Comparative assessment of induction efficacy of propofol preparations

Goksen Oz, MD, Sennur Uzun, MD, Didem Dal, MD, Seda B. Akinci, MD, Ulku Aypar, MD.

ABSTRACT

Objectives: To compare the hypnotic effects (using Bispectral Index [BIS]), hemodynamic parameters, injection pain and quality of anesthesia during induction of anesthesia of the 3 commercial propofol preparations (Abbott Propofol, Abbott Laboratories), Pofol (Dongkook Pharm. Co. Ltd.), and Propofol 1% Fresenius (Fresenius Kabi).

Methods: After Ethics Committee Approval, a prospective, randomized, double-blind study was designed in Hacettepe University Hospitals Operating Theaters in 2005. The patients aged 18-65 years, American Society of Anesthesiologists (ASA) grades I and II scheduled for elective surgery under general anesthesia with orotracheal intubation. Ninety patients were randomized into 3 groups with 30 patients in each group. Propofol infusion rate was 2.5 mg. seconds^{-1}. Induction time and doses to reach BIS level of 50 ± 10, injection pain, BIS values and hemodynamic parameters were recorded every minutes for the first 7 minutes and than every 2 minutes for 15 minutes. We used a special chart to assess the induction quality.

Results: Demographical parameters and ASA Physical status were similar in all groups. There were no significant differences in induction quality, induction time and doses, injection pain, BIS values and hemodynamic parameters.

Conclusion: Abbott Propofol, Pofol and Propofol 1% Fresenius have similar effects on anesthesia induction quality and the cost should be taken into consideration when choosing the type of commercial formulation propofol emulsions.

Saudi Med J 2007; Vol. 28 (7): 1055-1058

From the Department of Anesthesiology and Reanimation, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

Received 26th November 2006. Accepted 11th February 2007.

Address correspondence and reprint request to: Dr. Sennur Uzun, Department of Anesthesiology and Reanimation, Faculty of Medicine, Hacettepe University, Ankara 06100, Turkey. Tel. +90 (312) 3051250. Fax. +90 (312) 3109600. E-mail: sennuruzun@superonline.com

Propofol (2, 6 di-isopropyl phenol) is an ultra-short, intravenous anesthetic with high solubility in fat. Short half-life and inactive metabolites make it popular for short ambulatory procedures.[1,2] Initially its major disadvantage was its high cost, but the price has decreased significantly since the end of the patent period and many commercial propofol emulsions have been introduced. Abbott Propofol, pofol and propofol 1% are 3 of the new generic formulations of propofol (Diprivan) manufactured by different drug companies. These products do not contain any sulfite additive, which has now been available in the market. But there is a generalized belief that generic formulations are less effective than the original emulsion (Diprivan, Astra Zeneca, Sweden). Food and Drug Administration (FDA) approval of generic substitutions stipulates bio-equivalent variance within 25% compared to brand name drugs.[3] Under the light of all these, the objective of this study was to investigate whether any of the 3 different generic propofol preparations (Abbott Propofol [Abbott Laboratories], Pofol [Dongkook Pharm Co. Ltd]), Propofol 1% Fresenius [Fresenius Kabi]) was superior to others with respect to hypnotic effects (using Bispectral Index [BIS]), injection pain, induction quality and hemodynamic parameters.

Methods. After Ethics Committee Approval, 100 patients, American Society of Anesthesiologists (ASA) grades I and II, aged 18-65 years who were scheduled for elective surgeries under general anesthesia and orotracheal intubation were recruited for this study. The study was carried out in Hacettepe University Hospitals Operating Theaters in 2005. Patients weighting >50% of their ideal body weight, having neurological or metabolic disease, receiving sedatives, analgesics, hypnotics, anticonvulsants, having abnormal liver or renal function tests and those with known adverse reactions to study drugs were excluded from the study. Ten patients were excluded and were not included into the study and statistics. Remaining 90 patients were allocated

randomly into 3 groups of 30 patients each (Abbott propofol; Pofol; Propofol 1% Fresenius) by a previously prepared lottery of closed envelopes with the name of the commercial emulsion to be used in each case. A prefilled, numbered syringe was given to the anesthetist who was blinded to the group affiliation of the patient and the propofol preparation being used. Patients were not premedicated. In addition to routine monitoring (heart rate [HR], non-invasive arterial pressure, pulse oximeter), the electroencephalogram-bispectral (BIS) index was recorded using 3 electrodes (BISTM, A-2000, Aspect Medical System, Newton MA) applied to the forehead. After 2 minutes preoxygenation, anesthesia was induced with propofol 2.5 mg. kg^{-1} intravenously (iv) followed by fentanyl 1 µg. kg^{-1} iv and vecuronium 1 mg. kg^{-1} iv through a 20-gauge iv cannula on the dorsum of the hand. Ten seconds before induction 2 cc of prilocaine 2% was injected through cannula to prevent the injection pain of propofol. For induction, propofol (2.5 mg. kg^{-1}) was administered with a perfusor (Alaris Medical Systems, IVAC P6000) at an infusion rate of 2.5 mg. $seconds^{-1}$. A total dose of propofol was given and at the time the BIS reach 50 ± 10 at the end of the infusion the basal HRs, systolic (SBP), diastolic (DBP) and mean arterial pressures (MAP), pulse oximetry, BIS index values were recorded. Throughout the induction period HR, SBP, DBP, MAP, pulse oximetry and BIS index values were marked by 1 min intervals for 7 min, then by 2 min intervals until the 15 min. (in total 12 measurements including basal values). Oral endotracheal intubation was performed 3 minutes after induction. Fentanyl was added when BIS index values reached 50 ± 10. Anesthesia was maintained with 2% sevoflurane in a 50% nitrous oxide and oxygen mixture. Assessment of pain on injection (consisting of a 4-point scales: 0 = no pain; 1 = mild pain [facial grimacing]; 2 = moderate pain [verbal complaint], and 3 = severe pain [verbal complaint and movement of extremity]) was performed at 30 sec after the injection of propofol by a blind anesthetist to the drug used.[4] The quality of the anesthetic induction was assessed by the same anesthetist who was unaware of the propofol preparation, on a 4-point scales: 1 = poor (slow onset, hypotension and tachycardia lasting 3-6 min), 2 = fair (transient hypotension or tachycardia, or both lasting 1-2 min), 3 = good (15-25% changes in MAP or HR values), and 4 = excellent (rapid onset, ≤15% changes in MAP or HR values). All 3 formulations contained in addition to the active substance, soybean oil, purified egg phosphatide, glycerol and sodium hydroxide to adjust pH. Sodium bisulfite was not used as preservative in any of the preparations.

Statistical analysis was carried out using the Statistical Program for Social Science for Windows (release 10.0; SPSS, Chicago). Chi-square, Analysis of Variance test, Kruskall-Wallis tests were used for statistics. A probability value of <0.05 was considered statistically significant. Data were presented as mean values ± SD or number of patients.

Results. Ninety patients were included in the study, data from 30 patients in each group were analyzed. There were no differences in respect to demographical parameters (age, weight, height, body mass index, gender and ASA status) (**Table 1**). No difference was found in the induction time and induction doses among 3 groups (p=0.929, p=0.284) (**Table 2**). Injection pain scores were statistically similar. No patient in Abbott Propofol had grade 3 pain score (severe pain) and one patient in the other 2 groups had severe pain.[21,22,25] Patients in each group did not reported any injection pain, grade 1 pain was reported by 6, 5, 3 and grade 2 pain by 2, 3, 1 patients in each groups (p=0.813). Induction quality was evaluated by a 4-point scale (1 = poor, hypotension and tachycardia lasting 3-6 min, 2 = fair, transient hypotension and/or tachycardia lasting 1-2 min, 3 = good, 15-25% changes in heart rate and mean blood pressure values, 4 = excellent, rapid onset, <15% changes in HR and mean blood pressure values). The groups were similar in regard with induction quality (p=0.217) (**Table 3**). There were no statistically important difference between groups in regard with HR, SBP, DBP, MAP, and BIS scores (**Figures 1 & 2**).

Discussion. Our results show no differences among 3 generic propofol formulations regarding induction quality, induction time and induction dose to reach BIS

Table 1 - Demographic parameters (Mean ± SD).

Parameters	Abbott Propofol (n=30)	Pofol (n=30)	Propofol 1% Fresenius (n=30)
Age (year) (min-max)	42.27 ± 13.22 (18-65)	42.17 ± 11.95 (19-65)	40.80 ± 14.05 (18-62)
Weight (kg) (min-max)	70.60 ± 14.24 (45-100)	73.20 ± 12.60 (52-96)	70.30 ± 13.88 (46-100)
Height (cm) (min-max)	168.00 ± 10.19 (145-184)	161.06 ± 30.83 (142-187)	165.43 ± 9.48 (149-188)
Body mass index (min-max)	24.91 ± 3.98 (18.03-32.65)	26.43 ± 4.55 (17.51-33.87)	25.55 ± 3.87 (18.97-34.6)
Female/male	15 / 15	19 / 11	21 / 9
ASA (I/II)	14 / 16	14 / 16	20 / 10

ASA - American Society of Anesthesiologists (ASA) grades I and II

Table 2 - Induction doses and induction time when Bispectral Index = 50% ± 10% (p>0.05) (mean ± SD).

Inductions	Abbott Propofol (n=30)	Pofol (n=30)	Propofol 1% Fresenius (n=30)
Induction time (second)	79.14 ± 13.47*	77.73 ± 14.06*	78.27 ± 14.87*
Induction doses (mg) (min-max)	177.60 ± 33.30† (100-240)	171.27 ± 31.11† (115-228)	175.23 ± 35.68† (115-245)

*p=0.929, comparison among groups.
†p=0.760, comparison among groups.

Table 3 - Induction quality between groups.

Grades	Abbott Propofol	Pofol	Propofol 1% Fresenius
Grade 1	2	0	0
Grade 2	7	10	12
Grade 3	19	16	17
Grade 4	2	4	1

*p=0.217, no difference between groups. Grade 1 = poor, Grade 2 = fair, Grade 3 = good, Grade 4 = excellent

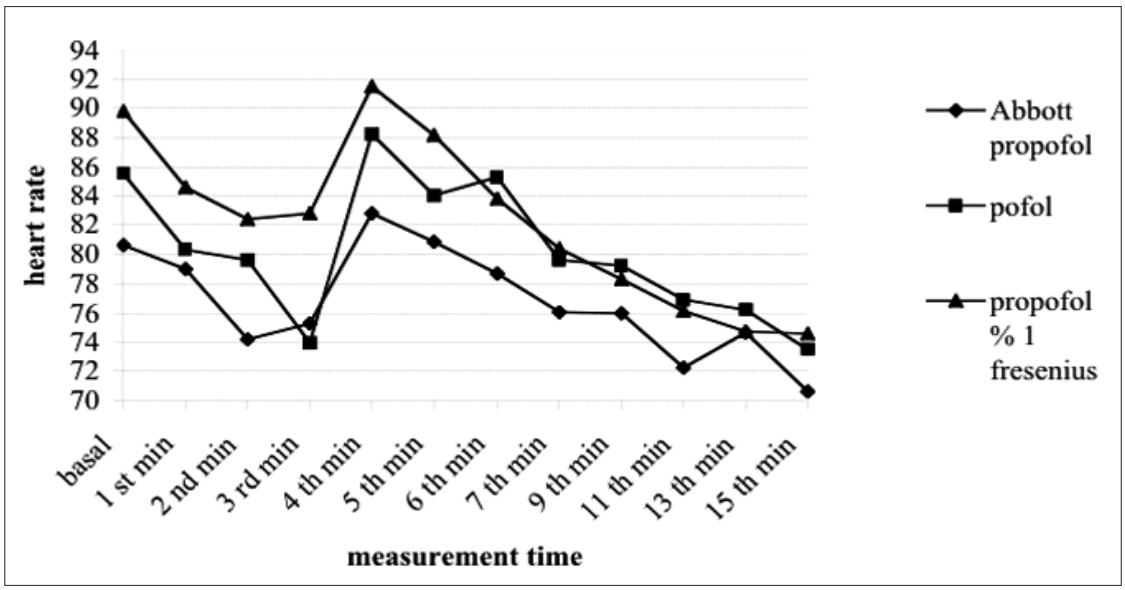

Figure 1 - Heart rate variability of 3 different generic propofol preparations (p>0.05).

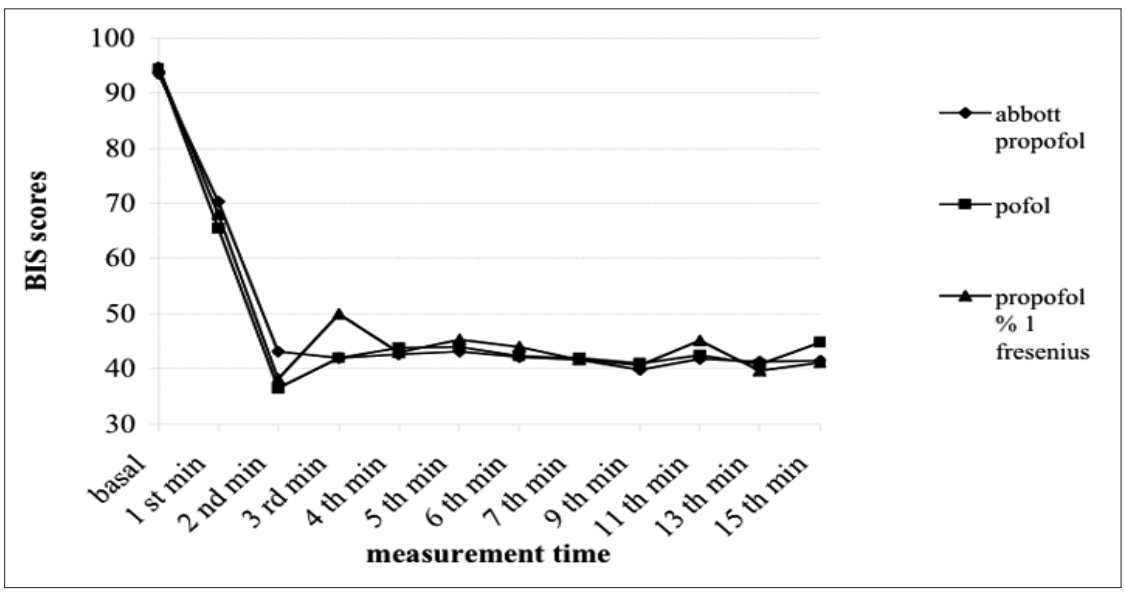

Figure 2 - Bispectral index scores (BIS) of 3 different generic propofol preparations (p>0.05).

50% ± 10%. Injection pain scores were also similar in the 3 groups. The changes in hemodynamic parameters were not statistically significant at any measurement time. Abbott Propofol, Pofol and Fresenius 1% propofol are 3 new generic formulations, which are analogs of Diprivan propofol (Astra Zeneca, Sweden). They do not contain any sulphate additive and were found similar in anesthetic efficacy to original emulsion Diprivan in many studies.[5-8] Bispectral Index was developed from a database of electroencephalography segments, which correlated well with the hypnotic and sedation level in volunteers given increasing and decreasing doses of several anesthetics.[9-11] We chose a 50% BIS value as the induction end point because there is no awareness has been described with a BIS <50% and it was reported that the induction dose of propofol to reach BIS level of 50% is less than the actually used induction dose (2 mg kg^{-1}).[12,13] In the present study, we used BIS to control the hypnotic effects of the propofol emulsions and to compare BIS values at an induction dose of 2.5 mg kg^{-1}. Olufolabi et al,[5] also used BIS monitor to control the depth of anesthesia and compared one of the generic propofol preparations and Diprivan®, their study revealed no difference in the mean total propofol doses delivered between generic propofol and Diprivan® ([90 (30) μg.kg^{-1}.min^{-1} versus 90 (20) μg.kg^{-1}.min^{-1}), nor in time of emergence or the incidence of respiratory adverse effects. Induction time in this study is shorter than the usual, this might be because of the high speed of injection (900 cc. $hour^{-1}$, 15 cc. min^{-1}), and this issue should be further investigated with different injection speeds. Another reason might be the latency of processing EEG wave by the BIS monitor in 20-30 sec delay. Shao et al,[4] in their study comparing the bisulphite containing propofol with Diprivan reported an induction time of 4-5 ± 3 min. Heart rate, SBP, DBP, MAP and BIS scores values increased approximately 4 min, which coincided with the intubation time (induction period of approximately 77-78 sec [1.2 min] added to 3 min interval before intubation). Induction time was too short probably because of the high injection speed. The incidence of pain during injection that occurred in this study was higher than in a previous report.[14] In a study examining the effect of propofol at induction of anesthesia, pain on iv injection was observed to be less with generic propofol compared to Diprivan® (5% versus 11%) with no difference in hypnotic effect.[4] We administered 2% prilocaine before propofol per our routine in order to decrease pain, but we speculate that patients must be informed before drug administration for pain awareness and side effects. The possible criticism of this study is the lack of a forth group (in order to compare the Diprivan™ [Astra Zeneca, Sweden] with the 3 generic formulations). The reason behind is that it has been too much time since the end of the patent, it has been impossible to find the original emulsion.

In conclusion, the 3 generic propofol preparations were similar with regard to their induction quality, compared by BIS monitoring, induction time, injection pain and hemodynamic parameters. New generic propofol preparations used for induction are not superior to each other, other factors such as cost should be taken into consideration when choosing the propofol emulsion.

References

1. Doze VA, Westphal LM, White PF. Comparison of propofol with methohexital for outpatient anesthesia. ***Anesth Analg*** 1986; 65: 1189-1195.
2. Johnson R, Noseworthy T, Anderson B, Konopad E, Grace M. Propofol versus thiopental for outpatient anesthesia. ***Anesthesiology*** 1987; 67: 431-433.
3. Patnaik RN, Lesko LJ, Chen ML, Williams RL and the FDA Individual Bioequivalence Working Group. Individual bioequivalence: new concepts in the statistical assessment of bioequivalence metrics. ***Clin Pharmacokinet*** 1997; 33: 1-6.
4. Shao X, Li H, White PF, Klein KW, Kulstad C, Owens A. Bisulfite-containing propofol: Is it a cost-effective alternative to diprivanTM for induction of anesthesia? ***Anesth Analg*** 2000; 91: 871-875.
5. Olufolabi J, Gan TJ, Lacassie HJ, White WD, Habib AS. A randomised, prospective double-blind comparison of the efficacy of generic propofol (sulphite additive) with Diprivan®. ***Eur J Anaesthesiol*** 2006; 23: 341-345.
6. Fassoulaki A, Paraskeva A, Papilas K, Patris K. Hypnotic and cardiovascular effects of proprietary and generic formulations do not differ. ***Can J Anaesth*** 2001; 48: 459-461.
7. Weksler N, Rozentsveiq V, Tarnoploski A, Gurman GM. Commercial propofol solutions: is the more expensive also the more effective? ***J Clin Anesth*** 2001; 13: 321-324.
8. Shao X, Li H, White PF, Klein KW, Kulstad C, Owens A. Bisulfite-containing propofol: is it a cost-effective alternative to Diprivan for induction of anesthesia? ***Anesth Analg*** 2000; 91: 871-875.
9. Singh H. Bispectral index (BIS) monitoring during propofol-induced sedation and anaesthesia. ***Eur J Anaesthesiol*** 1999; 16: 31-36.
10. Rampill IJ. A primer for EEG signal processing in anesthesia. ***Anesthesiology*** 1998; 89: 980-1002.
11. 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: 836-847.
12. Chan MTV, Gin T. What does the bispectral EEG index monitoring? ***Eur J Anaesthesiol*** 2000; 17: 146-148.
13. Masuda T, Yamada H, Takada K, Sagata Y. Bispectral index monitoring is useful to reduce total amount of propofol and obtain immediate recovery after propofol anesthesia. ***Masui*** 2002; 51: 394-399.
14. Sanderson JH, Blades JF, Park A. Multicentre study of propofol in day case surgery. ***Anaesthesia*** 1988; 43 Suppl: 70-73.