A controlled investigation of propofol, thiopentone and methohexitone

Martin I. Gold MD, Edward C. Abraham MD, Claire Herrington RN

This was a randomized study of 180 ASA physical status I and II patients, 60 in each group who received propofol (PROP), 2.5 mg·kg^{-1}, thiopentone (THIO), 4 mg·kg^{-1}, or methohexitone (METH), 1.5 mg·kg^{-1}. Control values, followed by changes after induction and during a 3-min delay before intubation were recorded for the following parameters: heart rate (HR), systolic and diastolic blood pressures (SBP, DBP), respiratory rate (RR), end–tidal CO_2 ($P_{ET}CO_2$), and induction time (IT). In addition, the incidence of adverse reactions and time for recovery from anaesthesia were noted. The IT (mean ± SE) was 35 ± 1 sec for propofol, 35 ± 1.2 sec for thiopentone and 34 ± 1.4 sec for methohexitone. Ninety-three per cent of the PROP group fell asleep with one dose and required no additional doses. Fifty per cent of each of the THIO and METH groups required additional agents ($p < 0.05$). METH was associated with the highest elevation in HR, PROP the least ($p < 0.05$). PROP was associated with the most decrease in SBP and DBP and in addition respiratory depression ($p < 0.05$). The incidence of injection pain or excitatory activity was equal in the three groups with the exception that 14 patients who received METH developed hiccoughs while none did in the other groups. PROP was associated with the most rapid recovery, particularly with respect to the orientation time. We conclude that PROP is an effective alternative to barbiturate induction and that the published recommended doses of THIO and METH are often ineffective.

Key words

ANAESTHETICS, INTRAVENOUS: propofol, thiopentone, methohexitone; ANAESTHESIA, GENERAL: induction, recovery.

From the Department of Anesthesiology, University of Miami School of Medicine and the Veterans Administration Medical Center, Miami, Florida.

Address correspondence to: Dr. Martin Gold, VAMC, 1201 N.W. 16th Street, Miami, Florida 33125.

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Propofol (PROP) is a highly water insoluble intravenous induction agent which is chemically related to phenol, with two substituted propyl groups.[1] It has an extremely rapid elimination half-life[1–4] of 55 min which is much shorter than either methohexitone (METH) or thiopentone (THIO) (1.5 to 4 hours and 5–12 hours respectively).[5] Propofol was introduced in 1980 in a cremophor preparation but in view of the high incidence of adverse allergic reactions to cremophor the preparation was withdrawn from human experimentation. Propofol has since been reformulated in a lipid emulsion consisting of lecithin, egg white, and other fatty preparations.[4] In the United Kingdom, where most studies have been done, a number of investigations have indicated some advantages to propofol and it appears that with the new preparation allergic reactions are no longer a concern. The purpose of this study was to evaluate and compare the efficacy and safety of 2.5 mg·kg^{-1} of PROP compared with 4.0 mg·kg^{-1} of THIO and 1.5 mg·kg^{-1} of METH for induction of anaesthesia. These are reported to be equipotent doses.[5–10] The ED95 induction doses of propofol, thiopentone, and methohexitone are respectively 2.4 mg·kg^{-1}, 3–5 mg·kg^{-1} and 1.5 mg·kg^{-1}.[5–10]

Methods

With the approval of the Human Research Committee at the University of Miami we conducted a randomized study of 180 ASA physical status I and II patients, all of whom gave their informed consent. The patients underwent abdominal, orthopaedic, genito-urinary, ear, nose and throat, or plastic surgical procedures. The first 144 patients were studied such that the investigators and the observers knew which drug was being administered, because propofol's milky emulsion made it difficult to blind the observer to the drug being used. The last 36 patients were studied in a manner in which the induction drug was blinded to the observers. This was accomplished by a third investigator who prepared the correct amount of drug to be injected in a taped syringe, utilized taped intravenous tubing and injected the agent while a towel covered syringe and tubing. Patients excluded from the study were those with known allergy to the trial drug constituents or who had clinically significant organic

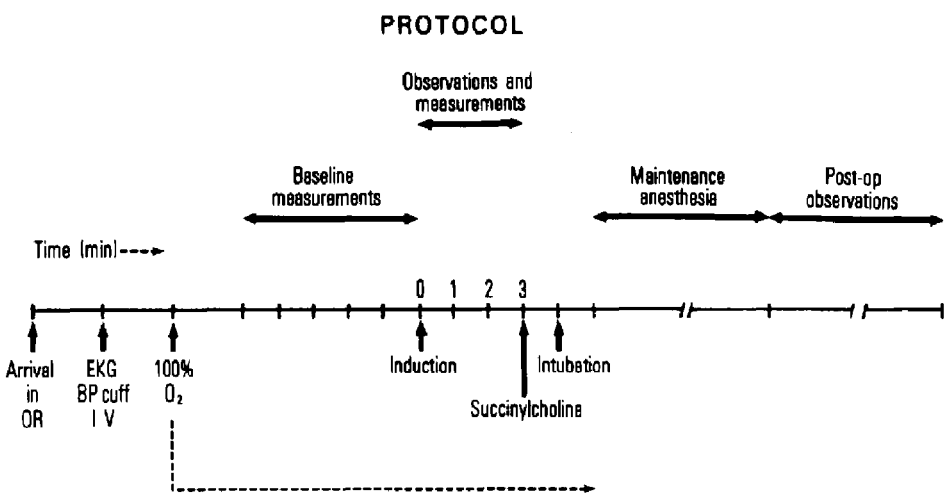

FIGURE 1 Protocol including time on the horizontal axis in minutes with description of procedures performed.

disease. All patients underwent a thorough physical examination, standard laboratory tests, an ECG and chest *x*-ray. All tests were done both preoperatively and postoperatively.

On the night before surgery each patient received flurazepam (15–30 mg) and on-call to the operating theatre each patient received diazepam, 0.1 $mg \cdot kg^{-1}$, meperidine, 0.7 $mg \cdot kg^{-1}$ and glycopyrrolate, 3 $\mu g \cdot kg^{-1}$ IM. Patients were assigned to one of the three groups in a randomized fashion. An individual envelope for each patient was opened prior to the induction of anaesthesia. The contents of the envelope indicated the induction agent which was to be used. Propofol was supplied as a white emulsion in 15 ml ampules containing 10 $mg \cdot ml^{-1}$, which had been shaken thoroughly. The other drugs included commercially available 2.5 per cent thiopentone and one per cent methohexitone. When patients arrived in the operating room, each was monitored with a continuous V_5 ECG lead and an automatic blood pressure device (Acutorr, Datascope). An intravenous infusion was started in the arm opposite the blood pressure cuff, in a large vein above the wrist.

The patient then breathed 100 per cent O_2 for approximately five minutes (Figure 1) and control values for HR, SBP, DBP and RR were obtained. We also measured end-tidal carbon dioxide ($P_{ET}CO_2$) with a scanning mass spectrometer (SARA, Allegheny International Medical). Induction was begun with the administration of the agent during a 20-second period while the patient counted out loud. Induction time was measured by a stop watch and judged by loss of consciousness and loss of eyelid reflex. All feelings of pain and discomfort at the injection site were recorded if the patient spontaneously commented. Physiologic variables were then measured each minute for a three-minute period. Apnoea and its duration and any other side effects were noted. We were particularly interested in any excitatory activity, such as myoclonus or limb jerking. If the patient did not fall alseep within the first minute or showed evidence of awakening, through movement of the head or extremities, moaning or actual response to verbal command, a second induction dose already prepared, consisting of 50 per cent of the original dose was given. At the end of three minutes of observation, succinylcholine 1.5 $mg \cdot kg^{-1}$ was administered. If the patient subsequently showed signs of awakening *before* paralysis 50 per cent of the original amount of the induction agent was given. After paralysis the trachea was intubated and maintenance anaesthesia provided with 0.5–2 per cent isoflurane, and 60 per cent nitrous oxide in oxygen.

Recovery from anaesthesia was evaluated postoperatively in the following manner. Awakening time was recorded from the end of the administration of anaesthesia to the spontaneous opening of the eyes. Response time was defined as that from the end of the administration of anaesthesia to the time required to follow simple commands. Orientation time was recorded from the end of the administration of anaesthesia to that time when the patient could recall his/her name, date of birth and present location.

Statistical analyses were performed on all data. The last 36 patients were investigated in a double-blind fashion

TABLE I Demographics

	No. of patients	Mean age ± SE	Mean weight (kg) ± SE	Mean BSA (m^2) ± SE	ASA I	ASA II
Propofol	60	48 ± 2	78 ± 2	1.95 ± 0.02	16	44
Thiopentone	60	45 ± 2	79 ± 2	1.96 ± 0.02	14	46
Methohexitone	60	44 ± 2	82 ± 2	2.00 ± 0.02	12	48
Total	180				42	138

and at first were treated differently. However, when both groups' data were compared statistically there were no differences with the single exception of systolic blood pressure for patients receiving propofol; therefore, all of the data were pooled and treated identically and are reported as the mean information for all 180 patients. Data on a nominal scale were subjected to Chi-square analysis. Data on a ratio scale were subjected to standard t test when comparing two groups and when more than two groups were compared, to analysis of variance. Significance was accepted at $p < 0.05$. With a 20 per cent difference in response considered "clinically" significant, the relatively large number of patients (180) allowed us to confer a power of greater than 84 per cent on all of our results.[11] This implies that a type II error or false-negative conclusion was avoided.

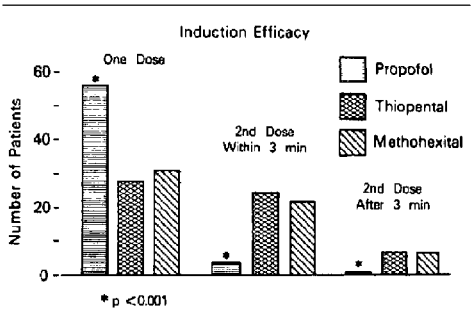

FIGURE 2 Efficacy of induction with the three anaesthetic agents with one dose, second dose within three minutes and after three minutes.

Results

The demographic results are reported in Table I in each group of 60 patients. There were no significant differences in weight, age, body surface area but there were more ASA II than ASA I patients. There was no difference in the relative distribution among groups.

There were no statistically significant differences in the pre- or posttreatment values between and among anaesthetic agents. In Table II the general physiologic effect of the three induction agents are displayed. Induction time was approximately 35 seconds in all groups.

Figure 2 is a display of induction efficacy. The number of patients is shown on the vertical axis and on the horizontal each group was divided into three categories: those initially induced successfully with a single dose, those who required a second dose because they exhibited moaning, awakening or extremity movement within the three-minute evaluation period, and those few patients receiving a second dose after the administration of succinylcholine but prior to paralysis. All of the patients were successfully "induced" with the initial injection. We then waited three minutes. The majority of patients receiving PROP (93 per cent) required a single dose only for successful induction and three-minute maintenance; only seven per cent required a second dose. In contrast, in patients receiving THIO or METH, approximately 50 per

TABLE II Physiologic effects (mean ± SE)

Drug	Induction time (sec)	Heart rate change	Blood pressure change (mmHg) Systolic	Blood pressure change (mmHg) Diastolic	Respiratory rate change (breaths·min^{-1})	End-tidal CO_2 (mmHg) change	Apnoea duration – number of patients None	<30 sec	30–60 sec	>60 sec
Propofol	35 ± 1	+5* ± 1.2	−14† ± 2.0	−8† ± 1.2	−7† ± 1.0	−1 ± 1.0	3	7	8	42‡
Thiopentone	35 ± 1.2	+10* ± 1.2	−1 ± 1.0	+4 ± 1.0	−4 ± 1.1	−2 ± 0.7	11	3	21	25
Methohexitone	34 ± 1.4	+20* ± 2.1	−1 ± 1.0	+2 ± 1.0	−4 ± 1.2	−1 ± 1.2	7	5	25	28

*$p < 0.001$ (compared with both other drugs).
†$p < 0.001$.
‡$p < 0.01$.

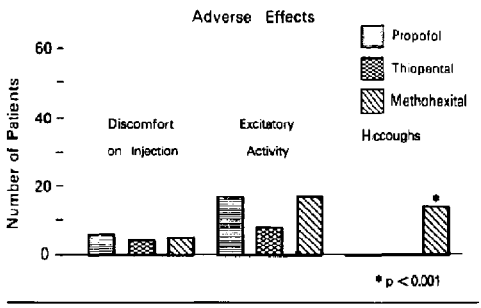

FIGURE 3 Adverse effects ranging from discomfort on injection through excitatory activity to hiccoughs.

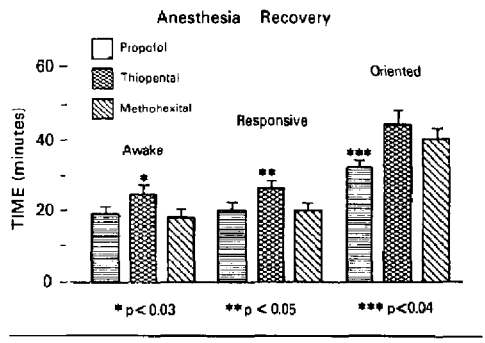

FIGURE 4 Anaesthesia recovery including awake, response, and orientation times.

cent received a single dose and the remainder required the second dose after the first dose, as described ($p < 0.05$).

In Table II the average change in heart rate from control is depicted. METH was associated with the highest elevation, an average of 20 beats·min^{-1}. The HR in the THIO group increased by 10 beats·min^{-1} while the PROP group had the smallest change in HR, with an average elevation of 5 beats·min^{-1}. Each of the increases in HR was different from the other two ($p < 0.05$). Table II also depicts the average change in systolic and diastolic pressures (SBP and DBP). Both barbiturates were associated with unchanged SBP and DBP, whereas PROP was associated with a decrease respectively of 14 ± 2.0 and 8 ± 1.2 mmHg ($p < 0.05$). PROP was associated with a decrease in RR of 7 breaths·min^{-1} compared with 4 breaths·min^{-1} with the barbiturates ($p < 0.05$). The end-tidal carbon dioxide was unchanged in all groups.

The patients were divided into four categories: those without apnoea after administration of the induction agent, those apnoeic for less than 30 seconds, those apnoeic for 30–60 seconds and those apnoeic for more than one minute. In the last category there was a greater difference with PROP, since once apnoea occurred, it persisted for more than a minute in most instances ($p < 0.05$).

Figure 3 summarizes the adverse effects occurring after induction. In terms of discomfort on injection or excitatory activity there were no differences among the three groups. However, all of the 14 instances of hiccoughs were associated with METH ($p < 0.05$).

We evaluated recovery after anaesthesia. Patients were divided into three groups according to the duration of anaesthesia: patients anaesthetized for two hours or less, for more than two and up to four hours, and for more than four hours. There were no significant differences in the relative distribution among groups. Figure 4 displays anaesthesia recovery and is an assessment of the awake, response and orientation times (see Methods). Patients receiving THIO required more time to awaken and respond to simple verbal commands whereas patients who received PROP and METH took less time and were similar in this regard ($p < 0.05$). On the other hand, the PROP group required a considerably shorter time to become oriented compared to patients who received barbiturates ($p < 0.05$).

Discussion

Propofol, or di-isopropyl-phenol, was first used as an induction agent in 1977;[1] within a few years it had created interest in the anaesthesia community.[2] Because of its rapid metabolism and the short elimination half-life,[3,4] initial studies indicated that it would be satisfactory for bolus administration and also continuous infusion.[2] These impressions grew stronger with experience, since there was little evidence of accumulation and, on the other hand, a great deal of evidence for rapid recovery with relative freedom from side effects.[4,7] Propofol was initially formulated in Cremophor EL since it is extremely water insoluble. Cremophor EL was, however, directly implicated as a causative agent in hypersensitivity reactions and pain on injection.[12] Currently an alternative formulation is used which is an aqueous emulsion containing ten per cent soya bean oil, 1.2 per cent egg phosphatide and 2.3 per cent glycerol.[4] This formulation is slightly less potent than the original.[4] In animal studies, propofol was shown to have anaesthetic properties similar to the Cremophor EL preparation.

A number of comparative human studies have now been performed indicating that propofol is not unlike thiopentone,[9,13] methohexitone,[9] etomidate,[14] and thiamylal.[15] Comparative studies indicate that 2.5 mg·kg^{-1} of propofol is equipotent to 1.5 mg·kg^{-1} of methohexitone and 4–5 mg·kg^{-1} of thiopentone.[5–10] Therefore propofol is less potent than methohexitone but it is more so than

thiopentone. It does not depress cortisol synthesis as does etomidate.[16] However, it does depress the cardiovascular and the respiratory systems[9] more so than do the barbiturates. In fact, while it does not alter heart rate, cardiac output or stroke volume it does depress systemic vascular resistance.[6] It is associated with more rapid awakening and orientation times than the barbiturates,[2,9] and therein lies its attraction and prime interest for anaesthesia.

This investigation was a comparison of the safety and efficacy of three induction agents, propofol, thiopentone and methohexitone for general anaesthesia and recovery after various surgical procedures. Propofol is similar in many ways to the barbiturates. Since this was not originally a double-blinded study we were concerned that investigator bias might have influenced results. We attempted to solve this problem by blinding the observers to the drug in 36 patients, as Edelist did.[17] Comparing the results of these 36 patients with those of the first 144 we were able to verify that, with the exception of a single parameter (systolic blood pressure), there were no statistical differences between blinded and open label patients and no apparent investigator bias. Therefore, the data for the "blinded" 36 patients were added to the data for the original 144 making a total of 180 patients.

This study involved ASA physical status I and II patients and excluded ASA III and IV patients. Furthermore, our protocol did not resemble the typical clinical induction–intubation sequence since we waited three minutes from the time of induction to the administration of succinylcholine. Therefore, we were able to detect signs of awakening during this time period which would ordinarily involve laryngoscopy and intubation and uncover the presence of side effects such as tremors, myoclonus or hiccoughs. All of these side effects would have gone unnoticed in the usual induction where succinylcholine paralysis closely follows the administration of the induction agent and probably masks both awakening and some of these side effects.

Consequently, we found 2.5 $mg \cdot kg^{-1}$ of propofol to be more effective in providing adequate induction depth of anaesthesia than 4.0 $mg \cdot kg^{-1}$ of thiopentone and 1.5 $mg \cdot kg^{-1}$ of methohexitone, even though these are published comparable doses.[5–10] It is possible of course that 2 $mg \cdot kg^{-1}$ of methohexitone and 5 $mg \cdot kg^{-1}$ of thiopentone would have provided a different comparative potency situation. However, we believe the implication of our data is that the doses used of thiopentone and methohexitone are not sufficient in relatively healthy patients.

The heart rate was more stable with propofol than with the barbiturates. However, we found a significant decrease in blood pressure with propofol and not with the barbiturates. The possibility that propofol may interfere with baroreceptor function requires investigation.

All of these induction agents can cause some degree of respiratory depression, but propofol did so more than the others. It was certainly associated with more and longer lasting apnoea and also a longer decrease in respiratory rate. This is probably clinically unimportant since respirations are usually assisted if a mask is used or controlled in the clinical setting were succinylcholine is administered and an endotracheal tube inserted.

We found no more adverse effects with propofol than with thiopentone and this includes discomfort on injection and excitatory activity. However, in the methohexitone group a significant number of patients developed hiccoughs, although identical injection rates were used. This is a disadvantage particularly in patients who are not going to be intubated but will receive mask anaesthesia.

Patients who received thiopentone clearly required more time to recover from anaesthesia. This is a disadvantage, especially with outpatient surgery. However, orientation time was significantly faster for propofol, a property which will probably make it advantageous for short procedures and daycare surgery. Our conclusions are: (1) thiopentone 4.0 $mg \cdot kg^{-1}$ and methohexitone 1.5 $mg \cdot kg^{-1}$ and were not effective in inducing and maintaining unconsciousness for three minutes in about half of our patients whereas propofol 2.5 $mg \cdot kg^{-1}$ was effective in almost all (93 per cent) patients. (2) Methohexitone was associated with an extremely high incidence of hiccoughs (approximately 25 per cent). (3) Propofol is an effective alternate induction agent to the barbiturates. (4) Propofol does have some undesirable side effects the most notable being a decrease in blood pressure and respiratory depression. (5) Because of its rapid elimination propofol appears to be advantageous for short procedures. The clinical result is that recovery time and particularly orientation time is faster with propofol.

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Résumé

Voici une étude aléatoire de 180 patients de statut physique ASA I et II, divisés en trois groupes de 60, qui ont reçu 2.5 mg·kg^{-1} de propofol (PROP), ou 4 mg·kg^{-1} de thiopental (THIO), ou 1.5 mg·kg^{-1} de méthohexital (METH). Les valeurs-témoins, suivies de changements après l'induction et durant un délai de trois minutes avant l'intubation, ont été enregistrées pour les paramètres suivants: fréquence cardiaque (FC), pression artérielle systolique et diastolique (PAS, PAD), fréquence respiratoire (FR), CO_2 de fin d'expiration ($P_{ET}CO_2$), et temps d'induction (TI). De plus, on a inscrit l'incidence de réactions adverses et le temps de rétablissement de l'anesthésie. Le TI (moyenne ± SE) était de 35 ± 1 sec pour le propofol, 35 ± 1.2 sec pour le thiopental et 34 ± 1.4 sec pour le méthohexital. Quatre-vingt-treize pour cent des patients du groupe PROP se sont endormis après l'administration d'une dose et n'ont requis aucune dose additionnelle. Cinquante pour cent des patients du groupe THIO et du groupe METH ont requis des doses additionnelles des agents respectifs ($p < 0.05$). La plus grande augmentation de la FC fut associée au METH tandis que la plus petite fut associée au PROP ($p < 0.05$). Le PROP fut associé à la plus grande diminution de la PAS et de la PAD et à une dépression respiratoire ($p < 0.05$). L'incidence de la douleur ou d'activité d'excitation à l'injection était égale dans les trois groupes à l'exception de 14 patients du groupe METH qui ont eu un hoquet alors que ceci ne s'est produit chez aucun patient des autres groupes. Le PROP a été associé au rétablissement le plus rapide, concernant plus particulièrement le temps d'orientation. Nous concluons que le PROP est une alternative efficace à l'induction aux barbituriques et que les doses recommandées de THIO et de METH dans les publications sont souvent inefficaces.