The effects of body habitus, age, and sex on adequate propofol dosing and infusion for general anesthesia

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Abstract

Propofol (Diprivan) is the most widely used intravenous (IV) anesthetic for the induction and maintenance of general anesthesia. Its rapid onset, fast recovery, and antiemetic properties make propofol a popular anesthetic drug over competing drugs, such as etomidate, ketamine, and halogenated gases. While there is general agreement about the physiological effects of propofol, inconsistent dosing metrics likely complicate its disputed effects on peri- and post-operative hemodynamics and cardiac function in the literature. This review provides the rationale for the recommended dosing metric of propofol and clarifies the bodily effects of dose-appropriate propofol use. This was achieved through a systematic review of propofol's mechanism of action and observed physiological effects with respect to body habitus, age, and sex.

Keywords: propofol, anesthesia, hemodynamics, induction

Introduction

Propofol is the most widely used intravenous (IV) anesthetic for induction and maintenance of general anesthesia. Its rapid onset, fast recovery, and antiemetic properties make propofol a popular anesthetic drug of choice over competing drugs, like etomidate, ketamine, and halogenated gasses. However, it does have complications. It is well documented in the literature that propofol has sympathetic inhibitory and cardiodepressant effects.[1–6] These are demonstrated by reduced sympathetic reflex responses (e.g., tachycardic baroreceptor reflex), peripheral vascular resistance, mean arterial pressure (MAP), stroke volume, and cardiac output. While there is general agreement about the physiological effects of propofol, its dose-dependent effects on peri- and post-operative hemodynamics and cardiac function remain disputed. A review of the literature indicates that the severe cardiovascular instability observed in some peri- and post-operative care is likely major sequelae of improper dosing, often seen in the anesthetic overdosing of obese patients. As such, the use of more recent validated dosing metrics increases patient safety and reduces negative outcomes with propofol-induced anesthesia.

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Results

Pharmacokinetics and pharmacology

As a preface to the pharmacokinetics and pharmacology section, it is important to note that the mechanism of action of propofol–like most other general anesthetics–is not well understood but is attributed to its effect on gamma-aminobutyric acid (GABA)-mediated chloride channels. As an inhibitory neurotransmitter, GABA regulates cellular excitability through synaptic inhibition. By decreasing the dissociation of GABA from neural synapses, propofol's anesthetic properties potentiate the inhibitory effects of this neurotransmitter. This, in turn, keeps the channel activated for a longer period, resulting in an increase in chloride conductance across the neuron, causing a hyperpolarization of the cell membrane, and making it harder for a subsequent action potential depolarization.[7] While the inhibition of neuronal calcium channels is

responsible for the primary anesthetic effect, concomitant inhibition of vascular calcium channels likely potentiates the cardiodepressant properties of propofol (e.g., increased peripheral vasodilation and reduced mean arterial pressure, left-ventricular preload, stroke volume, and cardiac output). Due to propofol's lipophilic properties, the termination of anesthesia is primarily driven by redistribution in body tissue; metabolism and excretion have a secondary role.[8] As discussed in a subsequent section, this affinity for lipophilic tissue serves as an important factor in drug distribution and maintenance of propofol-induced anesthesia in obese patients.

Dosage and rate of infusion

Propofol dosage and rate of infusion have critical roles in proper anesthetic technique. Its administration is most commonly performed via manual bolus injections or through the use of computer-controlled infusion pumps (CCIP). Regardless of approach, the accepted rule of thumb used to estimate propofol dosage for patients has been 1–2 mg/kg and maintenance/induction follows the popularized "10-8-6" rule used for adult infusions.[9–10] However, the broad application and adherence to such guidelines forfeits key physiological factors that have been proposed to alter the required dosing and rates of infusion to maintain adequate anesthesia with minimal complications. These key factors are discussed in subsequent paragraphs which outline the relationship between the dosing of propofol and body habitus, age, and sex.

Body habitus

Muscle mass, water volume, and body fat percentages are highly variable among patients, and such differences represent key complicating factors in achieving therapeutic levels of anesthesia. Due to the pharmacokinetic properties of propofol, guidelines used for induction doses and maintenance doses can differ, especially concerning morbidly obese patients with a body-mass index (BMI) greater than 35 kg/m^2. It has been demonstrated that propofol infusion rates based on total body mass (TBM), while convenient and sometimes sufficient, can result in underdosing of lean patients and overdosing of obese patients.[11–13] In morbidly obese patients, the increased cardiac output and absolute circulation and overestimation of primary distribution volume primarily affect the early pharmacokinetic parameters of propofol, thus making increasingly obese patient more susceptible to overdosing. This overdosing of propofol can produce severe cardiovascular depression in obese patients due to altered pharmacokinetics.

Since the administration of propofol on a per weight basis is associated with relatively higher rates of improper dosing, it has been suggested that the TBM metric should be replaced with lean tissue mass (LTM).[14–16] While not as convenient or immediately available as TBM, determination of LTM appears to be a more accurate metric in propofol dosing. Chassard et al. reported that LTM can be determined by bioelectrical impedance (BIA) and corrected body mass index (BMI). Bioelectrical impedance is designed to determine fat-free mass and total body water using a low-level current passed between electrodes. By measuring resistance drops across the body, lean body mass can be calculated. However, the pitfall of BIA is its impracticality in clinical use. Thus, authors suggest use of corrective BMI (which was demonstrated in the same study to have high correlation with BIA) as a surrogate means to estimate lean body mass when BIA is not available.[17] In addition, the use of a corrective formula (ideal weight + 0.4 × excess weight) prevented propofol accumulation in morbidly obese patients. When this correction was performed, results showed dosing schemes expressed in mg/kg are the same as those in normal patients.[1,18]

Age

In general, as the age of the patient increases, the dose required for adequate induction and maintenance of anesthesia decreases. Therefore, children often require higher induction doses and infusion rates of propofol than adults for induction and maintenance of clinical anesthesia. Such differences have been attributed to altered pharmacokinetics and compartment volumes of distribution between age groups.[9] However, a notable finding demonstrated by Crankshaw et al. was that there appeared to be no age-related change

in propofol ED50 values when using LTM to calculate dose. This contrasts with TBM calculated ED50 values that show a decrease in dose requirement for propofol. In essence, lean tissue mass appears to indicate the pharmacological active mass of the patient more accurately. Thus, dosing based on LTM removes the previously observed differences in patient responses between both age groups and the sexes.

Relatively simple algorithms are used in effective clinical use of propofol infusions. Traditionally, one such popular algorithm is the "10-8-6 rule" used for adult infusions.[10] The rule includes a loading does of propofol at 1 mg/kg followed by an infusion of 10 mg/kg/hr for a period of 10 minutes, then 8 mg/kg/hr for the next 10 minutes, and finally 6 mg/kg/hr for the subsequent time period. However, reports demonstrate that the use of this rule is inadequate in pediatric patients due to differences in volume compartment distribution, metabolism, clearance, and other pharmacokinetic properties. Current manual infusion rate recommendations for children are an extension of the "10-8-6" rule and are generally accepted in the field.[19]

Studies have suggested that decreased preload associated with propofol is partially compensated for by reduced total peripheral resistance (TPR), resulting in improved heart function and compensated cardiac output. However, studies also demonstrate that in older patients, stroke volume remains decreased, contributing to decreased cardiac output. Side effects were more marked with rapid injection or doses in excess of 1.75 mg/kg, causing significant hypotension and apnea in older patients. These studies reveal marked sensitivity to propofol in the elderly with respect to both induction dose and acute toxicity.[20–21] Older and sicker patients generally have higher basal levels of sympathetic tone and body fat percentages as well as reduced baroreflexes. These, in addition to relatively poorer volume status, may amplify the negative inotropic and hemodynamic effects of propofol-mediated sympathoinhibition.[22]

Sex

Pharmacodynamics, body habitus, and age are among the major factors that influence propofol dosing. However, even though there are important differences in these factors between male and female patients, there is little research available that analyzes propofol dosing differences and hemodynamic outcomes in males and females. From the limited articles available, studies demonstrated no significant dosing or blood plasma level differences between the sexes with regard to dose or infusion rates.[1,4,23] However, Hoymork et al. did observe more rapid declines in plasma propofol concentrations in females compared to males, likely explaining why women tend to awake from anesthesia faster than men. Our experience and discussion with clinical faculty suggest that males tend to require increased concentrations of propofol for adequate anesthesia, but this has not been demonstrated in formal studies. The effect of sex on propofol dosing requirements and hemodynamic outcomes needs further investigations.

Case studies

Often cases are reported with the conclusion that propofol use caused the death of the patient due to cardiodepressive effects. While there may be some merit to these claims, it is not unreasonable to question the propofol dosage and speed of administration. For example, some studies state that patients receiving propofol over extended periods of time can develop myocardial failure and death.[25] The study mentioned the measure of (mg/km/h) being used to dose the patient that resulted in cardiodepressive effects related to the patient's death. This study failed to report any alternative dosing strategy and strictly attributed propofol overdose for cause of patient death. If different dosing metrics were considered, such as dosing based on lean tissue mass, perhaps an overdose event could have been avoided and proper use of the anesthetic would have been implemented.

Another study focused on the death of an 18-year-old male who suffered several injuries, coma, and additional complications. As a result, he required ventilation and anesthesia using propofol.[26] The study mentioned using (mg/hr) to dose propofol in this patient but again but did not mention a dosing strategy. Therefore, it is most likely that the undesired cardiodepressive effects caused by overdose in this

patient could have potentially been avoided since the appropriate dosing of propofol does not have drastic cardiodepressant effects. When appropriate measures are taken, such as using lean tissue mass instead of body mass to dose propofol, fewer cardiodepressant effects will occur in clinical settings.

Discussion

While propofol is known for its sympathoinhibitory and cardiodepressant characteristics, the appropriate dosing of propofol minimizes the risks associated with under- and over-therapeutic anesthetic levels. A review of the literature suggests that the severe cardiovascular instability observed in some peri- and post-operative care is likely major sequelae of improper dosing, especially as seen in the anesthetic overdosing of obese populations. As such, the use of more recent validated dosing metrics can reduce poor patient outcomes associated with propofol-induced anesthesia. When appropriate measures are taken, such as using lean tissue mass instead of body mass and accounting for age and body habitus, patients will be more properly dosed and thus be at lower risk for developing severe cardiac and hemodynamic instability.

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