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Propofol as an Intravenous Agent in General Anesthesia and Conscious Sedation

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Propofol has been shown in clinical studies to be a safe, effective, hypnotic, and amnesic anesthetic agent at induction doses of 2–2.5 mg/kg and maintenance doses of approximately 9 mg/kg per hour. Significant post-induction hypotension reported earlier can be reduced to a fall in MAP of less than 25% when the drug is used alone (without nitrous oxide or narcotic premedication). Post-induction apnea is minimized by avoidance of pre-induction hyperventilation. Acute and long term venous tolerance is acceptable. Emergence from anesthesia induced and maintained with propofol is rapid, predictable and relatively free of postoperative complications. Incidence of drug interaction is low. Propofol causes no adrenocortical suppression and is not potentiated by ethanol, diazepam, amitriptyline or phenelzine. Preliminary investigation of propofol as an intravenous sedative agent at subanesthetic doses has been favorable.

Outpatient or ambulatory surgery has been shown to hold many benefits for both patient and practitioner in the performance of minor elective surgical procedures in the healthy patient. Nowhere has this been demonstrated more successfully than in the practice of dentistry and oral and maxillofacial surgery. The increasing popularity of outpatient surgery and the trend toward shorter hospital stays after elective surgery has accelerated the search for shorter acting, more receptor specific anesthetic agents that are less likely to produce intraoperative and postoperative complications. Agents recently produced with this goal in mind that are used commonly in clinical practice are methohexital, fentanyl, sufentanil, alfentanil, midazolam, and etomidate. These drugs have been shown to possess many advantages when applied to the ambulatory surgical setting, and are partly responsible for the widespread acceptance that this form of health care delivery has earned.

Another drug known for its short duration of action and specificity is propofol (2,6-diisopropylphenol). As a phenol, propofol exhibits very limited aqueous solubility. This property has presented difficulty in preparation of a clinically acceptable vehicle. Produced by Imperial Chemical Industries in the late 1970s, it was virtually abandoned due to reports of severe pain on injection, anaphylactoid reactions and venous sequelae subsequent to its intravenous administration. Since that time, the cremaphor EL solubilized preparation has been replaced with a one percent aqueous emulsion containing ten percent soya bean oil and egg lecithin,[1] eliminating the anaphylactoid and venous complications noted earlier. In this form the desired pharmacologic and anesthetic properties were retained, enhancing propofol's potential as a short duration anesthetic agent. It has since been used alone for induction and maintenance of general anesthesia, in combination with regional anesthesia, with and without premedications, in combination with inhalation anesthesia, and most recently in intravenous sedation. It has been compared with methohexital, thiopental, and etomidate in clinical studies with favorable results. Extensive studies have been conducted in Europe and are presently in progress in the United States. This brief report reviews the pharmacological and clinical characteristics of propofol that have been studied and reported in the literature.

USE FOR ANESTHETIC INDUCTION

Propofol has been described as a potent hypnotic drug producing anesthesia within one arm-brain circulation time at induction doses of 1.5–2.5 mg/kg, possessing a rapid recovery time and causing minimal postoperative sequelae. Dose-response studies have indicated bolus

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induction doses of 2.0 mg/kg[1–7] and 2.5 mg/kg,[8–18] and maintenance infusion rates of 6–9 mg/kg per hour.[1–6,9,16,19] Bolus inductions are effective at both dosages, but the lower dosage resulted in more rapid dissipation of anesthesia. Propofol at either dose, however, demonstrated less anesthesia offset on intubation than thiopental.[16] Induction of anesthesia with propofol has been reported to be as rapid as with thiopental and methohexital, with a lower incidence of hiccups and excitatory side effects.[15,16] Early reports mention a significant dose-dependent fall in blood pressure on induction with propofol. It has also been associated with a slightly higher incidence and longer period of post-induction apnea when compared to both methohexital and thiopental. Venous tolerance is acceptable without significant acute or long term sequelae noted, although administration via a superficial hand vein results in reports of mild to moderate pain on injection.

Hemodynamic changes associated with the administration of propofol intravenously have ranged from no clinically significant change (i.e., MAP decrease of less than 25%) to a 55% decrease in systolic blood pressure compared to awake values. Significant decreases in blood pressure on induction with propofol were noted to be similar to that seen with methohexital, minaxolone, and althesin. This fall in blood pressure was accompanied by a reduction of cardiac output. It should be noted that these effects were demonstrated with the concomitant administration of nitrous oxide. Nitrous oxide exerts a vasodilatory effect on cutaneous, renal, and cerebral circulation[20] which may be additive with propofol's vasodilatory effects. Used alone for induction and maintenance, without nitrous oxide or narcotic premedication, no significant hypotension was reported.[2,16,21] As induction doses are increased above those accepted as appropriate, incidence and extent of hypotension increases.[13] It appears that narcotic premedication and concomitant administration of nitrous oxide potentiate any hypotensive effects that propofol may demonstrate alone. Little effect on heart rate during induction and maintenance has been demonstrated in any of the literature reviewed.

Propofol on induction (2 mg/kg IV bolus) demonstrates an incidence of apnea of 48% with a mean duration of 51 seconds in patients breathing room air spontaneously.[9] During the first minute (post-injection), a mean decrease in respiratory rate of 15% (±55%) was noted, whereas during the second minute, a mean increase of 25% (±46%) above baseline was reported.[23]

Used for induction (2.5 mg/kg IV bolus) and maintenance (100 μg/kg per minute), breathing 100% O_2 by facemask, tidal volume was reported to decrease to 70% of awake values and respiratory rate increased 30% over baseline. This resulted in a minute volume of 70–140% of awake values.[9] In this study apnea occurred in 70% of patients with a duration of up to two minutes. The authors reported that this may have been exaggerated by pre-induction hyperventilation. These figures indicate a wide individual variation in ventilatory response to induction agents, a clinical characteristic similar to other agents used commonly at this time.

When compared with methohexital, propofol demonstrated an increased occurrence of apnea and longer duration of the episode, but a significantly lower incidence of hiccups and excitatory effects.[7,14,24]

The most striking advantage of propofol over other induction agents is its rapid and relatively complication-free recovery period. Its rapid recovery time is due mainly to its rapid distribution into the tissues, giving it a large volume of distribution (approximately 300–700 L)[24–28] and blood concentration half-life of two to four minutes.[24] The post distributive phase half-life (indicative of metabolic clearance) was found to be 34–45 minutes.[29] Elimination of the drug is renal in nature as illustrated by the excretion of 88% of a subanesthetic dose of ^{14}C labeled propofol in the urine. Less than 0.3% of that which was excreted into the urine was unchanged propofol. The remainder were the conjugates 1- and 4-glucuronides and 4-sulphate of 2,6-diisopropyl-1,4-quinol and -propofol glucuronide. Proportions of these metabolites were constant over the 1–24 hour period, indicating the extended terminal phase of elimination. Less than 2% of the dosed radioactivity was contained in feces illustrating an insignificant biliary excretion component in propofol's elimination.[29] The long final phase (elimination half-life) of 220–290 minutes[22,23] is thought to reflect propofol's slow release from the third compartment, mainly poorly perfused fat.[23,25,29] Metabolism of the drug appears to be extra-hepatic since clearance exceeds hepatic blood flow.[23,25,29,30] Systemic clearance was reported to be approximately 1800 ± 200 mL per minute.[22,23,26,28,30] This open, three compartment model would suggest that the fastest recovery time would result from single bolus injections. This has been demonstrated for single bolus induction and maintenance with inhalation agents resulting in eye opening on command in approximately five minutes following termination of anesthesia.[31] In contrast, with continuous infusion maintenance, eye opening on command took approximately 20 minutes.[31] Used for induction only, reaction time tested at 90 minutes post-emergence and at regular intervals during the first two postoperative days, those patients receiving propofol were consistently and significantly faster at all postoperative points than the patients receiving methohexital and thiopental.[10] Another study comparing propofol with methohexital and thiopental reported that recovery following induction was faster than with methohexital and twice as fast (30 vs. 60 minutes) as with thiopental.[31]

Induction with propofol at a dose of 2 mg/kg and maintenance with continuous infusion of propofol at 9 mg/kg per hour and fentanyl at 7.5 mg/kg per hour for less than one hour resulted in a termination of anesthesia to eye opening on command time of 10.5 minutes. The time from termination of anesthesia to unimpaired cognition was 11.5 minutes.[1] Without the infusion of fentanyl, the time from termination of anesthesia to eye opening on command was 8.3 minutes, and time to correct response to question was 10 minutes.

Minor postoperative complications (confusion, vomiting, drowsiness, depression, headache) were not noted following induction with propofol in the immediate postoperative period,[31] or after three hours post-emergence.[1] Propofol exhibited a recovery as rapid as methohexital, a smoother induction, and a significantly lower incidence of postoperative nausea when used for induction in dental and oral surgical procedures with enflurane anesthesia. Authors and patients report rapid cerebration return post-anesthetically,[9] and patients have volunteered how well they felt compared to previous anesthetic experiences.[31]

Amnesic properties of propofol reported have been largely dose-dependent, with complete transoperative amnesia occurring in 80–90% of patients receiving continuous infusion at a rate of 9 mg/kg per hour.[32] This amnesia had not affected memory for new facts at discharge.[32]

No difference in acute or long term vein tolerance was noted between propofol and methohexital, administered via superficial veins of the hand.[3,14] Compared to thiopental, propofol had a significantly higher incidence of pain on injection using superficial veins of the hand.[16] Being injected into antecubital veins versus superficial veins of the hand decreased the incidence of pain on injection from 30% (hand) to 2% (antecubital). No long term sequelae (thrombophlebitis) were noted in any of the references reviewed for any of the induction agents used.

Other Characteristics

Propofol was not found to have any potent agonist or antagonist properties, or any effect on bronchomotor or gastrointestinal motility, platelet aggregation, or whole blood clotting time. It is without ganglion blocking or α-adrenergic antagonist properties. Pretreatment with ethanol did not potentiate the effects of propofol as it did with thiopental. Similarly, four daily doses of phenelzine (MAO inhibitor), amitriptyline (tricyclic antidepressant), diazepam, and ethanol did not potentiate propofol's effects in mice 24 hours later. The antiarrhythmic threshold to epinephrine was higher utilizing propofol (in cats) than when using halothane for maintenance of anesthesia. The acute administration of the beta-blockers atenolol and propranolol was tolerated well in pigs anesthetized with propofol.[33] Additionally, little or no adrenocortical suppression to surgical stress or ACTH stimulation occurred, as has been seen in association with induction with etomidate.[8,33] No pharmacokinetic differences have been shown for cirrhotic patients as compared with normohepatic patients[25] which has indicated an extensive extra-hepatic metabolic mechanism. In the pediatric patient, spontaneous movement on induction was noted in 65% of cases induced with propofol, and produced a mean fall in blood pressure and heart rate of 20% and 10% respectively.[34] Propofol will require further study to determine its value, if any, in the treatment of the pediatric patient.

USE AS A SEDATIVE AGENT

Propofol has been administered in subanesthetic doses via continuous infusion in conjunction with regional anesthesia, and in the postoperative management of the cardiac surgery patient. The infusion rate used was approximately 4 mg/kg per hour (patients over the age of 65 requiring approximately 3 mg/kg per hour)[35] for good surgical sedation—defined as sleep with preservation of eyelash reflex and purposeful reaction to verbal or mild physical stimulation (ear tug)—accompanying regional anesthesia. Patients in the immediate postoperative period following cardiac surgery required a mean infusion rate of 13 μg/kg per minute as a result of the post-anesthetic sedation and the level of sedation desired.[36] In combination with regional anesthesia, the mean time from termination of anesthesia to eye opening was four minutes. Mean duration of infusion for this study was 97 minutes and mean duration of surgery was 70 minutes. The mean time from end of infusion to full consciousness was 4.4 minutes and no postoperative sequelae were noted. Depth of sedation could be easily and rapidly adjusted by altering the infusion rate. Sedation could be converted to general anesthesia by increasing the infusion rate to approximately 10 mg/kg per hour. This technique was described by the author as safe, simple, and versatile with an impressive recovery time (full return of orientation within five minutes of infusion termination). No discomfort or pain was noted on infusion and hemodynamic changes were compatible with spinal anesthesia, and not a result of administration of propofol per se. Although the preliminary investigation cited used subjective data, it did bring to light several apparent advantages of this technique. Use of intravenous propofol for sedation appears to merit further study and may be of benefit in the practice of dentistry and oral and maxillofacial surgery.

CONCLUSION

Through extensive study in Europe and the United States, propofol (2,6-diisopropylphenol) has been found to be an effective potent hypnotic and amnesic. It has the ability to produce good surgical conditions safely in the healthy patient. Rapid onset of action, rapid recovery time, little post-anesthetic sedation, and few related post-anesthetic sequelae make it a drug well suited to the ambulatory surgical setting. Significant hypotension on induction appears to be minimized when the drug is used alone (without nitrous oxide), which also eliminates the potential hazard to surgical and anesthesia personnel through chronic exposure to low level nitrous oxide. Incidence and duration of post-induction apnea appears to be dose related and may be minimized by avoiding pre-induction hyperventilation. Evidence suggests that fewer excitatory symptoms are noted with induction of anesthesia with propofol as compared with methohexital and thiopental. Patient acceptance is good due to low incidence of pain on injection (antecubital veins), rapid return of psychomotor function and minimal postoperative sequelae. Long term venous tolerance is good without any thrombophlebitis reported following propofol's administration. Ethanol's inability to potentiate propofol's effects is a definite advantage as well. Continued study and the eventual FDA approval suggest that propofol may be a valuable agent for the performance of minor surgical procedures in the ambulatory setting.

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