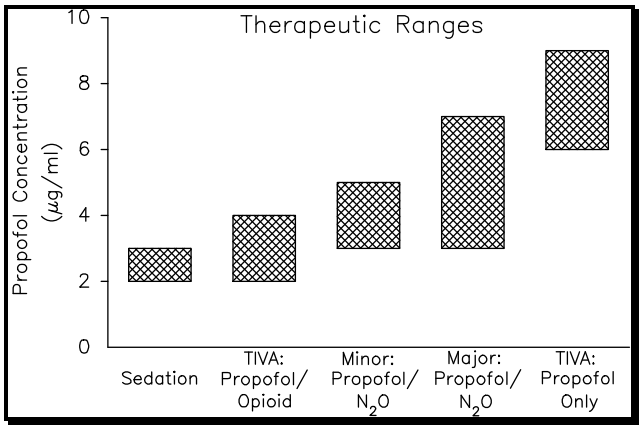

Figure 4: Propofol therapeutic ranges for different anesthetic techniques. TIVA refers to Total IntraVenous Anesthesia.

The first page of the propofol guidelines show the infusion rates required to maintain concentrations in the therapeutic ranges shown in figure 4. The second page contains a series of caveats in an effort to spare the reader many of the traps that the authors discovered while learning how to use this novel drug. Additional information about propofol can be found in several excellent reviews.[13-16]

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