Effect Site Targeted Propofol Infusion In Clinical Practice: Comparison To Diprifusor

L Hollos, N Enraght-Moony

Citation

Abstract

Commercially available computerised target-controlled infusions of propofol control the blood concentration of the drug. We designed a study to compare the Diprifusor system with effect site targeted propofol infusion. Twenty ASA grade I and II patients undergoing total knee replacement under spinal anaesthesia were randomly assigned to receive either blood or effect site targeted propofol infusion. Initial target concentration of 5 ug.ml-1 was decreased to 4 ug.ml-1 in 0.25 ug.ml-1 stepped fashion. Induction of anaesthesia was significantly faster in patients receiving effect site targeted propofol infusion, 83.2(19.3) vs. 57.4 (11.2) sec. (p=0.0019). During anaesthesia systolic blood pressure decreased significantly in both groups compared to preinduction levels, however there were no significant changes in diastolic and mean blood pressures in the effect site targeted group. In this group means of all latencies of auditory evoked potentials showed linear proportion to propofol concentration. Effect site targeted propofol infusion gave better control of anaesthesia and cardiovascular stability

BACKGROUND

Diprifusor, the stand-alone syringe driver with target-controlled infusion (TCI) incorporated has been popular since its launch in 1996. Earlier studies evaluating different administration techniques during general anaesthesia have shown its superiority over both intermittent bolus injections and manually controlled delivery [1,2]. These pumps use three compartment pharmacokinetic settings published by Mars at al. [3] and target the blood concentration of propofol. It is now possible to display the predicted effect site concentration using the distribution coefficient between plasma and brain based on electroencephalographic (EEG) studies. [4] When targeting the effect site, the preset level will relate to the calculated propofol concentration in the brain rather than in the blood. This will allow the blood levels of propofol to exceed the preset target levels thus allowing the blood-brain equilibrium to be developed faster. This may mean shorter induction time and better control of anaesthesia, but higher blood concentration may result in less cardiovascular stability. It is not possible to change the settings in Diprifusor pumps, but flexibility is available in computer software used to control a syringe driver (STELPUMP). [5] Effect site targeted pumps are not in the clinical practice, and – to our knowledge – have not been compared with ordinary Diprifusor system that targets the blood concentration.

Therefore we designed this study to examine the clinical usefulness of effect site targeted propofol TCI in comparison to a Diprifusor pump.

MATERIALS AND METHOD

With the approval of institutional ethics committee written informed consent were obtained from 20 patients scheduled for total knee replacement under spinal anaesthesia, ASA status I or II. Patients with hearing impairment and/or weighing more or less 20 % of their ideal body weight were excluded from this study. Patients were praemedicated with 10 mg temazepam and 40 mg omeprasole one hour before operation. Large bore intravenous catheter for fluid, and small one for propofol administration were inserted. Patients were monitorised using a three lead electrocardiograph, a pulse oximeter, non-invasive blood pressure monitor (Hewlett Packard 78352C, Hewlett-Packard GMBH, Germany). End-tidal carbon dioxide was also monitored. A subarachnoid block using 0.5% heavy bupivacaine was performed at L3-L4 level, followed by administration of 800 ml of compound sodium lactate infusion. Midlatency auditory evoked potentials (MLAEP) were obtained using AMPLAID® MK10 Single Channel Multisensory Evoked Potential System (AMPLAID S.P.A. Milan, Italy). Auditory stimuli were delivered via headphone at 100 dB level, and electrodes' resistance were kept below 5 Kohms. Latencies of peaks of Na, Pa and Nb waves were recorded (Figure 1).

For propofol delivery a Grasby® 3400 syringe driver was used controlled by an Intel® Pentium® 100 MHz based laptop computer running STELPUMP program. [5] Before the commencement of general anaesthesia, patients were randomly assigned into one of two groups. Both groups had pharmacokinetic settings set as published by Marsh et al. [3] In the Group B the blood, and in the Group E the effect site was targeted.

After induction of propofol TCI atracurium 0.4 mg.kg-1 was given and laryngeal mask airway (LMA) was inserted to allow the patients' lungs to be ventilated with oxygen enriched air (40% oxygen) maintaining end tidal carbon dioxide level at 35 – 40 mmHg. The initial target concentration of 5 ug.ml-1 was decreased to 4 ug.ml-1 by 0.25 ug.ml-1 in a stepped fashion. Cardiovascular parameters and latencies of the peak of Na, Pa and Nb were recorded before the commencement of anaesthesia and each time after the target concentration has been reached. After induction, in the blood-targeted group, the first measurements were made at five minutes time. The time of loosing response to verbal command was also recorded.

Results are expressed in means and standard deviations (SD). Data were analysed with unpaired t test, ANOVA with Dunnett's post test and linear regression using GraphPad InStat, while retrospective power analysis was done using GraphPad Stat Mate software package (GraphPad Software, San Diego, California, USA). Retrospective power analysis showed that our sample size was enough large to reach the conventionally acceptable study power of 80%. Probability values of <0.05 were considered significant.

Figure 1: Recorded and measured waves of Na, Pa and Nb in MLAEP before induction of anaesthesia in one of patients in the study. pumps (area under curve)

Figure 1
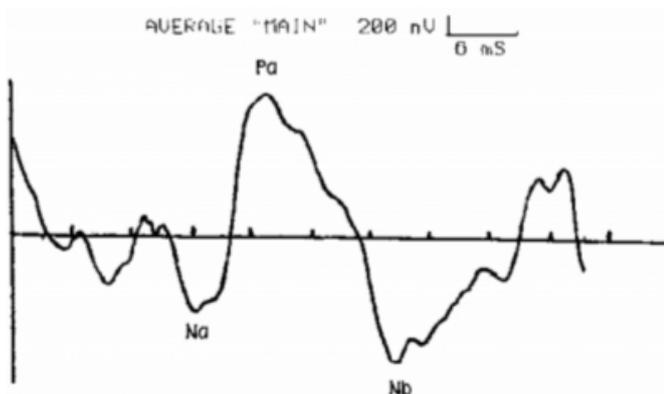
RESULTS

The demographic data of patients in the two groups were comparable (table 1). There was significant difference between the two groups in the induction time of anaesthesia. With Diprifusor system, the induction time was 83.2 (19.3) sec., while in the effect site targeted group; it was 57.4 (11.2) sec. (p=0.0019). Figure 2 shows the pumps' delivery pattern during the first five minutes. There was no significant difference however, between the amounts of propofol delivered by these pumps during the first five minutes (area under curves, 173.7 mg SD=22.7 vs. 203.7 mg SD=41.5 for the blood targeted and effect site targeted groups, respectively p=0.068).

Figure 2

Table 1: Demographic data of patients

	Group B	Group E
N	10	10
Age; years	70.9 (5.2)	69.1 (8.2)
Gender; (M/F)	3:7	3:7
Weight; kg	73.9 (12.0)	67.0 (11.6)

Figure 3

Figure 2: The figure shows the mean delivery pattern of TCI pumps in blood and effect site targeted groups, represented by solid and dotted line, respectively. When the effect site was targeted, the pump was running in higher rate and longer time then in blood targeted group, but stopped at 3 minutes for at least half a minute. There was no statistical difference between the doses of propofol delivered by pumps (area under curve)
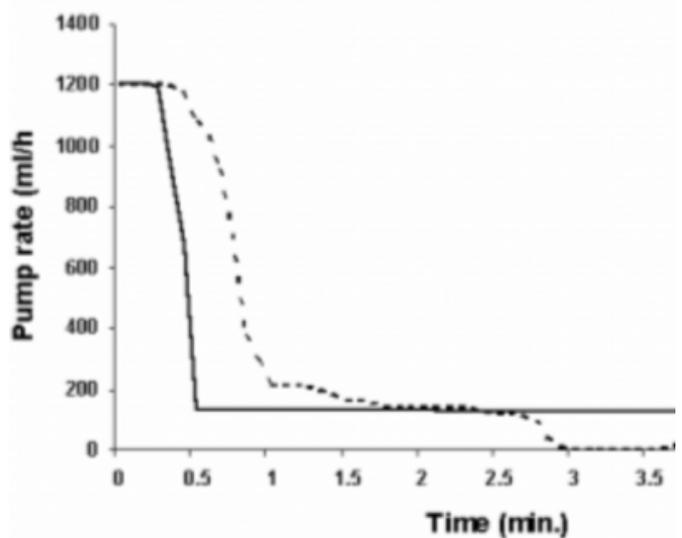
Cardiovascular parameters are shown in table 2. There was no difference between the groups in baseline levels at all

measured parameters. Heart rates were stable in both groups apart at 4 ug.ml-1 predicted plasma concentration in group B, where the difference became significant when compared to baseline values. The systolic blood pressure decreased in similar way in both groups after induction of anaesthesia. Decreasing of both diastolic and mean blood pressure were statistically significant in group B, but not in the effect site targeted group.

Figure 4

Table 2: Cardiovascular parameters during anaesthesia with Diprifusor (gr. B.) and effect site targeted propofol infusion (gr. E.). HR: heart rate (1/min.), SBP:systolic, DBP:diastolic, MBP:mean BP (mmHg), * P<0.05 vs. baseline, ?P<0.01 versus baseline

		Target propofol concentration (ug/ml)				
	0	5.0	4.75	4.5	4.25	4.0
HR gr.B	80.2 (13.8)	81.2 (10.7)	76 (8.2)	73.4 (8.1)	73 (8.1)	72.6 (8.6)*
gr.E	75.9 (11.3)	75.7 (18.4)	69.7 (15.6)	70.6 (16.3)	71 (17.2)	71.8 (18.0)
SBP gr.B	155 (12.3)	114 (21.4)ı	112 (15.0)ı	116 (15.4)ı	119 (13.4)ı	128 (19.5)ı
gr.E	149 (20.2)	121 (17.3)ı	120 (24.2)ı	121 (25.4)ı	124 (31.1)ı	127 (29.9)ı
DBP gr.B	82.2 (9.6)	71.1 (11.7)*	68.2 (10.6)ı	68.9 (13.4)ı	67.9 (8.7)ı	74.7 (11.4)
gr.E	73.8 (13.3)	70.0 (8.0)	67.4 (11.7)	69.6 (13.9)	65.9 (12.1)	65.6 (10.5)
MBP gr.B	103 (10.6)	88.9 (15.6)*	85.9 (12.1)ı	87.6 (14.2)*	85.1 (9.4)ı	94.4 (15.5)
gr.E	97.6 (15.8)	87.9 (11.4)	87 (17.5)	89.7 (17.5)	84.6 (17.2)	85.4 (13.9)

Table 3 shows recorded latencies of Na, Pa and Nb waves of MLAEP. Apart from the Pa potential at 5 ug.ml-1 predicted plasma propofol concentration in the blood targeted group, all other latencies were delayed significantly when compared to baseline values.

Figure 5

Table 3: Mean values and standard deviations of the latencies of Na, Pa and Nb in milliseconds. gr. B: blood targeted group, gr. E: effect site targeted group. ▯ P

		Target propofol concentration (ug/ml)				
	0	5.0	4.75	4.5	4.25	4.0
Na gr.B	19.05 (1.5)	24.00 (2.8) ı	24.94 (3.7) ı	25.86 (4.1) ı	23.10 (2.3) ı	22.80 (1.8) ı
gr.E	19.14 (2.2)	27.64 (3.0) ı	26.46 (3.2) ı	25.26 (3.5) ı	25.44 (3.6) ı	24.48 (2.8) ı
Pa gr.B	27.99 (3.2)	33.48 (3.2)	36.84 (3.9) ı	40.12 (8.3) ı	39.38 (8.6) ı	38.22 (9.4) ı
gr.E	25.38 (2.5)	41.3 (8.0) ı	39.36 (6.5) ı	39.62 (7.3) ı	39.52 (5.1) ı	38.40 (4.5) ı
Nb gr.B	35.73 (2.6)	48.72 (5.6) ı	53.04 (5.2) ı	55.16 (7.3) ı	54.54 (7.0) ı	52.36 (7.4) ı
gr.E	33.54 (2.0)	55.7 (10.6) ı	54.42 (9.9) ı	54.12 (9.8) ı	52.62 (6.4) ı	50.62 (7.8) ı

Latencies vs. propofol concentrations are shown on Figure 3. Linear regression analyses were performed in latencies of the MLAEP waves. In the effect site targeted group means of all recorded parameters showed linear proportion to propofol concentration. There was no similar relationship found in the blood targeted group as latencies of Pa and Nb could not fit into a line with 95% confidence interval.

Figure 6

Figure 3: Latencies of MLAEP vs. propofol target concentration. Values of mean and SD are shown. Dotted and solid lines represent the effect site and the plasma site targeted group, respectively.
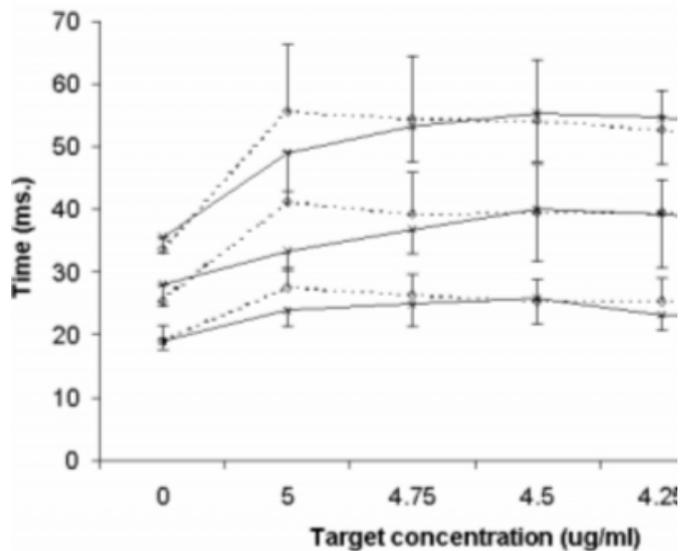

DISCUSSION

The pharmacokinetic model incorporated in a TCI system continuously calculates the concentration in different compartments in order controlling the rate of infusion to maintain stable concentration in the desired compartment. In this pharmacology based mathematical modelling the only compartment represented is the blood. The effect site occurs as a "fourth" compartment, which has it's own distribution coefficient, [4] but this is not taken account in the pharmacokinetic of the drug used.

Figure 7

Figure 4: Computer simulation of maximum blood propofol concentration (ug.ml-1) vs. induction dose (mg.kg-1) in a weight range from 55 to 80 kg.
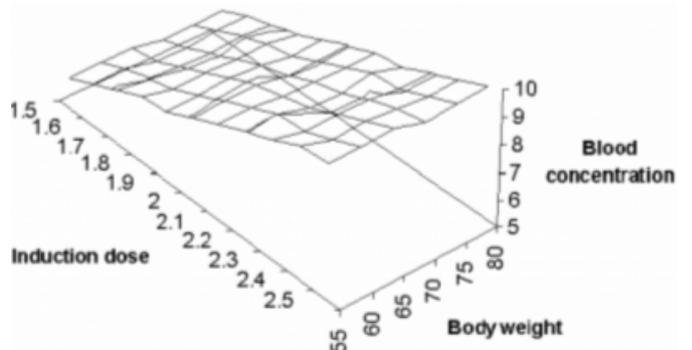
However this compartment can be targeted in the same way as the central compartment but differs from the blood-

targeted system as drug concentration are allowed to reach higher levels in the central compartment than that desired in effect compartment. The key is determining the maximum blood concentration of propofol that will allow equilibrium to develop. To do this, we made a computer simulation of Diprifusor model (laptop computer running STELPUMP), shown on Figure 4. There is a linear correlation between the maximum blood concentration and induction dose in each body weight group. Furthermore, any TCI pump assumes instant mixing of drug in the blood, which obviously never happens. [6] The Marsh model [3] used in the Diprifusor system is not age adjusted (apart from the lowest age of 16, below which the Diprifusor system is not licensed for use). In a comprehensive study, Coetzee at al. found this model to perform better than that developed by Dyck and Shafer, which is age adjusted. [7] Chaudhuri at al. found the success rate of induction of anaesthesia with propofol TCI to be 90 % at 5 ug.ml-1 target blood concentration in patients premedicated with 20-30 mg of temazepam and aged 42-45 years. [8] Casati at al. found the mean target plasma concentration of propofol required to place a LMA was 4.3 ug.ml-1. [9] Moreover, co-administration of nitrous oxide and/or opioids decrease propofol requirement, [10] suggesting the use of lower target concentration. Our patients were premedicated with 10 mg of temazepam and had a subarachnoid block. Neither opiates nor nitrous oxide were used during the surgery. The aim of our study was to compare the two delivery systems for general anaesthesia rather than for sedation. We decided on a target concentration of 5 ug.ml-1 for induction and 7.5 ug.ml-1 limit blood concentration for patients in the effect site targeted group. This limit of blood concentration can be reached giving less than 1.9 mg.kg-1 propofol as induction dose at rate of 33 mg over 10 seconds.

There was a significant decrease in systolic blood pressure in both groups after induction, but in the effect site targeted group the changing of both diastolic and mean blood pressure did not reach significant levels. The blood-targeted pump ceased the initial 1200 ml.h-1 infusion rate earlier than the effect site targeted pump, but maintained continuous delivery, while the effect site targeted pump stopped after around three minutes for minimum of 30 seconds (Figure 1). However, the delivered dose of propofol did not differ significantly between groups. Age also has an effect on cardiovascular response. In elderly patients increasing propofol concentration will result in a greater degree of systolic blood pressure drop, which occurs more slowly. [11] We did not experience this effect. All of our patients had

subarachnoideal block about 30 minutes before commencement of propofol infusion, and the 800 ml crystalloid infusion was administered during this time minimising the effect of spinal anaesthesia to cardiovascular response during study period. We assume the different delivery pattern could be responsible for the difference in the cardiovascular response.

In our study we found statistically significant reduction in induction time with the effect site controlled TCI pump, however this difference may not be important in clinical practice. This is to be expected as this pump delivered a higher dose for induction, resulting in a high concentration gradient between blood and brain. The blood-brain equilibrium time depends on the blood-brain coefficient (keo). In our study the keo was 0.291 as this value is incorporated into Diprifusor system. However, recent studies used different values from 0.2 to 0.63! [12,13] This value is extremely important in effect site targeted system as the delivery pattern is based on blood-brain equilibrium. To determine, whether the target concentration influences the equilibrium time, we made another computer simulation using the same technique described above and shown in Figure 5. The time needed for equilibrium (by two decimal punctuality) was from 20.90 to 23.20 minutes depending on target concentration from 2.5 ug.ml-1 to 5.0 ug.ml-1, respectively. In clinical practice this time is much shorter as the calculated time reflects pharmacokinetic analysis and does not reflect the pharmacodynamic effect.

Figure 8

Figure 5: Time needed for development of blood–brain equilibrium vs. initial target blood concentration during TCI
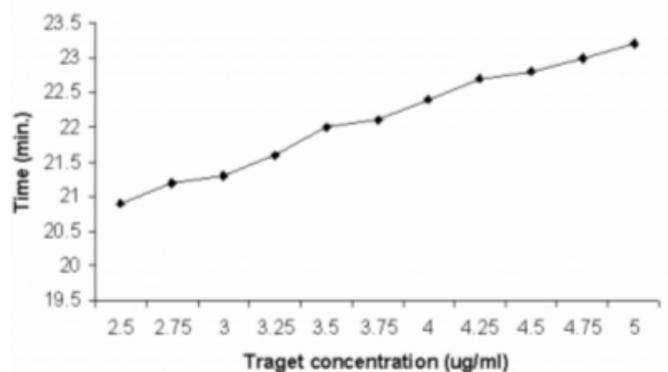
Latencies of Pa and Nb waves in MLAEP correlates well with a transition from awake to unconsciousness. [14] In our study the latency of Pa wave did not differ significantly after induction whichever system was used. All measurements were taken at the time when the target concentrations were

reached. As discussed above, in the blood-targeted group this meant that the effect site concentration was lower than blood concentration as equilibrium between blood and brain had not yet developed. There were no clinical signs of insufficient anaesthesia in this group of patients (analysis of MLAEP showed the Nb waves were significantly prolonged). In a study, Tooley at al. found the latency of Nb wave as useful discriminator between the presence and absence of an eyelash reflex, [15] using a value of 53 ms had a sensitivity of 100% and a specificity of 96%. In our study the mean latency of Nb wave was just below this level in the blood targeted group using a 5 ug.ml-1 target concentration. The above authors, however, used continuous propofol infusion followed by dose-concentration calculation, rather than TCI for delivery. They also found linear correlation of latencies of Pa wave and non-linear correlation of latencies of Nb waves to propofol blood concentration. Our findings, however, slightly different, as in the effect site targeted group both latencies of Pa and Nb waves followed a linear correlation, but not so in the blood targeted group. At the time measurements were performed, it must be assumed that the effect site concentration was somewhere around the target level, but these levels are never the same. Although the effect site concentration is also shown on the computer screen, we did not record this value, as most of GRASBY 3500 pump do not display this value. In practice there might be difficulty in adjusting the pump if estimation of effect site concentration is not displayed. Fortunately, newer pumps are capable of showing this information.

We did this small study to evaluate the usefulness of effect site targeted TCI in clinical practice. Our patients belonged the elderly age group and they were relatively fit, so these results cannot be interpolated to patients belonging ASA III or IV categories. We also felt, it was necessary to paralyse and ventilate our patients to eliminate the effect of respiratory depression which could have caused alteration in cardiovascular parameters. Further investigations are needed to confirm our findings. Bispectral analysis seems promising, as the only available stand alone monitoring technique for on-line feedback of depth of anaesthesia. Recently published studies found this useful to control TCI pump. [16,17] Only the effect site targeted TCI system can be used with feedback system, as this one eliminates the

inaccuracy, which occurs between blood and effect site concentration.

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Author Information

Laszlo Hollos, MD DEAA
Consultant Anaesthetist, Anaesthetic Department, Kettering General Hospital

Nick Enraght-Moony, MB, BS, FRA (SA)
Consultant Anaesthetist, Anaesthetic Department, Kettering General Hospital