Anaesthesia, 2002, **57**, pages 242–248

Propofol effective concentration 50 and its relationship to bispectral index

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Summary

Sixty unpremedicated healthy adult patients were studied during induction of anaesthesia with intravenous propofol delivered by a 'Diprifusor' target-controlled infusion. Bispectral index (BIS) and spectral edge frequency (SEF_{95}) were measured concurrently with the predicted blood and effect site propofol concentrations. Logistic regression was used to calculate the predicted propofol blood and effect site concentrations required to produce unconsciousness and no response to a noxious stimulus in 50% and 95% of patients and to correlate BIS with these end-points. The Diprifusor TCI software produces anaesthesia at consistent target concentrations. Bispectral index correlates well with clinical end-points and may be useful during propofol anaesthesia.

Keywords *Anaesthetics, intravenous*: propofol. *Brain*: electroencephalography.

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Accepted: 01 October 2001

Minimum alveolar concentration (MAC) is defined as the minimum steady state alveolar concentration of an inhalational anaesthetic that will suppress gross purposeful motor response to a skin incision in 50% of patients [1]. It has been used to determine relative anaesthetic potency and guide the anaesthetist in delivering concentrations that should produce adequate anaesthesia [2]. A similar concept has been proposed for intravenous anaesthetic drugs in relation to their blood concentration and is referred to as the effective concentration 50 (CP_{50}) [3]. Previously, this was of very little practical clinical value as it is not possible to measure intravenous anaesthetic blood concentrations in real time. However, a number of pharmacokinetic-based computer-controlled infusion systems have been developed to achieve and maintain target blood concentrations of propofol with a reasonable degree of accuracy [4, 5], and such a system has now become commercially available (Diprifusor – AstraZeneca Pharmaceuticals UK) [6]. With the development and increasing use of these target-controlled infusion (TCI) systems, there is a need to correlate drug concentrations with dynamic effects. We investigated how a commercially-available TCI system will produce anaesthesia in clinical practice and how standard end-points determining anaesthesia and loss of consciousness relate to the bispectral index (BIS) and predicted blood and effect site concentrations of propofol.

Methods

Sixty Chinese patients scheduled to undergo general anaesthesia were entered into the study. Approval was granted by the local institutional ethics committee and written informed consent was obtained from all participants.

Patient demographic and anaesthetic data were collected. Patients with a history of anaesthetic problems or allergy, recent administration of sedative drugs, age < 18 or > 60 years, body weight not within 20% of ideal and impairment of cardiac, hepatic, renal or respiratory function were not studied.

The TCI system used was the 'Diprifusor' incorporated into a Graesby 3500 syringe pump and using version 2 of the software. This device is programmed with the

Table 1 Patient demographic data. Results are expressed by mean (SD) [range] or numbers.

Age; years	37.3 (11.6) [18–60]
Weight; kg	61.2 (10.8) [43–87]
ASA physical status I/II; *n*	42/18
Sex; M/F	30/30

3-compartment pharmacokinetic parameters that describe the distribution and elimination of propofol [4]. Following the additional input of an individual patient's age and weight, a predicted target concentration of propofol ($\mu g.ml^{-1}$) can be selected and the computer will then make the necessary calculations as to the dose of propofol required to achieve and maintain this concentration and infuse the drug accordingly. This system is also programmed to calculate and display the propofol effect site concentration. This is an estimate of the drug concentration at its site of action (receptors and membranes in the biophase) according to the equilibration half-time ($t_{1/2}$ k_{eo}) and is based on EEG studies [5, 7].

Patients were unpremedicated. Following positioning on the operating table, the EEG signal was acquired using Zipprep™ electrodes (Aspect Medical Systems Inc., Natick, MA; all impedances < 5 kOhms) applied to the forehead and temple using a frontal-temporal montage. The bispectral index (BIS 3.0 algorithm, rev. 0.5 software version) and spectral edge frequency (SEF_{95}) were calculated and displayed in real time using an A-1000 EEG monitor (Aspect Medical Systems Inc.). The patient then had baseline measurements of pulse rate, oxygen saturation, non-invasive blood pressure and respiratory rate ($F_{\acute{E}}CO_2$ via a face mask). In this evaluation, an initial propofol target concentration of 1.5 $\mu g.ml^{-1}$ was chosen based on a previous study which found a median target concentration of 0.9 $\mu g.ml^{-1}$ required to produce adequate sedation using a similar TCI system [8]. The target concentration was then increased by 0.5 $\mu g.ml^{-1}$ every 2 min until loss of consciousness occurred. This was determined by the confluence of three end points: no response to verbal command, loss of eyelash reflex and inability to hold a 20-ml syringe. The propofol target and effect site concentrations, BIS, SEF_{95}, respiratory rate, heart rate and blood pressure were then recorded. Following loss of consciousness, the patient was given a tetanic stimulus to the ulnar nerve (50 Hz, 80 mA, 0.25 ms pulses for 4 s) at the wrist using a constant current peripheral nerve stimulator and observed for purposeful movement. Response to stimulation entailed a positive, gross, purposeful muscular movement, usually of the head or extremities. Twisting or jerking of the head was considered a movement response, but twitching or grimacing was not. Coughing, rigidity, swallowing, and chewing were not considered positive movement responses. The propofol target infusion was then increased by 0.5 $\mu g.ml^{-1}$ every 2 min and the stimulus repeated until no movement occurred. We defined this end-point as anaesthesia. Processed EEG, pharmacokinetic, cardiovascular and respiratory values were then recorded as before. During induction patients were asked about injection pain and asked to rate it as mild, moderate or severe.

At this point the study was stopped and surgery allowed to proceed as indicated. The target concentration was thereafter adjusted by the anaesthetist as required in the usual manner with adjuvant analgesic drugs or a local anaesthetic block administered as appropriate.

A quantal response model (Probit analysis) was used to calculate CP_{50} and CP_{95} at each end-point (loss of consciousness and no purposeful movement with tetanic stimulation) based on recordings of predicted target and effect site concentrations and BIS values. Assessment of the non-linear association between BIS values or predicted blood and effect site propofol concentrations and probability of unconsciousness and anaesthesia was achieved using logistic regression (SAS Institute Inc., Cary, NC – software version 8).

Results

Sixty patients of an equal sex distribution and of normal body mass index were studied. Demographic and surgical data are displayed in Table 1. During induction there was a moderate decrease in blood pressure, heart rate remained stable and there was a slight increase in respiratory rate (minute ventilation was not measured) (Fig. 1 and Table 2).

Patients were breathing 100% oxygen from an anaesthetic breathing circuit and no patient recorded any episodes of desaturation. Induction was smooth although seven patients experienced slight, and one had moderate, injection pain (overall incidence of 13.3%).

Loss of consciousness and subsequent anaesthesia occurred at fairly consistent target propofol blood and effect site concentrations (Table 3).

The probabilities of loss of consciousness and anaesthesia vs. BIS are displayed in Fig. 2. The probabilities of loss of consciousness and anaesthesia vs. predicted target and effect site propofol concentrations are displayed in Figs 3 and 4.

Discussion

Total intravenous anaesthesia (TIVA) using propofol is becoming an increasingly popular alternative to inhalational anaesthesia over which it confers a number of

advantages [9]. Many pharmacokinetic-based computer controlled infusion systems have been developed to achieve and maintain target blood concentrations of propofol with a reasonable degree of accuracy [4, 10] and improve the ease of use, although Schuttler's system could not change propofol concentration [10]. Such a system has now become commercially available and has been integrated with a number of infusion pumps (Diprifusor – AstraZeneca Pharmaceuticals UK) for use with the propofol 'prefilled syringe'. The software for this system has been extensively investigated and has a reasonable degree of bias and low inaccuracy [11]. We decided to use this system for our investigation because of its popularity and accessibility.

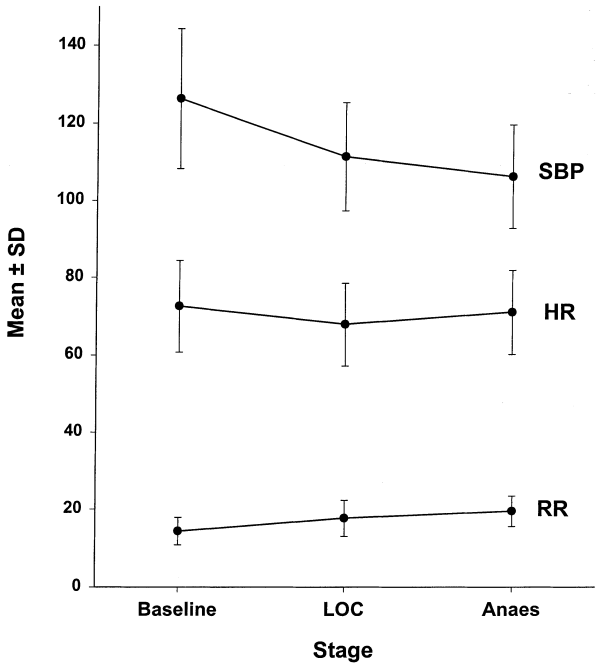

Figure 1 Heart rate (HR), systolic blood pressure (SBP) and respiratory rate (RR) during induction of anaesthesia.

Most anaesthetic drugs have potent physiological depressant effects and the danger of overdose has been well recognised since anaesthesia was first administered, and John Snow classified five degrees of ether anaesthesia in his textbook published in 1847 [12]. Other systems, such as Guedel's, for charting somatic and autonomic signs of anaesthetic depth were developed and refined over the years [13, 14]. However, since seven of the nine components of Guedel's classification involve skeletal muscle activity, which will be abolished by muscle relaxants, and autonomic responses are often unreliable, such charts are not very useful in modern anaesthetic practice and may not detect patient awareness, which has a reported incidence of 0.2–1.6% [15–17]. Anaesthetists are traditionally trained to use volatile anaesthetic agents, usually delivered with a calibrated vaporiser, and are comfortable and experienced with the concept of MAC values to help guide administration. The risk of patient awareness may be exacerbated by inexperience in the use of new techniques such as TIVA and few studies have been undertaken to correlate measured blood concentrations of propofol with anaesthesia in order to determine CP_{50} and CP_{95} [18–20]. Since there is no real-time plasma concentration monitor, it is not practical to measure blood propofol concentrations in the clinical setting. Therefore, we only measured target-controlled predicted blood and effect site concentrations. There is, obviously, a potential for bias and inaccuracy with such a system, although pharmacokinetic studies with the 'Diprifusor' indicate that this is acceptable for clinical purposes [11]. We were interested to determine if, when using TCI in the applied clinical situation, predicted target and effect site concentrations are a reproducible guide to

	Baseline	Loss of Consciousness	Anaesthesia
Systolic blood pressure; mmHg	126.3 (18.0)	111.3 (13.4)	106.1 (13.4)
Heart rate; beat.min^{-1}	72.6 (11.8)	67.9 (10.6)	70.9 (10.8)
Respiratory rate; breath.min^{-1}	14.4 (3.5)	17.7 (4.6)	19.5 (3.9)

Table 2 Cardiorespiratory changes during induction of anaesthesia. Data are mean (SD).

	CP50		CP95	
Stage	Target	Effect	Target	Effect
Loss of consciousness	3.92 (3.8 – 4.04)	2.66 (2.59 – 2.72)	5.38 (5.16 – 5.66)	3.82 (3.68 – 4.00)
Anaesthesia	5.56 (5.37 – 5.73)	4.47 (4.34 – 4.57)	7.40 (7.13 – 7.75)	6.39 (6.16 – 6.69)

Table 3 Predicted blood (target) and effect site concentrations of propofol (μg.ml^{-1}) that produce unconsciousness and anaesthesia. Data are mean (95% C.I.).

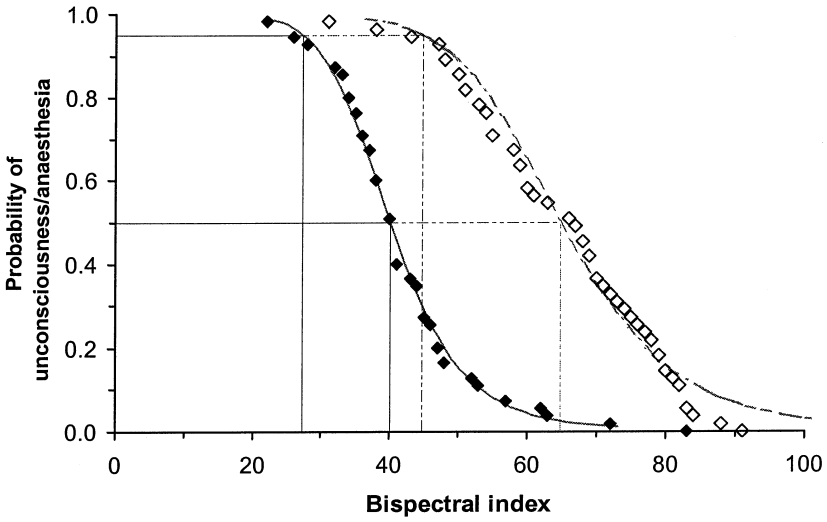

Figure 2 The probabilities of loss of consciousness and anaesthesia vs. bispectral index
Unconsciousness: observed ◇
Unconsciousness: predicted – – –
Anaesthesia: observed ◆
Anaesthesia: predicted ———

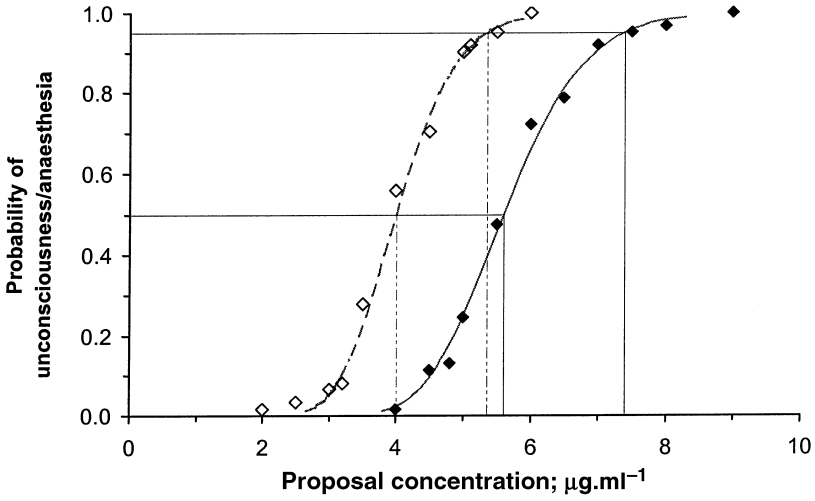

Figure 3 The probabilities of loss of consciousness and anaesthesia vs. target concentration of propofol
Unconsciousness: observed ◇
Unconsciousness: predicted – – –
Anaesthesia: observed ◆
Anaesthesia: predicted ———

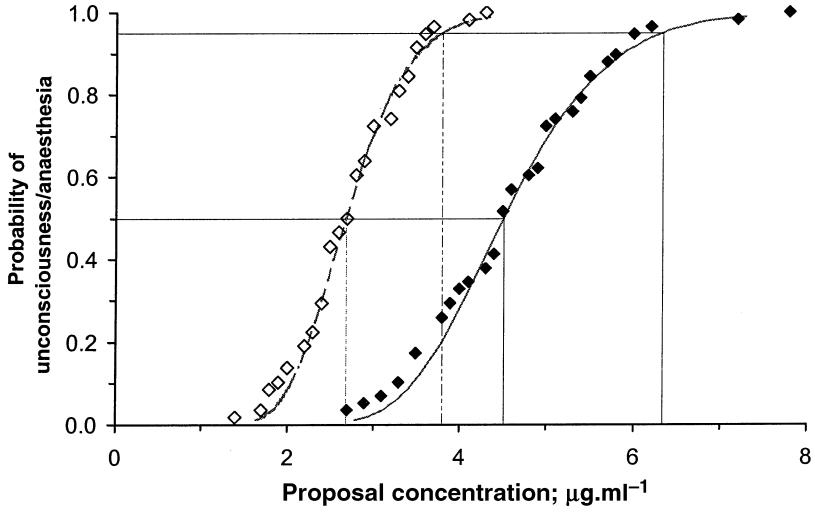

Figure 4 The probabilities of loss of consciousness and anaesthesia vs. effect site concentration of propofol
Unconsciousness: observed ◇
Unconsciousness: predicted – – –
Anaesthesia: observed ◆
Anaesthesia: predicted ———

anaesthetic depth. In this context and within this population we found that TCI was fairly consistent in producing anaesthesia and loss of consciousness. Loss of consciousness will often result in airway compromise and loss of protective reflexes and, since propofol TCI is commonly used in low doses for sedation [8], we felt it was also useful to determine concentrations and BIS values at which this occurs.

As a result of technological advances, there has been increasing interest in the use of processed EEG and auditory evoked potential monitoring to determine anaesthetic depth. Of these, the EEG is the most widely evaluated neurophysiologic tool. Bispectral analysis of the EEG determines the interfrequency coupling among all its component waves. The bispectral index is a univariate parameter computed from the bispectrum and other subparameters of the EEG ranked by ability to predict a clinical situation and then weighted to create a linear scale between two extremes [21]. Several investigators have studied its sensitivity as a measure of sedation [22, 23] and anaesthesia [24] in patients receiving propofol infusions. It has been shown to be a useful monitor of propofol sedation and anaesthesia, although the BIS value indicative of a certain level of consciousness varies somewhat between different anaesthetic techniques [25].

Rapid onset and offset of effect is an advantage for accurate drug titration in the face of temporal variation in dose requirements. When using intravenous anaesthetic drugs, it is important to remember the concentration at the effect site, the biophase concentration, determines the drug effect, not the plasma concentration. The mathematical first order rate constant, k_{eo}, and it's corresponding half-time determine the equilibration time between these compartments and the drug's pharmacodynamic onset. In the case of a single dose of propofol, peak effect concentration is obtained after about 4 min [26] while 80% of a final target concentration will be achieved in the effect site within about 6 min [27]. The plasma-effect site equilibration for BIS has been recently calculated to be approximately 2.3 min [28]. Effect site concentrations will exhibit hysteresis with adjustments in blood concentration. Also the blood concentrations at any particular time will not necessarily indicate the drug effect in the biophase, especially with frequent dose adjustments. It is therefore very useful to have a TCI system that can predict and display the effect site concentration. In performing this study, we deliberately increased the target concentrations in small increments allowing some time for equilibration and to minimise the discrepancy between blood and effect site concentrations. This may explain part of the difference between our results and the surprisingly high values for CP_{50} for propofol as a sole drug reported in previous studies [18, 19], where the effect site concentrations were not estimated. There is evidence to suggest that patients administered propofol to either a target plasma or target effect concentration will lose consciousness at the same effect site concentration irrespective of the plasma concentration at that time [29]. We propose that, because of the potential variability in central compartment concentrations, our data pertaining to effect site CP is the most clinically useful and the ability to display this information should be an integral part of all TCI systems.

Tetanic stimulation of the ulnar nerve has the advantage of ease of performance, repeatability, and reproducibility and has been used in place of skin incision in a number of studies [30–32]. A recent study showed no significant difference between CP_{50} tetanus and CP_{50} skin incision in somatic response, but significant differences in haemodynamic responses using this technique [33]. General anaesthesia is used to attenuate stress responses to surgery and render the patient unaware of the procedure taking place. Although the absence of a purposeful motor response has been traditionally used to determine anaesthetic potency [2], there is evidence to suggest that loss of consciousness and response to skin incision are not consistent with a scale of increasing 'depth' of anaesthesia but rather are two separate phenomena [34]. It has been shown that the prevention of movement by volatile anaesthetics is a spinal action, and the MAC of isoflurane in an isolated brain preparation is double the MAC concentration in the intact animal [35]. The addition of an opioid analgesic ablates these autonomic responses and reduces the concentration of propofol required to produce anaesthesia [33]. Such evidence suggests that both hypnosis and analgesia are important components of 'surgical' anaesthesia. The unconsciousness (hypnosis) produced by propofol may still result in arousal/awakening as a result of a noxious stimulus if the stimulus is not inhibited from reaching higher centres. This is achieved by the action of the opioid at opioid receptors within the spinal cord [36]. It can be seen that hypnotic agents, such as propofol in our study, can maintain unconsciousness and suppress movement at higher doses when used alone but, it may be surmised that this may result in less attenuation of stress, more peripheral side-effects and delayed recovery [37]. Much lower BIS values are obtained at propofol levels required to suppress purposeful movement, than just unconsciousness (Table 4). There is evidence to suggest that BIS values do not reflect all components of anaesthesia [38], since opioids do not produce the basic anaesthesia-related EEG pattern. In general, opioids produce a dose-related decrease in frequency and increase in amplitude of the EEG. If further doses of opioids are not given, alpha and beta activity will eventually return.

Table 4 BIS that is associated with unconsciousness and anaesthesia at EC50 and EC95. Data are mean (95% C.I.).

	BIS	
Stage	**CP_{50}**	**CP_{95}**
Loss of Consciousness	64.82 (63.29 – 66.18)	44.78 (41.75 – 47.32)
Anaesthesia	40.13 (39.37 – 40.88)	27.33 (25.93 – 28.53)

The rapidity of return depends on the initial dose and on the drug. Complete suppression of the EEG cannot be obtained with opioids and the potential interactive effect with hypnotics is an area worthy of further study.

Our patients were unpremedicated and presumably apprehensive prior to surgery so one might expect some diminution of sympathetic drive post induction. In addition, propofol causes direct vasodilatation and changes in sympathetic tone, as well as central depression of myocardial contractility [39, 40] and the baroreflex is reset to allow a lower heart rate for a given blood pressure [41]. Propofol has also been noted to decrease rate and depth of respiration [42]. However, in our study population, heart rate and blood pressure were well maintained and there was a tendency for respiratory rate to actually increase during induction (tidal volumes were not measured). This probably reflects an advantage of slow incremental propofol anaesthetic induction with TCI, where, by avoiding a rapid increase in blood concentration as seen with bolus dosing, one may minimise systemic side-effects [43]. Also, the dose–response curves for loss of consciousness (LOC) with propofol concentrations are much steeper than that for the BIS, indicating more consistency with the target values in obtaining LOC than the BIS.

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