Editorial

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/ija.IJA_244_18

Quick response code

Target controlled infusion total intravenous anaesthesia and Indian patients: Do we need our own data?

Use of propofol-based total intravenous anaesthesia (TIVA) has increased in the past two decades due to better understanding of pharmacokinetics of intravenous anaesthetic drugs. This knowledge has been applied to build mathematical models which can be implemented in clinical situations with the help of programmed or programmable syringe pumps to control target-controlled infusion (TCI). TCI systems achieve a targeted plasma concentration with a loading dose of propofol based on its initial volume of distribution and targeted plasma concentration. It follows this with a decreasing rate of infusion based on propofol distribution into peripheral compartments as well as metabolism and excretion. In this way, it maintains targeted plasma concentration and stable level of anaesthetic depth. Multi-compartmental pharmacokinetic (PK) models based on polyexponential equations are used for calculating the infusion rates of the drugs for targeting plasma concentration. Earlier generation TCI systems controlled plasma concentration only. They required prefilled branded syringes of propofol for its functioning (Diprifusor) and were programmed with Marsh adult PK model.[1]

The peak clinical effect of a given plasma concentration of the drug is achieved a few minutes later due to delay in equilibration of the plasma concentration (Cp) with the effect site. The rate of this equilibration between plasma and effect site concentration (Ce) is described by the keo, which defines the proportional change of concentration gradient between plasma and effect site in unit time. This delayed response depends on the lipid solubility, degree of inonisation of the drug as well as cardiac output and cerebral blood flow.[2] Incorporation of the effect-site equilibration delay constant, keo, in the complex PK equations not only explains this delay in peak action of propofol but also helps to predict its concentration at the effect site at any given point of time of TCI infusion. This is useful information to the clinician who in a busy operation theatre environment is not able to solve complex mathematical equations. While higher keo values indicate quicker transfer or equilibration, lower values indicate slower or delayed equilibration with the effect site. The TCI systems which target Ce lead to the achievement of higher initial Cp for quickly achieving the target Ce. This temporary overshoot of the plasma concentration depends on the keo (smaller overshoot for larger keo and vice versa). This may result in increased haemodynamic disturbances due to higher plasma concentration.

TCI can be used for induction of anaesthesia in the patient by titrating this Cp or Ce to clinical endpoint of loss of consciousness (LOC) and later maintaining this TCI concentration to maintain optimum anaesthetic depth titrated further to other clinical endpoints or to objective anaesthetic depth indicators such as bispectral index or entropy during the surgery. Availability of these EEG derived anaesthetic depth indicators has further facilitated the use of TIVA TCI.

In this issue of the Indian Journal of Anaesthesia, Vasanth *et al*.[3] have evaluated effect site concentration of propofol for achieving LOC (Ce LOC) using an open TCI system using the Marsh model in patients undergoing spine surgery. They found mean propofol effect site concentration at LOC (Ce IND) to be 2.34 ± 0.24 μg/ml and corresponding spectral entropy (SE IND) 52 ± 8. Authors also found lower induction dosages for propofol, 1.17 mg/kg, as compared to typically reported dosages of 2 mg/kg in non-premedicated patients.[4] The mean Ce LOC of 2.34 μg/ml is lower than western data, but patients also received fentanyl 2 μg/kg before start of propofol induction with TCI. Struys *et al*. found Ce50 LOC

(effect site propofol concentration required for loss of eyelash reflex in 50% of patients) of 2.9 μg/ml when propofol was used alone without premedicants or adjuvant analgesics.[5] Another Indian study found that the Cp 50 for LOC was 2.3 μg/ml in healthy Indian controls when propofol was used alone before start of surgery.[6] They allowed 6 min wait time to allow effect site equilibration.

The target propofol concentrations required for induction of anaesthesia will be lower if fentanyl or other analgesics are used. This is both due to PK as well as pharmacodynamic (PD) interactions. The interaction may further get exaggerated by pre-operative administration of sedatives. PK interactions occur when the presence of one drug causes an alteration in distribution or disposition of another agent. These are common between propofol and different opioid agents. Cockshot *et al*. found that if 100 μg of fentanyl is given before a bolus of propofol, the subsequent propofol concentrations are 50% greater than expected.[7] Competition between the common binding sites, inhibition of cytochrome P450 and haemodynamic alterations are some of the mechanisms of these interactions. Further, higher concentrations of propofol can alter its own metabolism by affecting the cardiac output and hepatic blood flow. Synergism arising from PD interactions among anaesthetic agents (e.g Hypnotics and opioids) is also significant and commonly require decrease in target concentration of these agents.

Induction of anaesthesia involves administration of adequate intravenous anaesthetic agent dosages to produce LOC without producing haemodynamic disturbances. TCI of intravenous anaesthetic drugs based on the population PK models can help to achieve this efficiently.

With effect site targeting, the TCI system manipulates the blood concentrations of the drug to achieve the effect site target concentration as rapidly as possible. When the target concentration is increased by the user, the system calculates the optimum plasma concentration which will produce sufficient gradient to achieve the effect site concentration most rapidly without overshoot of target. After giving a bolus of drug to achieve this calculated higher plasma concentration, the system stops drug delivery temporarily to restart it once the blood and effect site concentration reach target simultaneously. One needs to bear in mind that there are a lot of assumptions while using these TCI systems. PK parameters and models based on population studies may not apply to an individual. The models derived from one set of the population may not apply to a population of different ethnicity as well as body structure. Hence, the measured blood concentrations may be different from those predicted by these models. One needs to evaluate these models in the individual setups to confirm their applicability. In spite of small differences in the Indian propofol PK model (PGI model)[8] with respect to Marsh model,[1] the two have been shown to perform fairly well in both healthy adults for non-cardiac surgery as well as cardiac surgery patients.[9]

The Marsh model for propofol which is most commonly used in clinical practice uses two different values for keo: The slower 0.26/min and faster 1.2/min. The latter has been recommended for use with Marsh model forming the "Modified Marsh Model" which has been implemented in open TCI systems such as Fresenius and Alaris. Slower keo requires a higher blood concentration for achieving a given effect-site target concentration. This also allows using this TCI system to be used in elderly patients where it is better to use faster keo to avoid harmful effects of higher blood concentrations.

Schneider model for Ce-targeted infusion,[10,11] though not popular (as it incorporates age, height, weight and lean body mass), has advantages of avoiding excessive overshoot or undershoot of blood concentrations around Ce due to smaller volume of distribution (4.27 L for a 70 kg 170 cm height male as compared to around 16 L for Marsh model and around 13.5 L for PGI model[8]) used for initial bolus in spite of slow keo of 0.456/min. When the anaesthesiologist starts using Schneider model after using Marsh model, he should remember to use it in effect site mode and also use higher initial targets as this model gives much less propofol as compared to Marsh model in blood target mode.

Another advantage of using TCI devices is that the anaesthesiologist can track effect site concentration both during onset of anaesthesia (Ce LOC) as well as recovery (Ce REC). Theoretically, the real effect site concentration of propofol should be similar at loss and recovery of consciousness in the same patient. The time to reach this Ce after switching off anaesthetic can be predicted by the TCI device. This can help the anaesthesiologist in planning termination of the anaesthetic drug infusion at right time interval before the expected end of surgery. This can save not only

the operating room time but also help in predicting recovery from anaesthesia.

The difference in Ce LOC from Ce REC can be due to difference in PK environment at these two time points. If the concentration of other adjuvant drugs which can interact with the anaesthetic in question are different at these two points the Ce REC may not be same as Ce LOC. Difference in cerebral blood flow or cardiac output at these time points may be another reason for this difference. Further, there are wide variations in the estimated effect-site concentration depending on the selected PK models accounting for another reason for such difference.

The differences in PK or PD in different study populations may also be due to both genetic as well as acquired factors such as general health, nutrition, enzymatic induction or physical exercise (some of which are not very simple to control). These may also be responsible for inherent variation of data within the same study population. Ortolani *et al*. showed lesser propofol requirements as well as slower recovery in Indian patients as compared to Caucasians, Chinese and Malay in Malaysia.[12]

Although glucuronidation by Uridine 5'-diphospho-glucuronosyltransferase1A9 is the main propofol metabolic pathway, it is also metabolised in liver by cytochrome P450. CYP2B6 and to some extent CYP2C9 contribute to this later hydroxylation, but CYP2B6 is the principal determinant of inter-individual differences in propofol metabolism and may be responsible for even 20-fold inter-individual variation, due to genetic factors.[13] Interracial variability is well described for propofol anaesthesia.[6,12,14-17] Lampotang *et al*. made race specific propofol model for predicting LOC in different ethnic population based on the PD data of different peer-reviewed articles.[18] While analysing data from different studies they assumed identical PKs in different races based on the findings of Li *et al*.[19] They found reduced EC50 and EC95 for LOC (1.88 and 2.37 μg/ml respectively as compared to 2.8 and 4.1 μg/ml of Caucasians) from Indian data.[6]

Despite these flaws, TCI with effect site concentration estimating capability may be a useful tool for TIVA in any population/clinical scenario provided the clinicians are mindful of its limitations.

In spite of India having world's second largest population there is very limited Indian PK/PD data of anaesthetic drugs. So far the studies done in India[6] and other countries[12] have shown that Indians are more sensitive to propofol. The package inserts of different propofol formulations from India also claim the same though it needs to be substantiated by evidence from this country. The paper of Vasanth *et al*. in this issue is a small step in this direction.

Its high time for Indian anaesthesiologists to work on the PK/PD front to generate local data and their own PK models so as to use the drugs more efficiently. Despite these studies being tedious, laboratory and labour intensive with prolonged standardisation time and requiring finances, development of such models/systems are needed to assist the multitasking anaesthesiologist in the operation theatre. The Indian research funding agencies, as well as pharmaceutical industry, should come forward to support such studies, for the evolution of research in the field, which is the need of the hour.

Goverdhan Dutt Puri

Department of Anaesthesiology and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh, India
E-mail: gdpuri007@hotmail.com

REFERENCES

1. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 1991;67:41-8.
2. Absalom AR, Mani V, De Smet T, Struys MM. Pharmacokinetic models for propofol – Defining and illuminating the devil in the detail. Br J Anaesth 2009;103:26-37.
3. Vasanth S, Radhakrishnan A, Keshavan VH. Effect site concentration of propofol at induction and recovery of anaesthesia - A correlative dose-response study. Indian J Anaesth 2018;62:263-8.
4. Scheepstra GL, Booij LH, Rutten CL, Coenen LG. Propofol for induction and maintenance of anaesthesia: Comparison between younger and older patients. Br J Anaesth 1989;62:54-60.
5. Struys MM, Vereecke H, Moerman A, Jensen EW, Verhaeghen D, De Neve N, *et al.* Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. Anesthesiology 2003;99:802-12.
6. Puri GD, Mathew PJ, Sethu Madhavan J, Hegde HV, Fiehn A. Bi-spectral index, entropy and predicted plasma propofol concentrations with target controlled infusions in Indian patients. J Clin Monit Comput 2011;25:309-14.
7. Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. Studies using single bolus injections. Br J Anaesth 1987;59:1103-10.
8. Puri A, Medhi B, Panda NB, Puri GD, Dhawan S. Propofol pharmacokinetics in young healthy Indian subjects. Indian J Pharmacol 2012;44:402-6.
9. Mathew PJ, Sailam S, Sivasailam R, Thingnum SK, Puri GD. Performance of target-controlled infusion of propofol using two different pharmacokinetic models in open heart surgery – A

randomised controlled study. Perfusion 2016;31:45-53.
10. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, *et al.* The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998;88:1170-82.
11. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, *et al.* The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90:1502-16.
12. Ortolani O, Conti A, Chan YK, Sie MY, Ong GS. Comparison of propofol consumption and recovery time in Caucasians from Italy, with Chinese, Malays and Indians from Malaysia. Anaesth Intensive Care 2004;32:250-5.
13. Court MH, Duan SX, Hesse LM, Venkatakrishnan K, Greenblatt DJ. Cytochrome P-450 2B6 is responsible for interindividual variability of propofol hydroxylation by human liver microsomes. Anesthesiology 2001;94:110-9.
14. Ortolani O, Conti A, Sall-Ka B, Salleras JP, Diouf E, Kane O, *et al.* The recovery of Senegalese African blacks from intravenous anesthesia with propofol and remifentanil is slower than that of Caucasians. Anesth Analg 2001;93:1222-6.
15. Ortolani O, Conti A, Ngumi ZW, Texeira L, Olang P, Amani I, *et al.* Ethnic differences in propofol and fentanyl response: A comparison among Caucasians, Kenyan Africans and Brazilians. Eur J Anaesthesiol 2004;21:314-9.
16. Natarajan A, Strandvik GF, Pattanayak R, Chakithandy S, Passalacqua AM, Lewis CM, *et al.* Effect of ethnicity on the hypnotic and cardiovascular characteristics of propofol induction. Anaesthesia 2011;66:15-9.
17. Irwin MG, Hui TW, Milne SE, Kenny GN. Propofol effective concentration 50 and its relationship to bispectral index. Anaesthesia 2002;57:242-8.
18. Lampotang S, Lizdas DE, Derendorf H, Gravenstein N, Lok B, Quarles JP, *et al.* Race-specific pharmacodynamic model of propofol-induced loss of consciousness. J Clin Pharmacol 2016;56:1141-50.
19. Li YH, Yang J, Tian J, Xu J. Evaluation of predictive performance of Diprifusor target-controlled infusion system for propofol in Chinese patients. Chin J Anesthesiol 2004;24:889-92.

How to cite this article: Puri GD. Target controlled infusion total intravenous anaesthesia and Indian patients: Do we need our own data?. Indian J Anaesth 2018;62:245-8.