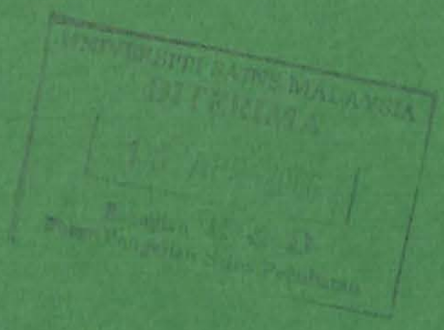
COMPARISON OF THREE DIFFERENT TARGET BLOOD CONCENTRATIONS OF PROPOFOL FOR GENERAL ANAESTHESIA USING TARGET CONTROLLED INFUSION (TCI) TECHNIQUE



By
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ANAESTHESIOLOGY DEPARTMENT
UNIVERSITI SAINS MALAYSIA

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AKHIR PROJEK

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3) Tajuk Projek: Comparison of three different target blood concentrations of propofol for induction of anaesthesia using target controlled infusion (TCI) technique

4) (a) Penemuan Projek/Abstrak

ABSTRACT

We studied three different target blood concentrations (TBC) of propofol for induction of anaesthesia using target controlled infusion (TCI) technique. One hundred and thirty five ASA I and II patients, between 18-55 years of age and undergoing any type of elective surgery were included in the study. All patients were premedicated with oral midazolam 7.5 mg in the ward an hour before induction. Patients were randomly divided into three groups. Group I (n = 45) received initial TBC of 2 µg/ml, group II (n = 45) TBC of 3 µg/ml and group III (n = 45) TBC of 4 µg/ml for induction of anaesthesia. Intravenous alfentanil 30 µg/kg bolus was given as analgesia. Patients were observed for success rate of induction, induction time, effect site concentration and haemodynamic parameters at baseline, 1 minute, 3 minutes and 5 minutes after induction.

Success rate of induction was 55.6 %, 86.7 % and 91.1 % in group I, II and III respectively, which showed significant difference only between group I and III. Effect site concentration was 0.6 µg/ml, 0.9 µg/ml and 0.8 µg/ml in group I, II and III respectively which showed significant difference only between group I and II. There was no significant difference in induction time and haemodynamic parameters among the three groups.

Hence, TBC 3 µg/ml was comparable with TBC 4 µg/ml for induction of anaesthesia using TCI technique. However TBC 2 µg/ml was not recommended for rapid induction.

ABSTRAK

Kami mengkaji tiga sasaran kepekatan dalam darah (SKD) yang berbeza bagi propofol dalam menghasilkan permulaan kesan bius (induksi) menggunakan teknik infusi kawalan sasaran (IKS). 135 pesakit dalam klasifikasi ASA I dan II, berumur di antara 18-55 tahun dan menjalani sebarang pembedahan yang dijadualkan, telah dimasukkan ke dalam kajian. Semua pesakit diberikan ubat midazolam 7.5 mg secara oral di dalam wad satu jam sebelum permulaan bius Pesakit dibahagikan secara rawak kepada 3 kumpulan. Kumpulan I (n= 45) menerima SKD permulaan 2 µg/ml, kumpulan II (n=45) menerima permulaan SKD 3 µg/ml dan kumpulan III (n=45) menerima permulaan SKD 4 µg/ml untuk menghasilkan induksi pembiusan. Ubat alfentanil 30 µg/kg diberi sebagai ubat penahan sakit secara suntikan melalui salur darah (intravena). Pesakit dinilai untuk kadar kejayaan untuk induksi bius, masa induksi, kepekatan pada tempat sasaran dan parameter hemodinamik direkodkan pada bacaan dasar, 1 minit, 3 minit dan 5 minit selepas induksi.

Kadar kejayaan induksi ialah 55.6 %, 86.7 % dan 91.1 % bagi masing-masing kumpulan I, II dan III yang mana perbezaan yang bererti hanya ditunjukkan di antara kumpulan I dan III. Kepekatan pada tempat sasaran ialah 0.6 µg/ml, 0.9 µg/ml dan 0.8 µg/ml bagi masing-masing kumpulan I, II dan III yang mana perbezaan yang bererti hanya ditunjukkan di antara kumpulan I dan II. Tiada sebarang perbezaan bererti untuk masa induksi dan kesemua parameter hemodinamik.

Oleh itu, SKD 3 µg/ml adalah setara jika dibandingkan dengan SKD 4 µg/ml untuk induksi pembiusan menggunakan teknik IKS. Walau bagaimanapun SKD 2 µg/ml tidak disarankan untuk permulaan induksi bius yang cepat.

(b) Senaraikan Kata Kunci yang digunakan di dalam abstrak:

Bahasa Malaysia	Bahasa Inggeris
Infusi kawalan sasaran	Target controlled infusion
Sasaran kepekatan dalam darah	Target blood concentrations
Permulaan kesan bius (induksi)	Induction of anaesthesia
Propofol	Propofol

5) Output Dan Faedah Projek

(a) Penerbitan (termasuk laporan/kertas seminar)
(Sila nyatakan jenis, tajuk, pengarang, tahun terbitan dan di mana telah diterbit/dibentangkan).

Penerbitan :

- Jurnal manuskrip telah dihantar pada bulan Disember ke 'Anaesthesia and Intensive Care Journal' yang diterbitkan di Australia tetapi tidak diterima untuk penerbitan melalui surat balasan daripada editor jurnal bertarikh Mac 2006.
- Seterusnya manuskrip akan dihantar ke jurnal yang lain iaitu 'Asean Journal of Anaesthesiologist' dan memerlukan masa 6-8 minggu untuk disemak oleh editor.

Kajian ini telah dibentangkan seperti berikut :

- Di "12th Congress of Asia Pacific Association For Respiratory Care (APARC)" pada 6-9 Ogos 2004
- Di "Annual Scientific Meeting of the Malaysian Society of Anaesthesiology & Intensive Care" pada 18-20 March 2005 di Bayview Beach Resort, Pulau Pinang dan telah berjaya memenangi anugerah "Young Investigator's Award"

(b) Faedah-Faedah Lain Seperti Perkembangan Produk, Prospek Komersialisasi Dan Pendaftaran Paten.
(Jika ada dan jika perlu, sila guna kertas berasingan)

Oleh kerana kajian ini merupakan kajian klinikal menggunakan satu teknik pembiusan baru menggunakan produk yang baru diperkenalkan di negara kita, hasil kajian ini dapat menjadi perintis kepada penggunaan teknik ini dengan lebih meluas di dalam kajian-kajian lain dan juga dalam praktikal pembiusan

(c) Latihan Gunatenaga Manusia

Pelajar Siswazah: Tiada

ii) Pelajar Prasiswazah: Tiada

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Background : General recommendations for initial target blood concentration (TBC) of propofol for general anaesthesia using TCI technique in premedicated patients is 4 μg/ml.

Objectives : To compare success rate of induction within 3 minutes, induction time and haemodynamic changes between three different TBC.

Methodology : In this prospective study, 135 ASA I and II patients in age between 18-55 years old and underwent any elective surgery were randomized into 3 groups. Group I received initial TBC of 2 μg/ml (n = 45), group II received initial TBC of 3 μg/ml (n = 45) and group III received initial TBC of 4 μg/ml (n = 45) for induction of anaesthesia. All patients were premedicated with oral midazolam 7.5 mg in the ward 30 minutes before induction and were given IV alfentanil 30 μg/kg bolus as an analgesia. Induction time was measured from starting of infusion until loss of verbal contact and induction was considered successful if loss of verbal contact was achieved within 3 minutes from starting of infusion. Haemodynamic parameters (SBP, DBP, MAP and HR) were recorded at baseline, 1 minutes, 3 minutes and 5 minutes after induction. Patients were subsequently paralyzed with IV rocuronium 0.6 mg/kg and intubated. Maintenance of anaesthesia was continued with total intravenous anaesthesia using TCI of propofol at TBC of 3-6 μg/ml and alfentanil infusion at 30-60 μg/kg/h.

Results : Success rate of induction was 55.6 % in TBC 2 μg/ml, 86.7 % in TBC 3 μg/ml and 91.1 % in TBC 4 μg/ml which showed a significant difference between 3 groups ($p < 0.05$). However from multi variate analysis using logistic regression test, success rate was only significantly difference between TBC 2 μg/ml and TBC 4 μg/ml ($p < 0.05$) but was not significantly difference between TBC 3 μg/ml and TBC 4 μg/ml. Estimated marginal means of induction time was 73.63 ± 7.33 s in TBC 2 μg/ml, 74.12 ± 5.81 s in TBC 3 μg/ml and 55.25 ± 7.30 s in TBC 4 μg/ml which showed no significant differences ($p > 0.05$). There was also no significant differences in all haemodynamic changes between 3 groups.

Conclusions : TBC 3 μg/ml was comparable with TBC 4 μg/ml for induction of anaesthesia with no significant differences in success rate of induction, induction time or haemodynamic changes.

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TARGET CONTROLLED INFUSION (TCI) TECHNIQUE: COMPARISON OF THREE DIFFERENT TARGET BLOOD CONCENTRATIONS OF PROPOFOL FOR INDUCTION OF ANAESTHESIA

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Background: General recommendation for initial target blood concentration (TBC) of propofol for induction of anaesthesia using TCI technique in premedicated patients is 4 µg/ml.

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Results: Success rate of induction was 55.6% in TBC 2 µg/ml, 86.7% in TBC 3 µg/ml and 91.1% in TBC 4 µg/ml, which showed significant difference between 3 groups (p = 0.000). However from multivariate analysis using logistic regression method, success rate were only significantly difference between TBC 2 µg/ml and TBC 4 µg/ml (p = 0.001) but were not significantly difference between TBC 3 µg/ml and TBC 4 µg/ml (p = 0.898). Estimated marginal means and 95% confidence interval of induction time were 73.63 (59.08, 88.18) s in TBC 2 µg/ml, 74.12 (62.58, 85.65) s in TBC 3 µg/ml and 55.25 (40.76, 69.75) s in TBC 4 µg/ml which showed no significant difference (p = 0.101). There were significant changes within all haemodynamic parameters but no significant differences between the groups.

Conclusions: TBC 3 µg/ml was comparable with TBC 4 µg/ml for induction of anaesthesia with no significant differences in success rate of induction, induction time or haemodynamic changes. TBC 2 µg/ml is not recommended for initial induction.

MANUSKRIP JURNAL

Comparison of Three Different Target Blood Concentrations of Propofol for Induction of Anaesthesia Using Target Controlled Infusion (TCI) Technique.

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ABSTRACT

We studied three different target blood concentrations (TBC) of propofol for induction of anaesthesia using target controlled infusion (TCI) technique. One hundred and thirty five ASA I and II patients, between 18-55 years of age and undergoing any type of elective surgery were included in the study. All patients were premedicated with oral midazolam 7.5 mg in the ward an hour before induction. Patients were randomly divided into three groups. Group I (n = 45) received initial TBC of 2 μg/ml, group II (n = 45) TBC of 3 μg/ml and group III (n = 45) TBC of 4 μg/ml for induction of anaesthesia. Intravenous alfentanil 30 μg/kg bolus was given as analgesia. Patients were observed for success rate of induction, induction time, effect site concentration and haemodynamic parameters at baseline, 1 minute, 3 minutes and 5 minutes after induction.

Success rate of induction was 55.6 %, 86.7 % and 91.1 % in group I, II and III respectively, which showed significant difference only between group I and III. Effect site concentration was 0.6 μg/ml, 0.9 μg/ml and 0.8 μg/ml in group I, II and III respectively which showed significant difference only between group I and II. There was

no significant difference in induction time and haemodynamic parameters among the three groups.

Hence, TBC 3 μg/ml was comparable with TBC 4 μg/ml for induction of anaesthesia using TCI technique. However TBC 2 μg/ml was not recommended for rapid induction.

Keywords: Target controlled infusion, propofol, induction of anaesthesia, target blood concentration

INTRODUCTION

Propofol is a fast-acting intravenous (IV) drug with a favourable pharmacokinetic profile for inducing and maintaining total IV anaesthesia. The development of computer-assisted target controlled infusion (TCI) system has given a new dimension to administer propofol infusion and provide the anaesthesiologist with a convenient method for directly controlling the blood concentration of anaesthetics[1]. TCI systems for propofol use a special infusion pump which is incorporated with 'Diprifusor' software[1-2]. This software consists of three-compartment pharmacokinetic model with a specific set of pharmacokinetic parameters for propofol and two independent infusion control algorithms[1-2].

In general, the recommendation by manufacturer of target blood concentration (TBC) of propofol for induction is 4-8 μg/ml. TBC of 4 μg/ml was recommended in premedicated patients and 6 μg/ml in unpremedicated patients (4). However, there is a wide interindividual pharmacokinetic and pharmacodynamic variability in propofol requirement. By giving an intravenous dose of propofol 2 mg/kg, resulted in a peak blood concentration that varied from 5-8 μg/ml between patients, thereby exhibiting different effects in different patients[2]. Some patients only required effect-site concentrations of propofol 1.5 μg/ml for induction of anaesthesia whereas others required more than 6 μg/ml (5). Even with inclusion of covariates (age and body weight), the interindividual variabilities remained relatively large, indicating a large variance of pharmacokinetics among patients (6). In view of a wide interindividual pharmacokinetic and

pharmacodynamic variability in propofol, there are also possible wide differences of pharmacological responses to propofol in our population.

The aim of this study was to determine TBC of propofol for induction of anaesthesia using TCI technique in our population in comparison with recommendation from the previous studies by comparing the success rate of induction within 3 minutes, induction time and haemodynamic changes between three different TBC of propofol (2, 3 and 4 μg/ml).

MATERIALS AND METHODS

After Institutional Ethics Committee approval, written concent was obtained from 135 ASA I and II patients, aged between 18-55 years old, scheduled for any type of elective surgery under general anaesthesia with an expected duration of less than 5 hours. Patients with a history of allergy to trial drugs or its constituents, pregnant women and obese patients (> 120 % of ideal body weight) were excluded from the study.

All patients were premedicated with oral midazolam 7.5 mg in the ward just before sending patients to the operation theatre (OT) which was about 1 hour before induction. The patients were randomly allocated to three groups by picking up sequentially one of the sealed opaque envelopes which contained group code inside. Each groups received different initial TBC of propofol for induction of anaesthesia: group I (n = 45) received TBC 2 μg/ml; group II (n = 45) TBC 3 μg/ml and group III (n = 45) TBC 4 μg/ml respectively. In the OT, intravenous access and standard anaesthetic monitoring were recorded including bispectral (BIS) index monitor, noninvasive arterial blood pressure, electrocardiogram, pulse oximetry and capnography.

Preoxygenation was given adequately for 5 minutes and subsequently slow bolus intravenous alfentanil 30 μg/kg was delivered. Immediately after that, patients were induced with TCI system of propofol with selected initial TBC that was earlier decided from randomization. TCI was administered by 'Terufusion' syringe pump TE-372 TCI/TIVA (Terumo®) incorporated with Diprifusor subsystem (Zeneca Ltd). Induction time was taken as the time from the start of propofol administration until successful loss of verbal contact within 3 minutes of achieving target blood concentration. If patients were still not successfully induced within 3 minutes, the induction was considered as fail

and TBC was immediately increased to 5 μg/ml. After induction, the patients were paralyzed with intravenous rocuronium 0.6 mg/kg and subsequently intubated. Effect site concentration which was displayed on infusion pump was also recorded at successful induction. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rare (HR) were recorded at baseline before induction, 1 minute, 3 minutes and 5 minutes after induction. Bispectral index (BIS) value was monitored to ensure adequate depth of anaesthesia.

During maintenance of anaesthesia, TBC was adjusted between 1.5 to 6 μg/ml in order to achieve adequate depth of anaesthesia based on BIS index value of 40-60. Oxygen was maintained with air mixture at FiO_2 0.4 throughout surgery. Intravenous alfentanil was continuously infused at 30 μg/kg/h. If it was necessary, alfentanil infusion would be increased every 5 μg/kg/h until the maximum of 60 μg/kg/h (0.5 to1.0 μg/kg/min). Haemodynamic parameters were continuously recorded at 10 minutes interval until end of surgery. Additional doses of intravenous rocuronium were given about one third of the initial dose when it was necessary.

Alfentanil infusion was stopped 10 minutes before the end of surgery. TBC was gradually reduced in about 15 minutes before the end of surgery until BIS index value between 60-70 and subsequently stopped 5 minutes before completed closure of surgical incision. When patients had spontaneous breathing, reversal was given using mixture of intravenous neostigmine 2.5 mg and intravenous atropine 1 mg. The patients were extubated when fully recovered and then observed in recovery room.

For statistical analysis, SPSS software version 11.0 was used. Success rate of induction within 3 minutes was analyzed by using chi-squared test and multiple logistic

regression analysis. The results were expressed in percentage. Induction time was analyzed by one-way analysis of covariance (ANCOVA) test and results were expressed as estimated marginal mean. Haemodynamic changes were analyzed by using repeated measures analysis of variance (ANOVA). All results were expressed as mean ± SD. Effect site concentrations were analyzed by using analysis of variance (ANOVA) and results were expressed as mean ± SD. A value of $p \leq 0.05$ was considered statistically significant.

RESULTS

Demographic data was shown in Table 1. There were no significant differences in all demographic data between 3 groups except for sex data ($p < 0.05$). Group III had more female patients, 84.4 % compared to the other groups, 57.8 % in group I and 60 % in group II. Male patients were only 15.6 % in group III, but 42.2 % in group I and 40 % in group II.

Success rate of induction within 3 minutes was highest in group III, 91.1 %, 86.7 % in group II and only 55.6 % in group I (Table 2). There were significant differences between three groups ($p < 0.05$). However from multivariate analysis using multiple logistic regression tests, comparing between each group, successful induction was only significant between group I and group III ($p < 0.05$) but was not significant between group II and group III.

Estimated marginal means and confidence interval of induction time were 74 (60, 88) seconds in group I, 74 (63, 86) seconds in group II and 55(63, 88) seconds in group III as shown in Table 2. There were no significant differences between the three groups.

Effect site concentrations at induction were 0.6 (0.3) μg/ml for group I, 0.9 (0.5) μg/ml for group II and 0.8 (0.3) μg/ml for group III (Table 2). There were significant differences in effect site concentrations at induction between the three groups ($p < 0.05$). However from multiple comparisons, the differences were only significant between group I and group II.

Mean ± SD of SBP, DBP, MAP and HR at baseline, 1 minute, 3 minutes and 5 minutes after induction for the three groups are shown in Table 3. There were significant

changes of SBP, DBP, MAP and HR from baseline to 5 minutes after induction within each group ($p < 0.05$). However there were no significant differences between the three groups.

DISCUSSION

Since it was introduced in 1996, most of the previous studies for TCI of propofol were done in United States and Europe. There were only a few studies found in the Asia region from the literature review. Short TG *et al.*, from Chinese University of Hong Kong did a study in 1996 to evaluate the algorithm of White and Kenny for pharmacokinetic model of propofol for TCI and it was found to perform adequately in their population[7]. Li YH *et al.*, did an assessment of predictive performance of a 'Diprifusor' TCI system in Chinese patients and they found that the accuracy of the 'Diprifusor' TCI system could be considered clinically acceptable[8].

From the previous studies of TCI, generally the recommended range of TBC for induction are between 4-8 μg/ml and for maintenance are between 3-6 μg/ml. For the initial induction TBC, 4 μg/ml was recommended in premedicated patients and 6 μg/ml in unpremedicated patients[4]. Chaudri *et al.* showed that propofol TBC of 3, 4 and 5 μg/ml could induce anaesthesia in 40 %, 75 % and 90 % respectively, in ASA I and II patients premedicated with termazepam[9]. Tzabar Y *et al.*, studied the effect of co-induction with intravenous midazolam at the dose of 1, 2 and 4 mg respectively on the success rate of induction using TCI when TBC was maintained at 3 μg /ml. Success rate was only 45 % without midazolam whereas the other 3 groups were 70 %, 85 % and 95 % respectively which showed more successful induction with increasing dose of midazolam[10]. Premedication was also associated with higher success rate of induction with an initial TBC of 4 μg /ml. In unpremedicated patient only 35 % of induction was successful

whereas success rate was up to 87 % of in premedicated patients with only oral diazepam 10 mg and 93 % when combined diazepam with intravenous alfentanil 10 μg/kg[4]. In 40 patients who received premedication with diazepam 10 mg orally and were given IV alfentanil 7.5 μg/kg immediately before induction, 80 % was successfully induced at TBC of 4 μg/ml and 95 % at TBC 6 μg/ml[11]. Masago K *et al.* from University of Tokyo studied the effect of IV fentanyl 2 μg/kg on success rate of induction with TBC of 3 μg/ml and showed success rate of 90 %[12]. However there was no previous study that used TBC of 2 μg/ml as an initial TBC for induction.

In our study, we compared three groups of TBC, 2, 3 and 4 μg/ml respectively for initial induction with all patients were standardized to receive oral midazolam 7.5 mg for premedication and IV alfentanil 30 μg/kg as an initial analgesia before starting TCI. There was a significant difference in sex distribution between the three groups. However by using multivariate analysis, this factor would not affect the results of statistical analysis. The result showed that success rate of induction was 55.6 % in TBC 2 μg/ml, 86.7 % in TBC 3 μg/ml and 91.1 % in TBC 4 μg/ml. However a significant difference was only between TBC 4 μg/ml and 2 μg/ml. This result was consistent with previous one which showed that majority of patients were still successfully induced with TBC 4 μg/ml. However TBC 3 μg/ml was almost comparable with TBC 4 μg/ml. Although there was no previous study comparing with TBC 2 μg/ml but our study showed with TBC as low as 2 μg/ml, more than 50 % of patients could still be successfully induced. TBC at 2 μg/ml was previously proved to be a concentration that could actually achieved a sedative effect. Janzen *et al.* did a study to determine sedation levels reached by TCI in 30 unpremedicated patients undergoing muscle biopsy under femoral nerve block. They

found that TBC of 2.1μg/ml was the ED50 of target propofol concentration for sedation at sedation levels 4 (responsive to physical stimulation only) [13].

The optimal dose of alfentanil for providing complete attenuation of the cardiovascular and catecholamine response to tracheal intubation is 30 μg/ kg[14]. We used this result as a reference to start alfentanil at the dose of 30 μg/kg before induction using TCI. Alfentanil is known to have a synergistic pharmacokinetic and pharmacodynamic interaction with propofol[5]. When administered at a constant rate of 45 μg/kg/h, alfentanil reduces the mean infusion rate of propofol needed for maintenance of anaesthesia to about 5 mg/kg/h[15]. Similarly when the propofol TBC is 2, 4 or 6 μg/ml, the mean infusion rate of alfentanil required to maintain adequate anaesthesia is about 76, 30 or 18 μg/kg/h respectively[5]. Alfentanil increases propofol concentrations by up to 20 %, administered by TCI, when given in combination at concentrations of 40-80 ng/ml associated with moderate degrees of sedation[16]. In healthy male volunteers, alfentanil reduces both the distribution and clearance of propofol, thus increasing blood propofol concentrations[17]. Plasma alfentanil concentrations also have been shown to increase in the presence of propofol, administered by TCI[16]. This is due to inhibition of the oxidative metabolism of alfentanil by cytochrome P450 enzyme after administration of propofol, although this has only been described *in vitro*[18]. Synergism also has been demonstrated between propofol and midazolam when given as intravenous boluses for induction of anaesthesia. Short T G *et al.* reported that administration of midazolam 0.13 mg/kg reduced the ED50 of propofol by 52 %[7].

Induction time of successful induction was 111, 116 and 103 seconds respectively at TBC 3 μg/ml, 4 μg/ml and 5 μg/ml in patients who were premedicated with

temazepam 20-30 mg[9]. Mean induction times were 78 seconds when patients received TBC of 4 μg/ml for induction after premedication with intravenous midazolam 0.03 mg/kg and alfentanil 10μg/kg[19]. At TBC of 4 μg/ml, induction time was 181 seconds without any premedications. When patients were premedicated with diazepam 10 mg orally alone or in combination with alfentanil 10 μg/kg, mean induction time was significantly faster to 88 and 79 seconds respectively[4]. Servin F S *et al.* also reported that induction time was 90 seconds at TBC 4 μg/ml and 65 seconds at TBC 6 μg/ml when patients in both groups were premedicated with diazepam 10 mg orally and were given alfentanil 7.5 μg/kg before induction[11]. In our study, patients were given higher dose of alfentanil at 30 μg/kg before induction and the results showed a faster induction time. Estimated marginal mean of induction time was 73.36 seconds in TBC 2 μg/ml, 74.12 seconds in TBC 3 μg/ml and 55.25 seconds in TBC 4 μg/ml which showed no significant differences between the groups.

Chaudri S *et al.* reported significant reductions in SBP and DBP at 3 min compared with baseline values within all the three groups, but there were no significant differences between the groups. The mean decreases in systolic arterial pressure ranged from 10-13 % which was improved if compared with induction by bolus doses and with continuous infusion[9]. At TBC 3 μg/ml, there were no significant differences of SBP, DBP and HR changes at baseline or at 3 min whether it was co-induced with 0, 1, 2 or 4 mg of IV midazolam. However there were reductions if compared between baseline and at 3 min[10]. These results were comparable with our study which showed no significant differences in SBP, DBP, MAP or HR between the groups at baseline, 1 min, 3 min or 5 min. However the changes within the group were significant if compared to the baseline

value but all values were still within acceptable reading. Overall all estimated marginal means of SBP are > 90 mmHg, DBP > 50 mmHg, MAP > 60 mmHg and HR > 50 either at 1, 3 or 5 minutes.

The TBC of propofol only relates to the depth of anaesthesia when there is equilibrium between the plasma and effect site. The effect site concentration during infusion can be calculated using the equilibrium rate constant (k_{eo}). If a constant plasma concentration is maintained, then the time for the effect site concentration to reach 50 % of the plasma concentration is given by $0.693/k_{eo}$. Conway DH *et al.* studied the influence of co-induction with remifentanil and midazolam on effect site propofol requirements at induction of anaesthesia. The effect site concentration of propofol alone was 2.19μg/ml. This was reduced to 1.55 μg/ml during co-induction with target-controlled remifentanil (3ng/ml) and further reduced to 0.64 μg/ml with midazolam premedication (0.03mg/kg) [20]. This is comparable with our study. Starting TCI at TBC 2, 3 or 4 μg/ml with co-induction using alfentanil 30 μg/kg and oral midazolam 7.5 mg premedication, mean total effect site concentration at induction was 0.77 ± 0.40 μg/ml. There was no big mean difference margin even though effect site concentration at TBC 2 (0.60 ± 0.31) was significantly difference from at TBC 3 (0.86 ± 0.47). Michel MRF *et al.* did a study to compare TCI device controlled the plasma concentration with TCI device to control the effect site concentration. They found that targeting the effect site concentration shortened the time to loss of consciousness compared with the targeting plasma concentration without causing hypotension[21]. In future, with some modification in pharmacokinetic parameters, TCI device to control the effect site concentration will become popular in clinical practice.

In conclusion, this study shows that TBC at 3 μg/ml is comparable with recommended initial TBC at 4 μg/ml for induction of anaesthesia using TCI technique without significant differences in success rate of induction, induction time, effect site concentration and haemodynamic changes. Although TBC at 2 μg/ml shows an encouraging result with 55.6 % of successful induction, it is not recommended if rapid and definite successful induction is required. Therefore in our population, it is recommended to start induction using TCI technique of propofol by TBC at 3 μg/ml and then to titrate accordingly when it is necessary.

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Table 1. Demographic data. Age and weight are given as mean (SD). All other categorical data are given in number of patients (%).

Initial TBC (μg/ml)	**GROUP I 2**	**GROUP II 3**	**GROUP III 4**
No. of patients ;n	45	45	45
Age ; years	34.0 (11.6)	33.8 (11.4)	38.2 (10.4)
Body weight ; kg	61.8 (14.2)	59.7(11.3)	59.8 (11.8)
*Sex; n (%)			
Male	19 (42.2%)	18 (40.0%)	7 (15.6%)
Female	26 (57.8%)	27 (60.0%)	38 (84.4%)
Race; n (%)			
Malay	40 (88.9%)	40 (88.9%)	41 (91.1%)
Chinese	3 (6.7%)	4 (8.9%)	4 (8.9%)
Indian	1 (2.2%)	0 (0.0%)	0 (0.0%)
Others	1 (2.2%)	1 (2.2%)	0 (0.0%)
ASA; n (%)			
I	36 (80.0%)	35 (77.8%)	31 (68.9%)
II	9 (20.0%)	10 (22.2%)	14 (31.1%)
Type of surgery ; n (%)			
Gynaecology	9 (20.0%)	11 (24.4%)	18 (40.0%)
Surgery	19 (42.2%)	19 (42.2%)	21 (46.7%)
Orthopaedic	16 (35.6%)	13 (28.9%)	6(13.3%)
Others	1 (2.2%)	2 (4.4%)	0 (0.0%)

TBC = target blood concentration
* $p < 0.05$

Table 2. Induction characteristics. Successful induction is expressed as number of patients (%), induction time as mean (confidence interval) and effect site as mean (SD).

Initial TBC (μg/ml)	**GROUP I 2**	**GROUP II 3**	**GROUP III 4**
Successful induction; n (%)	25 (55.6%)*	39 (86.7%)	41 (91.1%)*
Induction time ; s	74(60,88)	74(63,86)	55(63,86)
Effect site concentration at induction; μg/ml	0.6 (0.3)*	0.9 (0.5)*	0.8 (0.3)

* $p < 0.05$

Table 3. Mean of haemodynamic data (SD) at different time interval

Initial TBC (µg/ml)	GROUP I 2	GROUP II 3	GROUP III 4
SBP (mmHg)			
Baseline	125 (16)	128(18)	131(19)
1 min	103(12)	105(18)	102(16)
3 min	99(14)	102(18)	100(17)
5 min	99(17)	100(16)	97(16)
DBP (mmHg)			
Baseline	71 (11)	69 (10)	75 (11)
1 min	60 (12)	54 (9)	57 (10)
3 min	56(13)	55 (10)	58(13)
5 min	54(10)	53 (10)	56(11)
MAP (mmHg)			
Baseline	89(11)	89(11)	95(12)
1 min	75(10)	71(11)	73(12)
3 min	71(13)	72(13)	73(15)
5 min	70(14)	69(12)	71(12)
HR (beats/min)			
Baseline	77(17)	79(16)	78(17)
1 min	69(20)	72(13)	69(15)
3 min	68(18)	72(15)	69(14)
5 min	72(19)	81(16)	72 (16)

SBP = Systolic blood pressure; DBP = Diastolic blood pressure; MAP = Mean arterial pressure; HR = Heart rate. No significant differences between the three groups.

LAPORAN PENUH
KAJIAN

COMPARISON OF THREE DIFFERENT TARGET BLOOD CONCENTRATIONS OF PROPOFOL FOR GENERAL ANAESTHESIA USING TARGET CONTROLLED INFUSION (TCI) TECHNIQUE

By
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ABBREVIATIONS

TCI	Target Controlled Infusion
TBC	Target Blood Concentration
ASA	American Societies of Anesthesiologists
MDPE	Median Performance Error
MDAPE	Median Absolute Performance Error
IV	Intravenous
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
MAP	Mean Arterial Pressure
HR	Heart Rate
$CMRO_2$	Cerebral Metabolic Rate of O_2

ABSTRAK

Objektif:

Untuk membandingkan kadar kejayaan dalam menghasilkan permulaan kesan bius (induksi) dalam masa 3 minit, jangkamasa yang diambil untuk induksi dan perubahan-perubahan hemodinamik diantara tiga sasaran kepekatan dalam darah (SKD) bagi propofol yang berbeza di dalam populasi rakyat Malaysia yang didominasi oleh keturunan Melayu.

Tatacara:

Di dalam kajian prospektif ini, 135 pesakit dalam klasifikasi ASA I dan II, berumur di antara 18-55 tahun dan menjalani sebarang pembedahan yang dijadualkan, telah dibahagikan secara rawak kepada 3 kumpulan. Kumpulan I menerima SKD permulaan 2 μg/ml (n = 45), kumpulan II menerima permulaan SKD 3 μg/ml (n = 45) dan kumpulan III menerima permulaan SKD 4 μg/ml (n = 45) untuk menghasilkan induksi pembiusan. Semua pesakit diberikan ubat midazolam 7.5 mg secara oral di dalam wad 30 minit sebelum permulaan bius dan diberi alfentanil 30 μg/kg sebagai ubat penahan sakit secara suntikan melalui salur darah (intravena). Jangkamasa yang diambil untuk induksi bius dikira daripada permulaan aliran (infusi) ubat sehingga tiada lagi tindakbalas lisan dan pembiusan dikira berjaya jika ketiadaan tindakbalas lisan dicapai dalam masa 3 minit daripada permulaan infusi. Parameter-parameter hemodinamik (tekanan darah sistolik, tekanan darah diastolik, tekanan darah 'mean' dan kadar denyutan jantung) direkodkan pada bacaan dasar, 1 minit, 3 minit dan 5 minit selepas induksi. Pesakit seterusnya

dilumpuhkan dengan dengan suntikan intravena rocuronium 0.6 mg/kg dan diintubasikan. Pengekalan kesan bius diteruskan dengan pembiusan intravena secara keseluruhan menggunakan kaedah infusi kawalan sasaran (IKS) propofol pada SKD diantara 1.5-6 μg/ml dan infusi alfentanil 30-60 μg/ kg/ h.

Keputusan:

Kadar kejayaan induksi ialah 55.6 % bagi SKD 2 μg/ml, 86.7 % bagi SKD 3 μg/ml and 91.1 % bagi SKD 4 μg/ml di mana ia menunjukkan perbezaan yang signifikan (bererti) diantara ketiga-tiga kumpulan (p=0.000). Walau bagaimanapun berdasarkan analisa 'multivariate' menggunakan kaedah regrasi logistik, kadar kejayaan induksi hanya menunjukkan perbezaan yang signifikan diantara SKD 2 μg/ml dan SKD 4 μg/ml (p = 0.001) tetapi tidak signifikan diantara SKD 3 μg/ml dan SKD 4 μg/ml (p = 0.898). Anggaran 'marginal means' dan konfidens interval 95% bagi jangkamasa induksi adalah 73.63 (59.08, 88.18) saat bagi SKD 2 μg/ml, 74.12 (62.58, 85.65) saat bagi SKD 3 μg/ml and 55.25 (40.76, 69.75) saat bagi SKD 4 μg/ml yang mana ia tidak menunjukkan perbezaan yang signifikan (p = 0.101). Terdapat perbezaan perubahan yang signifikan di dalam semua parameter hemodinamik tetapi tiada perbezaan yang signifikan jika dibandingkan diantara ketiga-tiga kumpulan.

Kesimpulan:

SKD 3 μg/ml adalah setara jika dibandingkan dengan SKD 4 μg/ml untuk induksi pembiusan dengan tiada perbezaan yang signifikan dari segi kadar kejayaan induksi, jangkamasa induksi dan perubahan-perubahan hemodinamik. SKD 2 μg/ml tidak disarankan untuk permulaan induksi.

ABSTRACT

Objectives:

To compare success rate of induction within 3 minutes, induction time and haemodynamic changes between three different target blood concentrations (TBC) of propofol in a predominantly Malay Malaysian population.

Methodology:

In this prospective study, 135 ASA I and II patients in age between 18-55 years old and underwent any elective surgery were randomized into 3 groups. Group I received initial TBC of 2 μg/ml (n = 45), group II received initial TBC of 3 μg/ml (n = 45) and group III received initial TBC of 4 μg/ml (n = 45) for induction of anaesthesia. All patients were premedicated with oral midazolam 7.5 mg in the ward 30 minutes before induction and were given IV alfentanil 30 μg/kg bolus as analgesia. Induction time was measured from starting of infusion until loss of verbal contact and induction was considered successful if loss of verbal contact was achieved within 3 minutes from starting of infusion. Haemodynamic parameters (SBP, DBP, MAP and HR) were recorded at baseline, 1 minutes, 3 minutes and 5 minutes after induction. Patients were subsequently paralyzed with IV rocuronium 0.6 mg/kg and intubated. Maintenance of anaesthesia was continued with total intravenous anaesthesia using TCI of propofol at TBC of 1.5-6 μg/ml and alfentanil infusion at 30-60 μg/kg/h.

Results:

Success rate of induction was 55.6 % in TBC 2 μg/ml, 86.7 % in TBC 3 μg/ml and 91.1 % in TBC 4 μg/ml, which showed significant difference between 3 groups (p = 0.000). However from multivariate analysis using logistic regression method, success rate were only significantly difference between TBC 2 μg/ml and TBC 4 μg/ml (p = 0.001) but were not significantly difference between TBC 3 μg/ml and TBC 4 μg/ml (p = 0.898). Estimated marginal means and 95% confidence interval of induction time were 73.63 (59.08, 88.18) s in TBC 2 μg/ml, 74.12 (62.58, 85.65) s in TBC 3 μg/ml and 55.25 (40.76, 69.75) s in TBC 4 μg/ml which showed no significant difference (p = 0.101). There were significant changes within all haemodynamic parameters but no significant differences between the groups.

Conclusions:

TBC 3 μg/ml was comparable with TBC 4 μg/ml for induction of anaesthesia with no significant differences in success rate of induction, induction time or haemodynamic changes. TBC 2 μg/ml is not recommended for initial induction.

CHAPTER 1: INTRODUCTION

Propofol (Diprivan) was introduced in 1986 as an intravenous anaesthetic agent for the induction and maintenance of general anaesthesia. Widespread clinical experience with propofol has established the benefits relating to the quality of control of anaesthesia and the quality of recovery. Onset and offset of anaesthetic effects are rapid and reliable. Propofol offers rapid emergence, low incidence of postoperative nausea and vomiting (PONV) and a potential reduction in time to discharge. Total intravenous anaesthesia (TIVA) based on propofol has the general advantage of avoiding occupational exposure to inhalational agents.

Manual control of propofol infusion for maintenance of anaesthesia is sometimes viewed as "not as easy as" using vaporizer with an inhalational agent. There is, therefore, a general need for a more convenient method for infusing intravenous agent. Target controlled infusion (TCI) systems have been developed to provide improved convenience and control during intravenous anaesthesia. The basic principle is that the anaesthetist sets and adjusts the target blood concentration and depth of anaesthesia as required on clinical grounds. Infusion rates are altered automatically according to validated pharmacokinetic model. 'Diprifusor' (TCI software/ subsystem/ system) for propofol is such a development. 'Diprifusor' is the first commercially available TCI system and is incorporated in syringe pumps from major manufacturer.

TCI has several potential benefits over manually controlled infusion (MCI) technique. Benefits can be considered mainly in terms of convenience in use and control of anaesthesia. In term of convenience in use, it is simple to operate and easy to titrate the level of anaesthesia. It also displays calculated blood or plasma concentrations and

provides continuous process from induction through to maintenance. In term of control of anaesthesia, it has a good control of depth of anaesthesia and can also provide a stable anaesthesia. Furthermore it can improve cardiovascular and respiratory parameters stability.

From the previous studies, the recommended range for induction is 4-8 μg/ml and for maintenance is 3-6 μg/ml. For the initial induction target blood concentration (TBC), 4 μg/ml is recommended in premedicated patients and 6μg/ml in unpremedicated patients. Most of the previous studies for the propofol TCI were done in US and Europe. There are only a few studies found in the Asia region from the literature review. The aim of this study is to determine whether the recommended initial target blood concentration from the Western studies is also applicable to our local population. As for other anaesthetic agents, there are wide interindividual pharmacokinetic and pharmacodynamic variability in propofol requirement. Therefore there are high possibilities that our target blood concentrations requirement of propofol in either induction or maintenance are lower than recommendation if we base on our relatively smaller physical built, body weight, race and also genetic differences.

1.1. Objectives

1. To compare success rate of induction within 3 minutes of achieving the target concentration between three different target blood concentrations
2. To compare induction time of successful induction between three different target blood concentrations.

3. To compare haemodynamic changes between the three different target blood concentrations.

CHAPTER 2: LITERATURE REVIEW

2.1 Propofol

2.1.1 Chemical structure

Propofol is a new intravenous anaesthetic agent chemically unrelated to barbiturate, steroids, imidazole, or eugenol agents. It is one of a series of alkyl phenols, found to have anaesthetic properties in animals.The structure of propofol, 2, 6-diisoprophylphenol is shown in figure 2.1.

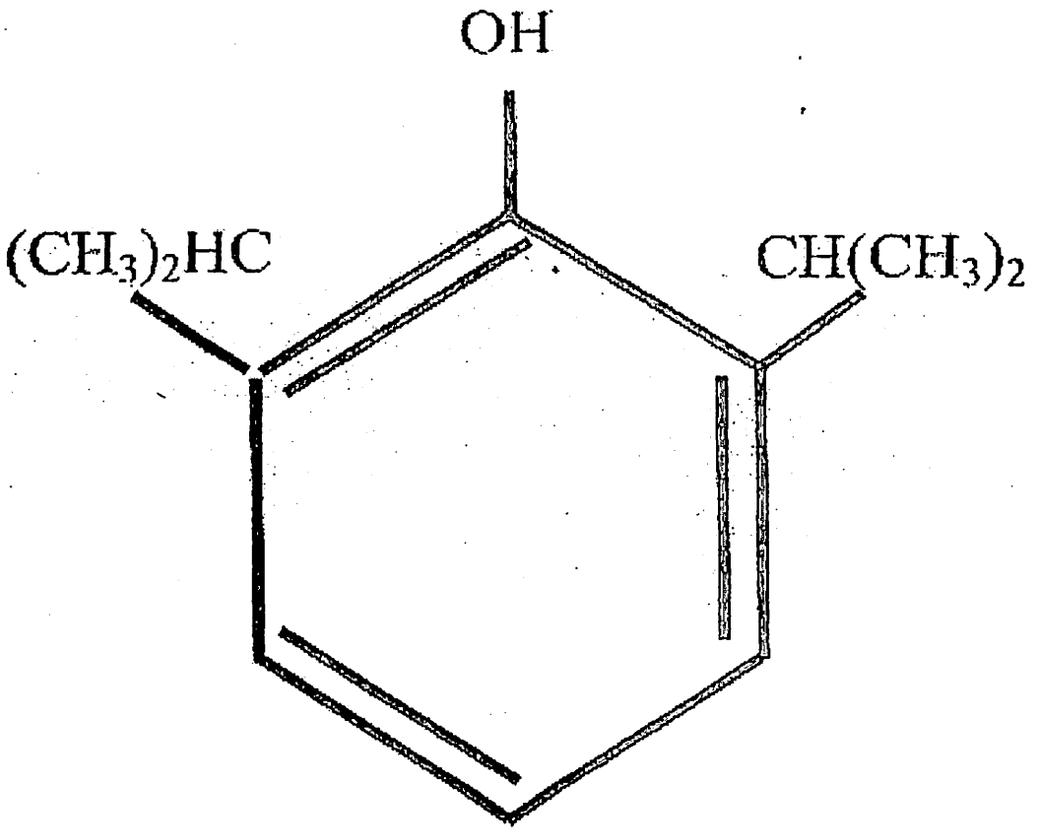

Figure 2.1: Chemical Structure of Propofol

2.1.2 Preparation

Propofol was originally formulated as a 1 % solution in 16 % polyoxyethylated castor oil (Cremophor EL). This preparation was associated with severe pain on injection and anaphylactoid reactions. Since 1982, propofol has been reformulated in a concentration of 10 mg/ml in fat emulsion. The present formulation consists of 1 percent (wt/vol) propofol, 10 percent soybean oil (long-chain triglycerides), 2.25 percent glycerol, and 1.2 percent purified egg phosphatide. It has a pH of 7 and appears as a slightly viscous, milky white substance. Propofol is available as a 1 percent solution in 20-ml clear glass ampules and 50-ml vials. It is stable at room temperature and is not light-sensitive. If a dilute solution of propofol is required, it is compatible with 5 percent dextrose in water.

The formulation has not been associated with known anaphylactoid reactions, but moderate to severe pain on injection is still a problem in 32%-67% of patients. Previous studies have shown that high concentrations of free propofol in the aqueous phase of emulsion are associated with pain on injection (Fragen RJ, 1988).

There is a new formulation of propofol in a 10 % fat emulsion consisting of long-chain triglycerides and medium-chain triglycerides which has infrequent incidence of moderate or severe pain. Doenicke AW *et al.* (1997) showed that there was a significant reduction in reported severe or moderate pain on injection after propofol 1% in the new formulation (9 %) than after standard formulation (59%).

2.1.3 Pharmacokinetics

The pharmacokinetics of propofol following a wide range of doses as well as following continuous infusions have been evaluated by numerous investigators and have been described by both two- and three-compartment models. Following a single bolus injection, whole blood propofol levels decrease very rapidly as a result of both redistribution and elimination. The initial distribution half-life of propofol is 2 to 8 minutes (Simons PJ *et al*, 1985). In studies using a two-compartment model, the elimination half-life has varied from 1.0 to 3 hours (Shafer A *et al*, 1988). Studies using a three-compartment model have given initial and slow distribution half-lives of 1 to 8 minutes and 30 to 70 minutes and an elimination half-life of 4 to 23.5 hours (Bailie GR *et al*, 1992).This longer elimination half-life is indicative of a deep compartment with limited perfusion, which results in a slow return of propofol back to the central compartment. Owing to the very rapid clearance of propofol from the central compartment, the slow return of propofol from this deep compartment contributes little to the initial rapid decrease in propofol concentrations. The context-sensitive half-time for propofol for infusions of up to 8 hours is less than 40 minutes (Hughes MA *et al*, 1992). As the required decrease in concentration for awakening following anesthesia or sedation with propofol is generally less than 50 percent, recovery from propofol will remain rapid even following prolonged infusions. The volume of distribution of the central compartment has been calculated as 20 to 40 L and the volume of distribution at steady state as 150 to 700 L. The clearance of propofol is extremely high at 1.5 to 2.2 L/min. This exceeds hepatic blood flow, and extrahepatic metabolism has been demonstrated. The keo (the first order rate constant for equilibration of the effect site with plasma concentration) for propofol is 0.291 min-1 and the t1/2 keo is 2.4 minutes

based on suppression of the EEG. The time to peak effect is 92 seconds (Dyck JB *et al*, 1991).

The pharmacokinetics of propofol may be altered by a variety of factors (e.g., gender, weight, pre-existing disease, age, and concomitant medication). Women have a higher volume of distribution and higher clearance rates, but the elimination half-life is similar for males and females (Kay NH *et al*, 1986). The elderly have decreased clearance rates but a smaller central compartment volume (Kirkpatrick T *et al*, 1988). Children have a larger central compartment volume (50 percent) and a more rapid clearance (25 percent) (Marsh B *et al*, 1991). Hepatic disease appears to result in a larger steady state and central compartment volumes; clearance is unchanged but the elimination half-life is slightly prolonged (Servin F *et al*, 1987). The effect of fentanyl administration on propofol pharmacokinetic parameters is controversial. Some studies suggest that fentanyl may reduce both intercompartmental and total body clearance rates as well as volumes of distribution (Benoni G *et al*, 1990).In a separate study fentanyl did not alter propofol pharmacokinetics following a single dose of both drugs (Gill SS *et al*, 1990). In in vitro studies on human hepatocytes, propofol inhibited in a dose-dependent manner the enzymatic degradation of both sufentanil and alfentanil (Janicki PK *et al*, 1992). Propofol kinetics is unaltered by renal disease (Morcos WE *et al*, 1985). Four published pharmacokinetic studies have been performed in children. Variations between these four studies may be attributable to differences in sampling interval (which influences the size of central compartment, small numbers of patients, the effects of adjunctive anaesthetic drugs, and the use of different modeling techniques (Fisher DM, 1994). Despite these intrastudy differences, all four studies demonstrated that the volume of propofol's central

compartment is larger (on a per kg body weight basis) in children than in adults. The clearance rate of propofol is also higher in children. Therefore, children will require a larger induction dose and increased maintenance infusion rate (per kilogram body weight) than adults (Hanallah RS, 1992). As in adults, other factors (e.g., the infusion duration) also influence the effect of propofol on recovery in children (Fisher DM, 1994).

2.1.4 Metabolism

Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulfate to produce water-soluble compounds, which are excreted by the kidneys. Less than 1 % propofol is excreted unchanged in urine, and only 2 % is excreted in feces (Simons PJ *et al*, 1985). The metabolites of propofol are thought not to be active. Because clearance of propofol exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination has been suggested. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver (Veroli P *et al*, 1992) .The lungs do not seem to be the site of this extrahepatic metabolism.

2.1.5 Pharmacodynamics

2.1.5.1 Effects on the Central Nervous System

Propofol is primarily a hypnotic. The exact mechanism of its action has not yet been fully elucidated; however, evidence suggests that it acts by enhancing the function of the GABA-activated chloride channel. Although propofol acts via the GABA receptor, its

action is pressure-reversible, and it adheres to the correlation exhibited by other general anesthetics between anesthetic potency and octanol/water distribution coefficient (Tonner PH *et al*, 1992). Unlike barbiturates, propofol is not antianalgesic. The onset of hypnosis following doses of 2.5 mg/kg is rapid (one arm-brain circulation). The ED50 of propofol is 1 to 1.5 mg/kg following a bolus. The duration of hypnosis is dose-dependent, being 5 to 10 minutes following 2 to 2.5 mg/kg (Major E *et al*, 1981). Age markedly affects the ED95 induction dose of propofol, being highest at ages less than 2 (ED95 2.88 mg/kg) and decreasing with increasing age (Aun CST *et al*, 1992). At subhypnotic doses propofol will provide sedation and amnesia (Mackenzie N *et al*, 1987; Wilson E *et al*, 1988). Propofol infusions of at least 2 mg/kg/h were necessary to provide amnesia in unstimulated volunteers. Awareness during surgery at higher infusion rates has been reported (Zacny JP *et al*, 1992). During surgical procedures very high infusion rates may be necessary to prevent awareness if propofol is used as the sole anesthetic. Propofol alters mood following short surgical procedures to a lesser extent than thiopental. Propofol also tends to produce a general state of well-being. Hallucinations, sexual fantasies, and opisthotonos have been reported following propofol administration.

The effect of propofol on the EEG as assessed after 2.5 mg/kg followed by an infusion demonstrates an initial increase in a-rhythm followed by shift to d and u frequency. High infusion rates produce burst suppression (Hazeau C *et al*, 1997). EEG power analysis indicates that amplitude increases after induction but is thereafter unaltered at propofol blood concentrations of 3 to 8 mg/ml. At propofol concentrations greater than 8 mg/ml, amplitude markedly decreases, with periods of burst suppression (Yate PM *et al*, 1986). There is a strong correlation between the logarithm of blood concentration of propofol and

the percentage of d activity content, and there is an inverse correlation with percentage of b activity content. The effect of propofol on epileptogenic EEG activity is controversial. Initial studies in mice indicate that propofol neither induced convulsions nor provided anticonvulsant activity. Several more recent reports have shown in a variety of models a direct anticonvulsant effect of propofol, which is dose-dependent (Heavner JE *et al*, 1992). In a few reports propofol has been used to treat epileptic seizures (Wood PR *et al*, 1988; Chilvers CR *et al*, 1992). Propofol also results in a shorter duration of motor and EEG seizure activity following electroconvulsive therapy as compared with methohexital (Dwyer R *et al*, 1988). Interestingly, propofol has been associated with grand mal seizures and has been used for cortical mapping of epileptogenic foci (Hodkinson BP *et al*, 1987). More importantly, there have been several reports of convulsions following propofol administration that have occurred several (up to 6) days following anesthesia. Although the majority of these patients had a history of previous convulsions, a few did not. The incidence of this adverse effect is rare (approximately 1 in 50,000 administrations). There have also recently been reports of tolerance developing to propofol following either repeat anesthetics or prolonged infusions (days) (Boyle WA *et al*, 1990).There have not been reports of acute tolerance during a single anesthetic. In addition to tolerance, addiction to propofol has been reported. Propofol produces a decrease in amplitude of the early components of somatosensory evoked potentials as well as a small nonsignificant increase in latency of the P40 and N50 components (Maurette P *et al*, 1988). Like other intravenous anesthetics, propofol does not alter brain stem auditory evoked potentials.There is, however a dose-dependent prolongation of latency and a decrease in amplitude of cortical middle latency auditory potentials, which are concentration-

dependent (Savoia G *et al*, 1988). Propofol will decrease ICP in patients with either normal or elevated ICP. In patients with normal ICP, the decrease in ICP (±30 percent) is associated with a small decrease in cerebral perfusion pressure (±10 percent) (Ravussin P *et a*l, 1988). The addition of small doses of fentanyl and of supplemental doses of propofol ablates the rise of ICP secondary to endotracheal intubation. Normal cerebral reactivity to carbon dioxide and autoregulation are maintained during a propofol infusion. In patients with elevated ICP, the decrease in ICP (30 to 50 percent) is associated with significant decreases in cerebral perfusion pressure and therefore may not be beneficial. Propofol reduces $CMRO_2$ to 36 percent (Stephan H *et al*, 1987). With a background of 0.5 percent enflurane, propofol still reduces $CMRO_2$ by 18 percent while lactate and glucose metabolism remain unchanged (Vandesteene A *et al*, 1988). Propofol administered to burst suppression results in significantly better neurologic outcome and less brain tissue injury in an incomplete ischemia model in rats, as compared with fentanyl. Propofol will also provide cerebral protective effects following an acute ischemic insult to the same degree as either halothane or thiopental (Gelb AW *et al*, 1993). Propofol acutely reduces intraocular pressure by 30 to 40 percent. As compared with thiopental, propofol produces a greater decrease in intraocular pressure, and following a small second dose it is more effective in preventing a rise in intraocular pressure secondary to succinylcholine and endotracheal intubation (Mirakhur RK *et a*l, 1997).

The propofol Cp50 for loss of response to verbal command is 3.5 mg/ml (Vuyk J *et al*, 1992). The propofol Cp50 (arterial whole blood concentration) to prevent movement on skin incision is 16 mg/ml. This is markedly reduced by increasing concentrations of fentanyl (Smith C *et a*l, 1992). The propofol Cp50 for skin incision when combined with

benzodiazepine premedication (lorazepam 1 to 2 mg) and 66 percent nitrous oxide is 2.5 mg/ml (venous) (Turtle MJ *et a*l, 1997). This concentration is reduced to 1.7 mg/ml when morphine (0.15 mg/kg) rather than lorazepam is used for premedication (Spelina KR *et al*, 1986). The concentration of propofol (when combined with 66 percent nitrous oxide) required during minor surgery varies from 1.5 to 4.5 mg/ml (Schuttler J *et al*, 1985) and that for major surgery varies from 2.5 to 6 mg/ml (Sanderson JH *et al*, 1988). Awakening usually occurs below a concentration of 1.6 mg/ml and orientation below 1.2 mg/ml. Age affects the propofol concentration required to provide adequate anesthesia.

2.1.5.2 Effects on the Respiratory System

Propofol affects the respiratory system in a manner qualitatively similar to the action of barbiturates. Apnea occurs after an induction dose of propofol. The incidence and duration of apnea appear dependent on dose, speed of injection, and concomitant premedication. An induction dose of propofol results in a 25 to 30 percent incidence of apnea (Sanderson JH *et al*, 1988; Taylor MB *et al*, 1986). The apnea occurring with propofol however, may be prolonged to more than 30 seconds. The incidence of prolonged apnea (longer than 30 seconds) is further increased by addition of an opiate, either as a premedication or just prior to induction(Sanderson JH *et al*, 1988), and is greater with propofol than with other commonly used intravenous induction agents (Gold MI et al, 1987). The onset of apnea is usually preceded by marked tidal volume reduction and tachypnea (Goodman NW *et al*, 1987). Following a 2.5 mg/kg induction dose of propofol, respiratory rate is significantly decreased for 2 minutes (Taylor MB *et al*, 1986), and minute volume is significantly

reduced for up to 4 minutes, which indicates a more prolonged effect of propofol on tidal volume than on respiratory rate.

A maintenance infusion of propofol (100 mg/kg/min) results in a 40 percent decrease in tidal volume and a 20 percent increase in respiratory frequency, with an unpredictable change in minute ventilation. Doubling the infusion rate from 100 to 200 mg/kg/min causes a further moderate decrease in tidal volume (455 to 380 ml) but no change in respiratory frequency. The ventilatory response to carbon dioxide is also decreased during a maintenance infusion of propofol. At 100 mg/kg/min there is a 58 percent reduction in the slope of the carbon dioxide response curve (Goodman NW *et al*, 1987). Propofol 1.5 to 2.5 mg/kg results in an acute (13 to 22 percent) rise in $PaCO_2$ and a decrease in pH. PaO2 does not change significantly (Aun C *et al*, 1984). During a maintenance infusion of propofol (54 mg/kg/min) PaCO2 is moderately increased from 39 to 52 mmHg (Coates DP *et al*, 1987). Doubling this infusion rate does not result in a further increase in PaCO2. Propofol (50 to 120 mg/kg/min) also depresses the ventilatory response to hypoxia (Blouin RT *et al*, 1992). Propofol induces bronchodilation in patients with chronic obstructive pulmonary disease (Conti G *et al*, 1993). Propofol, however, does not appear to provide as effective bronchodilating properties as halothane (Mehr EH *et al*, 1992).

observation that subhypnotic doses of propofol fail to increase plasma prolactin concentrations (Borgeat A *et al*, 1997). A rapid and distinct increase in plasma prolactin concentrations is characteristic of drugs that block the dopaminergic system. The antiemetic effect of propofol is not due to the intralipid emulsion in the formulation (Gan TJ *et al*, 1997).

Propofol at subhypnotic doses has also been reported to relieve cholestatic pruritus, as well as pruritus induced by spinal opiates (Borgeat A *et al*, 1992). The mechanism of the antipruritic effect may be related to the drug's ability to depress spinal cord activity. In this regard, there is evidence that intrathecal opioids produce pruritus by segmental excitation within the spinal cord.

Propofol possesses antiepileptic properties, presumably reflecting GABA-mediated presynaptic and postsynaptic inhibition. In this regard, propofol in doses of >1 mg/kg IV decreases seizure duration 35% to 45% in patients undergoing electroconvulsive therapy (Avramov MN *et al*, 1995). The incidence of excitatory movements and associated electroencephalogram (EEG) changes are low after the administration of propofol (Reddy RV *et al*, 1993). Propofol does not produce seizure activity on the EEG when administered to patients with epilepsy, including those undergoing cortical resection (Cheng MA *et al*, 1996; Ebrahim ZY *et al*, 1994; Samra SK *et al*, 1995).

Propofol has potent antioxidant properties that resemble those of the endogenous antioxidant vitamin E (Murphy PG *et al*, 1992). A neuroprotective effect of propofol may be at least partially related to the antioxidant potential of propofol's phenol ring structure. For example, propofol reacts with lipid peroxyl radicals and thus inhibits lipid peroxidation by forming relatively stable propofol phenoxyl radicals. In addition, propofol also

scavenges peroxynitrite, which is one of the most potent reactive metabolites for the initiation of lipid peroxidation. Because peroxynitrite is a potent bactericidal agent, it is likely that the peroxynitrite-scavenging activity of propofol contributes to this anesthetic's known ability to suppress phagocytosis (Krumholz W *et al*, 1994). Conversely, propofol might be beneficial in disease states, such as acute lung injury, in which peroxynitrite formation is thought to play an important role (Kooy NW *et al*, 1995).

2.1.6 Clinical uses

2.1.6.1 Induction and Maintenance of Anesthesia

Propofol is suitable for both the induction and maintenance of anesthesia. The induction dose varies from 1.0 to 2.5 mg/kg and the ED95 in unpremedicated adult patients is 2.25 to 2.5 mg/kg (Cummings GC et al, 1984). Premedication with an opiate and or a benzodiazepine tends to markedly reduce the induction dose (Briggs LP *et al*, 1985) Increasing age also reduces the dose of propofol required to induce anesthesia (Dundee JW et al, 1986). A dose of 1 mg/kg (with premedication) to 1.75 mg/kg (without premedication) is recommended for inducing anesthesia in patients over 60 years of age (Steib A *et al*, 1988).The ED95 (2.0 to 3.0 mg/kg) for induction is increased in children, primarily because of pharmacokinetic differences (Purcell-Jones G *et al*, 1987).

Propofol, when used for induction of anesthesia in shorter procedures, results in a significantly quicker recovery and earlier return of psychomotor function as compared with thiopental or methohexital, irrespective of the agent used for maintenance of anesthesia (Heath PJ *et al*, 1988; Mackenzie N *et al*, 1985). The incidence of nausea and vomiting

when propofol is used for induction is also markedly less than following the other intravenous induction agents, probably because of the antiemetic properties of propofol. Propofol, because of its pharmacokinetics, provides a rapid recovery and is thus superior to barbiturates for maintenance of anesthesia (Mackenzie N *et al*, 1995), and it appears equal to enflurane and isoflurane (Doze VA et al, 1988; Glass P *et al*, 1988). Recovery from desflurane is slightly more rapid than recovery from propofol (Van Hemelrijck J *et al*, 1991). Propofol can be given as intermittent boluses or as a continuous infusion for maintenance. Following a satisfactory induction dose, a bolus of 10 to 40 mg is needed every few minutes to maintain anesthesia. As these doses need to be given frequently, it is more suitable to administer propofol as a continuous infusion.

Several infusion schemes have been used to achieve adequate plasma concentrations of propofol (Roberts FL *et al*, 1988). Following an induction dose, an infusion of 100 to 200 mg/kg/min is usually needed. The infusion rate is then titrated to individual requirements and the surgical stimulus. Morphine, fentanyl, or alfentanil when combined with propofol reduces its required infusion rate and concentration (Thomas VL *et al*, 1988). For maintenance propofol has been used as a single mixture with alfentanil, containing 1 mg alfentanil (2 ml) to 400 mg propofol (40 ml). When this mixture was administered at infusion rates commonly used for propofol (i.e., 166 mg/kg/min for 10 minutes, 133 mg/kg/min for 10 minutes, and 100 mg/kg/min thereafter), it provided an outcome equal to that obtained by using the two drugs as separate infusions (Taylor IN *et al*, 1992). Increasing age is associated with a decrease in propofol infusion requirements (Hilton P et al, 1986; Schuttler J *et al*, 1992), which are higher in children and infants. The blood levels of propofol alone for loss of consciousness are 2.5 to 4.5 mg/ml, and the blood

concentrations (when combined with nitrous oxide) required for surgery are 2.5 to 8 mg/ml. Similar concentrations are necessary when propofol is combined with an opioid for a total intravenous technique. The knowledge of these levels and of the pharmacokinetics of propofol has enabled the use of pharmacokinetic model-driven infusion systems to deliver propofol as a continuous infusion for the maintenance of anesthesia. For short (hour) body surface procedures, the advantages of a more rapid recovery and decreased nausea and vomiting are still evident (Doze VA *et al*, 1988) However, if propofol is used for longer or more major procedures, both speed of recovery and the incidence of nausea and vomiting are similar to those following thiopental-isoflurane anesthesia (Doze VA *et al*, 1988).

2.1.6.2 Sedation

Propofol has been evaluated for sedation during surgical procedures and for patients receiving mechanical ventilation in the ICU. Propofol by continuous infusion provides a readily titratable level of sedation and a rapid recovery once infusion is terminated irrespective of the duration of the infusion (Beller JP *et al*, 1988). In a study of patients sedated in the ICU for 4 days with propofol, recovery to consciousness was rapid (about 10 minutes). Both the rate of recovery and decrease in plasma concentration were similar at 24 and at 96 hours, when the infusion was discontinued. Also, the plasma concentrations required for sedation and for awakening were similar at 24 and 96 hours, which implies that tolerance to propofol did not occur (Beller JP *et al*, 1988). As noted above, there have been more recent reports of tolerance with propofol. Infusion rates required for sedation to supplement regional anesthesia in healthy patients are half or less than half of those

required for general anesthesia (i.e., 30 to 60 mg/kg/min) (Fanard L *et al*, 1988). In elderly patients (over 65 years) and sicker patients the infusion rates that are necessary are markedly reduced (Grounds RM *et al*, 1985). Thus, it is important to individually titrate the infusion to the desired effect. A 1992 report has linked propofol with several deaths in children requiring sedation for mechanical ventilation secondary to upper respiratory tract infections (Parke TJ *et al*, 1992). The likelihood of propofol being the primary cause has been challenged. However, propofol is not yet approved for ICU sedation in children, and it should not be used for this purpose until definitive studies assessing its safety in this population are completed. No such adverse experiences have been reported in adults. A potential advantage for propofol for sedation of ICU patients is that it appears to possess antioxidant properties (Murphy PG *et al*, 1992).

Generally at propofol infusion rates greater than 30 mg/kg/min patients are amnestic (Fanard L *et al*, 1988). In comparison with midazolam used to maintain sedation, propofol provides equal or better control and more rapid recovery (Grounds RM *et al*, 1985). In mechanically ventilated patients, more rapid recovery translates to more rapid extubation when sedation is terminated. Propofol has also been used successfully in patient-controlled sedation. Propofol was rated better than midazolam when used by this technique, probably owing to its much more rapid onset and offset (Rudkin GE *et al*, 1992).

2.1.6.3 Ambulatory anaesthesia

The ideal anaesthetic technique for ambulatory surgery should provide rapid onset and stable operating conditions while ensuring rapid recovery of protective reflexes and of cognitive and psychomotor functions. In evaluating recovery from anaesthesia from in the outpatient setting, it is common to divide the recovery process into three distinct phases. Early recovery is usually referred to as emergence, and describes the time at which the patients awakenes from anaesthesia and obeys simple commands. Intermediate recovery describes the return of cognitive function and psychomotor function sufficient to permit discharge. Late recovery describes a complete return to preoperative state and resumption of normal activities. Anaesthetic techniques used in the ambulatory setting should be associated with a low incidence of postoperative side effects because they can delay the patient discharge and result in unanticipated hospital admissions. Since its introduction into clinical practice, propofol has become extremely popular intravenous anaesthetic for ambulatory surgery procedures because of its predictable recovery and favorable side effects profile. Recovery is not only rapid after a single bolus dose, but also after repeated doses or a titrated continuous infusion, thereby allowing propofol to be effectively used for maintenance of anaesthesia during ambulatory surgical procedures.

2.1.6.4 Monitored anaesthesia care

Monitored anaesthesia care usually involves the administration of intravenous adjuvants to produce sedation, anxiolysis and amnesia during minor diagnosis and therapeutic procedures or to supplement analgesic provided by local or regional anaesthetic technique. During monitored anaesthesia procedures, patients are monitored to ensure their safety and comfort during the operation. With the optimum sedation technique, the chosen drug (or combination of drugs) has sedative-hypnotic, anxiolytic, and amnestic properties, produces a low incidence of perioperative side effect (e.g., respiratory depression, nausea and vomiting), provides ease of titration to the desired level of sedation while providing rapid return completion of the procedure to a "clearheaded" state on completion of the procedure.

Traditionally, benzodiazepines have been widely used drug for sedation during monitored anaesthesia care. However, even drugs like midazolam or triazolam with relatively short elimination half-life values (2 to 4 hours) may be associated with prolonged sedation, and the resultant psychomotor impairment can delay recovery (Urquhart ML *et al*, 1989). Opiod analgesic (e.g. fentanyl and its newer analogs) are often administered in combination with sedative-hypnotics to reduce pain resulting from the injection of local anaesthetic solutions and traction on deeper tissue structures. Although a combination of midazolam and fentanyl is the most popular regimen, this combination can produce profound respiratory depression (Bailey PL *et al*, 1990). Compared with nonsteroidal anti-inflammatory ketorolac, adjunctive use of fentanyl provided for improved intraoperative patient comfort during propofol sedation (Ramirez-Ruiz M et al, 1995). However, when