Acta Anaesthesiol Scand 2011; **55**: 429–434
Printed in Singapore. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2011.02401.x

Onset time and haemodynamic response after thiopental vs. propofol in the elderly: a randomized trial

M. K. Sørensen, T. L. Dolven and L. S. Rasmussen
Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Background: The induction dose of hypnotic agents should be reduced in the elderly, but it is not well studied whether thiopental or propofol should be preferred in this group of patients. The aim of this study was to compare onset time, hypnosis level and the haemodynamic response after thiopental vs. propofol for induction of anaesthesia. Our primary hypothesis was that in the elderly, thiopental had a shorter onset time than propofol, defined as time to bispectral index (BIS) <50.

Methods: In this randomized and double-blinded study, we included 78 patients. Patients were eligible, if they were scheduled for elective surgery with general anaesthesia and aged 60 or older. Patients received alfentanil 10 μg/kg and either thiopental 2.5 mg/kg or propofol 1.0 mg/kg, and depth of anaesthesia was determined with BIS the following 120 s along with clinical assessment of anaesthetic depth. The primary endpoint was the time from start of injection of the hypnotic to a BIS value below 50.

Results: Time to BIS <50 was significantly shorter in patients receiving thiopental, where onset time was 52 s (median value) compared with 65 s in the propofol group ($P = 0.01$). Mean arterial pressure decreased 25.6 mmHg in the propofol group and 15.6 mmHg in the thiopental group ($P = 0.003$) within 120 s. Heart rate decreased 9.1 b.p.m. within 120 s in the patients receiving propofol compared with a decrease of 5.1 b.p.m. in patients receiving thiopental ($P = 0.04$).

Conclusion: Thiopental was found to have a faster onset than propofol in elderly surgical patients.

Accepted for publication 13 January 2011

An increasing proportion of surgical patients consists of elderly. It is recommended to use smaller doses of anaesthetics in the elderly, and for induction agents it may be appropriate to titrate according to the clinical response in order to avoid giving too high doses, which will lead to circulatory depression.[1] The induction dose of thiopental and propofol should probably be between 30% and 50% of the dose given to young adults, but there is a huge variation, not only as a result of altered sensitivity but also related to a slower distribution.[2–4]

Anaesthetic depth during induction can be assessed by clinical signs such as eye closure, lack of ciliary reflex and lack of response to verbal stimulation or pain. However, during classic rapid sequence induction and intubation (RSII), where preoxygenation is followed by bolus induction with a hypnotic, an opioid and a neuromuscular blocking agent (NMBA) in rapid succession along with cricoid pressure before intubation,[5–7] it is much more difficult to judge the necessary dose of the induction agent.

Effects of hypnotics on the brain can be assessed by the depth of anaesthesia monitors that are based on either spontaneous or evoked EEG.[8] The bispectral index (BIS) is an empirically derived algorithm processed EEG parameter[9] that enables a quantification of anaesthetic depth.

The aim of this trial was to assess the time from injection to an adequate anaesthetic state was reached in elderly patients when comparing propofol with thiopental, the primary outcome being the time from injection to a BIS below 50. We hypothesized that thiopental would have a shorter onset time than propofol in patients aged 60 years or more. In addition, we assessed the haemodynamic response.

Materials and methods

The Danish Medicines Agency and the Regional Ethics Committee approved the trial, which adhered to the International Conference on Harmonisation Good Clinical Practice standards. The trial was registered at ClinicalTrials.gov 24 August 2009; Identifier: NCT00965107. Written informed consent was obtained from all patients participating in this single centre trial. Patients were eligible if they were 60 years or older and scheduled to undergo elective surgery requiring general anaesthesia. We excluded patients with known allergic reactions to propofol, thiopental, alfentanil or lidocaine, a body mass index of below 18 kg/m^2 or above 35 kg/m^2, heart failure with New York Heart Association Functional Classification above II, or if the planned airway management technique included techniques other than laryngeal mask or tracheal intubation with a Macintosh blade.

Trial protocol

Patients were randomized 1 : 1 according to a computer-generated list (GraphPad Software® Inc., La Jolla, CA). An envelope was prepared for each allocation before the start of the trial, by staff with no other involvement in the trial. The intervention allocation list was securely stored from the investigators, along with an allocation key.

The patients were randomized to receive either propofol (1 mg/kg i.v.) or the equipotent dose of thiopental (2.5 mg/kg i.v.) for induction of general anaesthesia.

The patients were monitored with four lead ECG, non-invasive blood pressure measurement and pulse oxymetry. The BIS measurement was made with BIS VISTA® (Aspect Medical Systems Inc., Norwood, MA). A second to second BIS data collection was stored for each patient, and the BIS was set with a smoothing rate of 10 s. A distal intravenous access was placed on the upper extremity with running Ringer lactate infusion. The patient was instructed to hold a baseball (Official League®, 5 oz, 9 in.) in one hand, between the fingertips, and to keep the eyes open for as long as possible. The arm was supported, and the ball was held with the palm directed towards the floor and free from the table. The procedure was started with an injection of alfentanil 10 μg/kg i.v., followed by an injection of propofol 1 mg/kg or thiopental 2.5 mg/kg given as a bolus injection over 10 s i.v. One millilitre of lidocaine (40 mg/ml) was added to 20 ml of propofol (10 mg/ml). Mask ventilation was started when spontaneous respiration seized as evaluated by the anaesthesiologist responsible for airway management.

The time was started at injection of the investigational drug and outcome registration was performed the following 120 s. The primary outcome was 'Onset-time' (defined as the time from start of injection of investigational drug to a BIS value below 50 was reached). Secondary outcomes were time from start of injection to 'Loss of grip' (defined by the time the baseball hit the floor), time to 'Eye closure' (defined by the superior eye lid covering the pupil) and time to 'Disappearance of ciliary reflex' (defined as lack of ciliary reflex despite continuous stimulation after eye closure). Heart rate and non-invasive blood pressure were recorded after 60 and 120 s. This was performed by beginning inflation of the blood pressure cuff after 45 and after 105 s. No other personnel was allowed to touch the patient within the timeframe during which data collection occurred. The patient and the investigator evaluating the primary and secondary endpoints were blinded to the induction agent by injection of the drug under a cover by the attending anaesthesiologist, and by adding lidocaine to propofol to reduce pain upon injection. Pain upon injection could potentially unmask the intervention allocation for the patient and the investigator.[10] The personnel doing the data collection were blinded to the allocation by only being presented the allocation list without the allocation key. After statistical evaluation, an abstract and a conclusion were written in two copies, one for each allocation possibility. After completion of the abstract, the allocation key was revealed.

Statistics

Demographic data were presented as median values [interquartile range]. Continuous variables were reported using mean [standard deviation (SD)] or median [interquartile range]. We compared the onset time of the two groups using the Mann–Whitney test. $P < 0.05$ was considered statistically significant. We made an 'intention-to-treat' analysis on all randomized patients, who received an intervention. Proportions were reported with 95% confidence interval. Analysis were performed using SAS® statistical software version 9.1 (SAS Institute Inc., Cary, NC).

Sample size calculation was based on the following: A difference in onset time of 20 s was consid-

ered to be clinically relevant. A SD of 44 s for time to lowest BIS was found after propofol 2 mg/kg in one study,[11] and in another study a SD of 18 s was found for time to loss of ciliary reflex after thiopental 5 mg/kg, while the corresponding value was 36 s after propofol 3 mg/kg.[12] Because our patients were ≥ 60 years of age, we expected a SD of 30 s for time to BIS value below 50. Based on this, we calculated a sample size of 72 patients, assuming a power of 0.80 at the 5% significance level. We added six to take potential drop-outs into account, to a total of 78 patients.

Results

Between 3 November 2009 and 6 March 2010, we randomized 78 patients (Fig. 1, Table 1). All randomized patients who received either thiopental or propofol, were included in the 'intention-to-treat' analysis ($n = 75$). Three patients did not receive the intervention because of last minute cancellation of the operation, last minute change in airway management plan or a logistic failure. One patient received propofol but was allocated to receive thiopental.

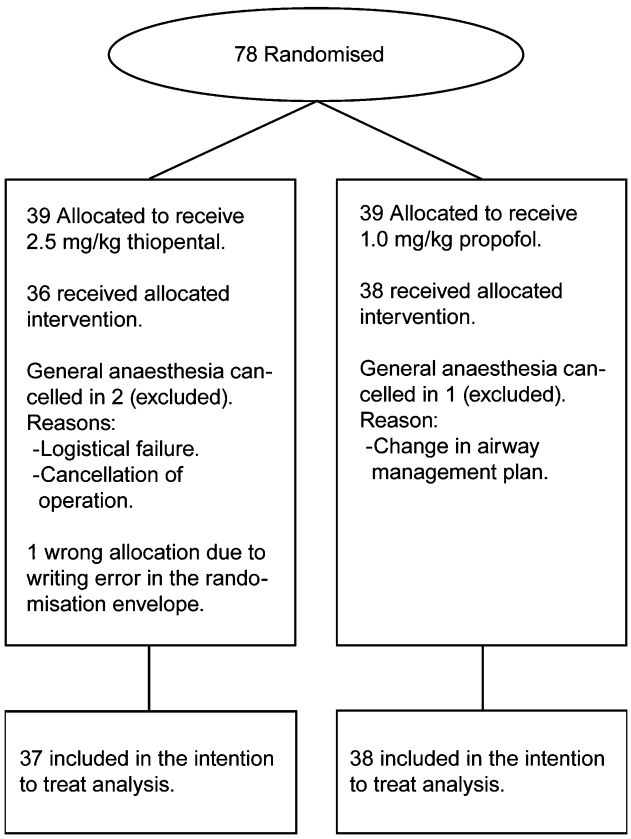

Fig. 1. Trial profile.

Table 1

Demographic data of elderly surgical patients allocated to either thiopental or propofol.

	Thiopental	Propofol
Age (years)	68 [64–75]	67 [65–72]
Sex (male/female)	20/19	17/22
ASA PS-class		
1	13	13
2	23	23
3	3	2
4	0	1
BMI (kg/m^2)	25.0 [21.9–28.4]	24.7 [22.0–27.7]

Values are median [interquartile range].

A BIS value below 50 was reached in 13 vs. 26, with thiopental and propofol, respectively. The time from start of injection of investigational drug to a BIS value below 50 was reached in 52 s (median value) in the thiopental group compared with 65 s in the propofol group ($P = 0.01$, Table 2, Fig. 2). The lowest BIS value (mean) recorded with propofol was 49.8 (SD 12.7) vs. 56.8 (SD 14.2) with thiopental ($P = 0.03$). There were no significant differences in the time to Eye Closure, Disappearance of Ciliary Reflex or Loss of Grip. All patients but one receiving the intervention obtained Eye Closure. Mean arterial pressure (MAP) decreased 25.6 mmHg (SD 15.0) in the propofol group and 15.6 mmHg (SD 13.2) in the thiopental group ($P = 0.003$) within 120 s. Heart rate decreased 9.1 b.p.m. (SD 9.4) within 120 s in the patients receiving propofol compared with a decrease of 5.1 b.p.m. (SD 7.3) in patients receiving thiopental ($P = 0.04$) (Table 2).

Discussion

We found that thiopental had a significantly shorter onset time, defined as time to BIS value below 50. Propofol was associated with a significantly greater decrease in blood pressure and heart rate. Clinical signs of sleep onset were not significantly different.

The primary strength of this trial is that our set-up reflected a common clinical practice and included several endpoints to assess onset time of general anaesthesia of two well-matched groups of elderly surgical patients. Our set-up also reflects induction of anaesthesia in an easily controlled environment and with a clear primary endpoint that was recorded from the BIS monitor and all other assessments of end points were also blinded to the investigator.

Table 2

Onset time and haemodynamic response in elderly surgical patients randomised to thiopental or propofol.

	Thiopental	Propofol	*P*-value
Time to BIS <50 (s)	52 [46–56]; (7.9), *n* = 13	65 [53–80]; (23.0), *n* = 26	0.01
Lowest BIS value	56.8 (14.2)	49.8 (12.7)	0.03
	CI 52.0 to 61.6, *n* = 36	CI 45.6 to 54.0, *n* = 37	
Time to BIS <65 (s)	53 [45–89]; (26.7), *n* = 25	59 [48–69]; (18.7), *n* = 32	0.48
Time to BIS <80 (s)	48 [41–57]; (21.9), *n* = 35	53 [45–60]; (13.8), *n* = 37	0.27
Time to lowest BIS value (s)	76.3 (22.0)	84.2 (24.7)	0.15
	CI 68.8 to 83.7, *n* = 36	CI 76.0 to 92.4, *n* = 37	
Eye closure (s)	38 [32–44]; (10.9), *n* = 35	35 [31–47]; (12.2), *n* = 37	0.92
Disappearance of ciliary reflex (s)	53 [44–61]; (20.9), *n* = 35	53 [42–66]; (17.8), *n* = 36	0.98
Loss of grip (s)	40 [34–45], *n* = 31	41 [35–48], *n* = 33	0.71
Change in MAP	−14.1 (13.3)	−21.6 (12.1)	0.01
after 60 s, mmHg	CI −18.5 to −9.7, *n* = 37	CI −25.5 to −17.6, *n* = 38	
Change in MAP	−15.6 (13.2)	−25.6 (15.0)	0.003
after 120 s, mmHg	CI −20.0 to −11.2, *n* = 37	CI −30.5 to −20.7, *n* = 38	
Change in Heart rate	−2.4 (8.3)	−6.5 (8.4)	0.04
after 60 s, b.p.m.	CI −5.2 to 0.3, *n* = 37	CI −9.2 to −3.7, *n* = 38	
Change in Heart rate	−5.1 (7.3)	−9.1 (9.4)	0.04
after 120 s, b.p.m.	CI −7.5 to −2.7, *n* = 37	CI −12.2 to −6.0, *n* = 38	

n specified for each endpoint and group.
Values are mean (SD) or median [interquartile range] or 95% CI.
CI, confidence interval; BIS, bispectral index; MAP, mean arterial pressure.

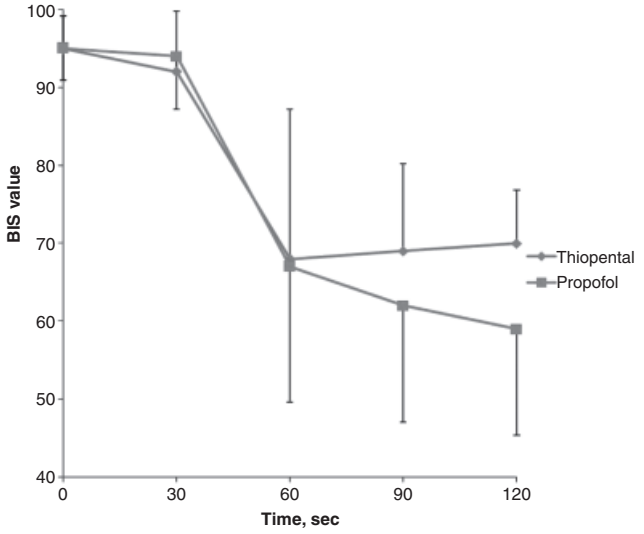

Fig. 2. BIS-values in elderly surgical patients given either thiopental or propofol.

The trial had several limitations. First, the BIS monitor is sensitive to movement in an awake patient, adding to noise during the transition from the awake to the anaesthetized state, and propofol induction may cause involuntary muscle activity. The detected difference in time to reaching the low BIS value could therefore result from electrical interference related to muscle contractions. On the other hand, there was not a major difference in the variability of BIS values between the groups (Table 2), and we found a consistent pattern in the drop in BIS with a more rapid but less profound decrease after thiopental (Fig. 2). There was no significant difference in the clinical endpoints for onset of sleep. Second, the primary endpoint was only obtained in approximately half of the patients due to low dosages of the interventional drugs. This was an unanticipated finding. Third, the blood pressure measurements were non-invasive and non-continuous. We only collected outcome data for a few minutes after giving the study drugs and we have no data on the long-lasting haemodynamic response or postoperative complications. However, these variables would be very difficult to link to the induction agent alone.

A 50% reduction of the propofol and thiopental induction dose has been recommended in elderly patients.[1] We therefore considered 2.5 mg/kg thiopental and 1 mg/kg propofol to be equipotent based on a former study.[13] Propofol 1 mg/kg was associated with the lowest BIS values and the doses may therefore not have been equally potent, but the onset time of propofol was still longer in our study when compared with thiopental 2.5 mg/kg.

Onset time of thiopental (4 mg/kg) was also faster than propofol (2 mg/kg) in a study assessing time to minimum BIS value in young adults.[14] Clinical signs of sleep onset may be more difficult to evaluate, and this adds to the biological variation. The time to clinical signs of sleep onset was

very similar and occurred in the same sequence in the groups. Eye closure and loss of grip occurred after approximately 40 s and disappearance of the ciliary reflex was observed 10–20 s later.

The primary endpoint of our study was set to a BIS value of below 50, as 50 is in the middle of the target range (BIS 40–60) set by the company producing BIS Vista®. Furthermore, a BIS level below 50 has been shown to be a reliable sign of unconsciousness and inability to recall events, when using propofol, midazolam or isoflurane.[15]

Only half of the patients reached a BIS below 50. The lowest BIS value in the thiopental group was 56.8 (mean) and in the propofol group 49.8. This was somewhat higher than expected. BIS values at loss of consciousness are higher in elderly patients given propofol for induction,[16] and this could explain the detected difference.

Alfentanil was given to all patients in our study and this could decrease the necessary concentration of the hypnotic at which patients lose consciousness as convincingly shown for propofol.[17] Thiopental and alfentanil have also been shown to interact.[18] Administration of opioids have a limited influence on the BIS and the alfentanil dose was quite small.[19]

The ideal hypnotic should have a short onset time and it should be associated with no significant circulatory depression. The huge variation among elderly patients may be managed by titrating the induction agent until an appropriate response has been observed. This strategy may prolong induction time and the time period in which there is an unprotected airway. In patients with an increased risk of pulmonary aspiration, it is therefore not feasible, and RSII is the preferred procedure. We did not include any patients with increased risk of pulmonary aspiration and an NMBA was not used during the data collection, but nevertheless the procedure was meant to mimic the sleep induction used in RSII, and we believe that our findings can guide the anaesthesiologist.

Other drugs for induction could be relevant to assess in the elderly, such as etomidate[20] and *S*-ketamine, especially in the setting of RSII.

In conclusion, in elderly surgical patients we found thiopental to have a faster onset than propofol, although the clinical endpoints of adequate anaesthesia were not significantly different. The effect on blood pressure and heart rate after propofol was significantly greater than after thiopental with a clinically relevant difference in MAP and heart rate. We conclude that thiopental seems to be a better choice than propofol for single bolus induction of anaesthesia in the elderly.

Acknowledgements

Funding: TrygFonden (Tryg Foundation), Lyngby Hovedgade 4, 2. floor, 2800 Kgs, Lyngby, Denmark. Research Fund, Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Denmark.
Coflict of interests: None.

References

1. Rivera R, Antognini JF. Perioperative drug therapy in elderly patients. Anesthesiology 2009; 110: 1176–81.
2. Dundee JW, Robinson FP, McCollum JS, Patterson CC. Sensitivity to propofol in the elderly. Anaesthesia 1986; 41: 482–5.
3. Homer TD, Stanski DR. The effect of increasing age on thiopental disposition and anesthetic requirement. Anesthesiology 1985; 62: 714–24.
4. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ. The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90: 1502–16.
5. Jensen AG, Callesen T, Hagemo JS, Hreinsson K, Lund V, Nordmark J. Scandinavian clinical practice guidelines on general anaesthesia for emergency situations. Acta Anaesthesiol Scand 2010; 54: 922–50.
6. El-Orbany M, Connolly LA. Rapid sequence induction and intubation: current controversy. Anesth Analg 2010; 110: 1318–25.
7. Rasmussen LS, Viby-Mogensen J. Rapid sequence intubation – how? Acta Anaesthesiol Scand 2007; 51: 787–8.
8. Rosow C, Manberg PJ Bispectral index monitoring. Anesthesiol Clin North America 2001; 19: 947–66, xi.
9. Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 1994; 10: 392–404.
10. Nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: a comparison of lidocaine with alfentanil. Anesth Analg 1996; 82: 469–71.
11. Blum J, Kochs E, Forster N, Schneider G. The influence of injection rate on the hypnotic effect of propofol during anesthesia: a randomized trial. PLoS Clin Trials 2006; 1: e17.
12. Fleischmann E, Akca O, Wallner T, Arkilic CF, Kurz A, Hickle RS, Zimpfer M, Sessler DI. Onset time, recovery duration, and drug cost with four different methods of inducing general anesthesia. Anesth Analg 1999; 88: 930–5.
13. Steib A, Freys G, Beller JP, Curzola U, Otteni JC. Propofol in elderly high risk patients. A comparison of haemodynamic effects with thiopentone during induction of anaesthesia. Anaesthesia 1988; 43 (Suppl.): 111–4.
14. Flaishon R, Windsor A, Sigl J, Sebel PS. Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. Anesthesiology 1997; 86: 613–9.
15. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology 1997; 86: 836–47.

16. Lysakowski C, Elia N, Czarnetzki C, Dumont L, Haller G, Combescure C, Tramer MR. Bispectral and spectral entropy indices at propofol-induced loss of consciousness in young and elderly patients. Br J Anaesth 2009; 103: 387–93.
17. Vuyk J, Lim T, Engbers FH, Burm AG, Vletter AA, Bovill JG. The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology 1995; 83: 8–22.
18. Mehta D, Bradley EL Jr, Kissin I. Effect of alfentanil on hypnotic and antinociceptive components of thiopental sodium anesthesia. J Clin Anesth 1991; 3: 280–4.
19. Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E. Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. Br J Anaesth 2001; 86: 523–7.
20. Arden JR, Holley FO, Stanski DR. Increased sensitivity to etomidate in the elderly: initial distribution versus altered brain response. Anesthesiology 1986; 65: 19–27.

Address:
Martin Kryspin Sørensen
Department of Anaesthesia
Centre of Head and Orthopaedics
Copenhagen University Hospital
Rigshospitalet
Blegdamsvej 9
2100 Copenhagen
Denmark
e-mail: martin@kryspin.dk