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Principles of total intravenous anaesthesia: practical aspects of using total intravenous anaesthesia

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Key points

- Co-administration of propofol and remifentanil by target-controlled infusion (TCI) is highly effective for obtunding response to noxious stimuli and constitutes 'ideal' total i.v. anaesthesia (TIVA).
- Currently, no evidence supports the use of one propofol TCI model over another and all have proved reliable in clinical practice.
- Titration of effect-site concentration to patient response is vital throughout induction and maintenance phases of TIVA.
- TIVA typically achieves a deep plane of anaesthesia—a processed EEG device is indicated principally for the prevention of excessive hypnosis.
- Awareness occurs with TIVA when technical failure prevents the administration of appropriate drugs—vigilance for such errors is essential.

Advanced pharmacokinetic models for target-controlled infusion (TCI) have facilitated an increasing use of total i.v. anaesthesia (TIVA) in various clinical settings. The technical complexity and labour-intensive methodology of TIVA can deter clinicians and lead to default use of a volatile agent.

Pharmacological agents used for TIVA

In theory, any combination of i.v. hypnotic(s) and opioid(s) can be used and opioid-free techniques are described. In practice, the synergy between TCI infusions of propofol and remifentanil proves highly effective at obtunding response to noxious stimuli[1] and for this article constitutes 'ideal' TIVA. This drug combination achieves equilibrium between adequate depth of anaesthesia and rapid recovery. Intermittent boluses of agents or manually controlled infusions may produce an inadequate effect.[2]

Types of surgery

The specific indications for TIVA are given in Table 1. TIVA is applicable to nearly all types of surgery but has particular value in clinical scenarios where a stress-free awake extubation free of laryngospasm is required. TIVA confers many advantages over a conventional volatile technique, particularly a better recovery profile with reduced risk of postoperative nausea and vomiting, and can facilitate intraoperative wake-up while retaining amnesia. The use of TIVA for cases requiring a rapid intubation sequence is controversial but is safely practiced.

Choice of propofol TCI model

Choice of propofol TCI model is determined principally by the programming available in commercial infusion devices, and whether the patient's age is ≥16 yr. Currently, there is no evidence to support the use of one model in preference to another and all have proved reliable in clinical practice. All models have similar limitations in terms of the accuracy and stability of predicted plasma and effect-site concentrations. Most anaesthetists have experience of using Marsh plasma-targeted infusions for sedation and are re-assured when embarking on TIVA that this model administers a larger mass of drug for any given numeric

target (Table 2). Migration to the Schnider or modified Marsh effect-targeted models occurs as confidence and experience accrue.

Starting the infusions

The TIVA novice typically asks '*are propofol and remifentanil infusions started simultaneously*?' Experienced TIVA practitioners have their preferred recipe for induction and the answer may vary.

- When both agents are to be given by effect-site targeting, the answer is undoubtedly yes.
- The situation is less clear when an effect-targeting propofol model is used with remifentanil in plasma-targeted mode. If the drugs are started simultaneously, the propofol effect-site concentration will increase much more rapidly than remifentanil and useful synergy of action is difficult to obtain early on. An alternative approach is to start the remifentanil first and allow equilibration at the effect-site before commencing propofol. This speeds subsequent induction as anaesthesia is achieved at lower propofol effect-site concentrations. Apnoea is a significant risk and effective pre-oxygenation must be accompanied by reminders to the patient to breathe deeply.
- When plasma-targeted infusions of both agents are started simultaneously, remifentanil equilibrates at the effect-site long before propofol. This can result in an apnoeic but potentially aware patient unless the propofol target is significantly 'over-pressured'. This latter approach is akin to a large manual bolus with the likelihood of adverse cardiovascular effects. Allowing remifentanil to equilibrate at the effect-site before starting the propofol is a useful technique with risks and benefits as described in the previous section.

Selecting TCI targets

Highly effective drug synergy allows the choice of high propofol/low remifentanil effect-site concentrations or the converse to achieve a desired clinical effect.[1] The use of a low propofol/high remifentanil combination allows more rapid recovery but is associated with apnoea and the need for assisted ventilation. Many clinicians use such a combination for short cases instead of allowing the patient to breathe a volatile agent spontaneously. Remifentanil has little hypnotic action and it is recommended that for the majority of patients, a minimum effect-site propofol concentration of 2 μg ml^{-1} (for patients ≥50 yr of age) or 3 μg ml^{-1} (<50 yr) is maintained. Individual clinical response to propofol and remifentanil TCI is highly variable and although effect-site concentrations may be suggested (Table 3), these cannot be guaranteed as invariably efficacious (see example in Fig. 1).

Table 1 Specific indications for TIVA

Malignant hyperthermia risk
Long QT syndrome (QTc ≥ 500 ms)
History of severe PONV
'Tubeless' ENT and thoracic surgery
Patients with anticipated difficult intubation/extubation
Neurosurgery—to limit intracranial volume
Surgery requiring neurophysiological monitoring
Myasthenia gravis/neuromuscular disorders, and situations where NMBs are of disadvantage
Anaesthesia in non-theatre environments
Transfer of an anaesthetised patient between environments
Daycase surgery
Trainee teaching
Patient choice

Around 150 new patients are referred to the Leeds National UK MH Unit every year. Out of these, 40–50 patients test susceptible to MH. Considering that about 2.8 million anaesthetics2 are performed in the UK every year, this translates into an approximate incidence of 1:50 000–1:70 000 for the UK population.Apr 24, 2017

Monitoring TIVA

At present, propofol plasma concentrations cannot be measured minute-to-minute in a practicable manner. Clinical calibration of the individual patient before 'knife-to-skin' can be achieved by noting the increments in effect-site concentrations which show:

- loss of response to shaking and shouting;
- loss of haemodynamic response or limb movement with vigorous jaw thrusting;[3]
- absence of tachycardia or even bradycardia with laryngoscopy and intubation.

This methodology provides three calibration points to guide the minimum and maximum targets to be used. If neuromuscular paralysis is required, it should not be given until a lack of response to jaw thrusting has been achieved. Titration of effect-site concentration to patient response during surgery is vital, particularly as excessive hypnosis is a more common problem than inadequate depth. It is possible to use Tivatrainer pharmacokinetic software (www.eurosiva.eu) to predict the necessary effect-site concentrations in real time during drug administration. This program graphically plots the 50 and 95% probabilities of lack of response to a noxious event (akin to 1 and 2 MAC for volatiles) when propofol and remifentanil TCIs are used simultaneously (Fig. 1). Clinical judgement and software predictions can be supplemented by the use of processed EEG data which

Table 3 Suggested minimum effect-site concentrations for TIVA in adult patients. These targets must be increased or decreased depending on individual patient response and/or processed EEG data

Suggested effect-site concentrations for TIVA				
Age (yr)	Spontaneous breathing		IPPV	
	Propofol (μg ml^{-1})	Remifentanil (ng ml^{-1})	Propofol (μg ml^{-1})	Remifentanil (ng ml^{-1})
<50	4–6	1–3	3–4	5–8
>50	2–4	1-2	2–3	3–6

Table 2 Comparison of the bolus dose of propofol and subsequent infusion rate administered to a male patient, 177 cm and 85 kg by three TCI models when the target is set at 3.5 μg ml^{-1}. Data derived from Tivatrainer 9 software (www.eurosiva.eu)

Patient age (yr)	Effect-targeted Schnider		Effect-targeted modified Marsh		Plasma-targeted Marsh	
	Bolus dose (mg)	Subsequent infusion rate (mg h^{-1})	Bolus dose (mg)	Subsequent infusion rate (mg h^{-1})	Bolus dose (mg)	Subsequent infusion rate (mg h^{-1})
40	63	830	100	1040	71	1100
80	53	670	100	1040	71	1110

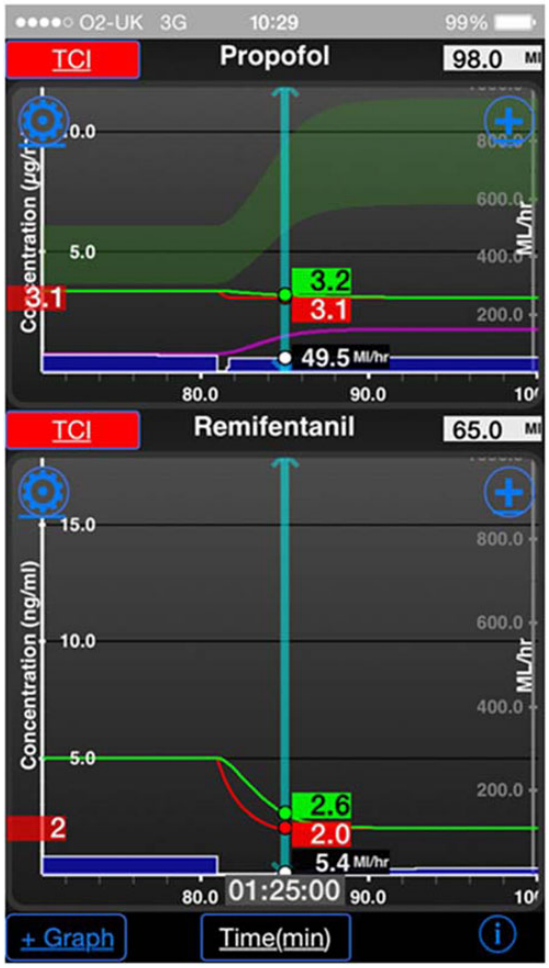

Fig 1 Screenshot from an Apple iPhone showing the perioperative use of Tivatrainer 10 software (www.eurosiva.eu). In this example, the drugs were administered using plasma-targeted models. The software is used to predict the outcome of a planned reduction in remifentanil target from 5 to 2 ng ml^{-1} when the propofol effect-site concentration is 3.2 µg ml^{-1}. The planned decrease in opioid concentration would increase the likelihood of response to noxious stimulus and could increase the chance of awareness. An increase in propofol target to 5–6 µg ml^{-1} would be needed to minimize such risk at the lower remifentanil concentration. Key: Red line/numerals, plasma target concentration; green line/numerals, effect-site concentration; blue line, pump infusion rate; green shading, range of propofol effect-site concentrations consistent with 50% (lower line) and 95% (upper line) probability of lack of response to noxious stimulus at the simultaneous remifentanil effect-site concentration. *X*-axis, time (min).

will detect excessive hypnosis but does not reliably predict response to noxious stimulus.[4]

ASA status and advanced age

TIVA is highly effective at achieving a deep plane of anaesthesia. Consequently, this technique must be used cautiously in patients compromised by advanced age or poor ASA status but still confers advantage in terms of recovery profile. The Schnider effect-model administers a lower dose of propofol (Table 2) for any given numeric target compared with the Marsh kinetics (despite the prediction of higher peak plasma concentration). Some clinicians consider this to be of advantage in the frail adult as haemodynamic side-effects are lessened. The Schnider model does include age as a modulating factor on bolus dose and infusion rate. However, this imposes only a small difference on the mass of drug administered between ages (Table 2) and should not be relied upon to prevent an exaggerated cardiovascular response. When the Minto model is used in effect-targeting mode, the bolus dose is three to four times greater than with plasma-targeting. This higher plasma concentration increases the likelihood of chest wall rigidity or severe bradycardia via non-vagal mechanisms. Consequently, Minto effect-targeting is best reserved for younger robust patients. In practice, a slowly incremented approach to the final effect-site concentration of both drugs is advocated in frail subjects irrespective of the models chosen. The clinician must assess the patient's level of consciousness and cardiovascular status before every increment in target.

Table 4 Checklist for setting up TCI systems

1. Use only dedicated pharmacokinetic TCI pumps
2. Ensure that you are trained in use of the chosen pump and pharmacokinetic model
3. Ensure the pumps have been serviced in the past 12 months
4. Ensure the pumps are plugged into the mains
5. Ensure the batteries are charged
6. Ensure that the drug dilutions are correct and are entered correctly into the pump
7. Ensure that the correct syringe type and size data are entered and that the syringes are mounted correctly
8. Ensure that the pump is programmed for the drug actually attached to it
9. Ensure that the low and high infusion pressure alarms are set (to warn of disconnection and a 'tissued' cannula, respectively)
10. Ensure that the correct patient data are entered
11. Consider if the targets set are appropriate to the patient's age and ASA status
12. What is plan B if the pump(s) fail?

Table 5 Recommendations for preventing technical problems with TIVA

1. Complete the TCI system checklist
2. Affix the i.v. cannula firmly to the patient's skin
3. Keep the site of TIVA infusion visible so that disconnection, leakage, or a 'tissued' cannula are readily detected
4. Use only a dedicated two- or three-way TIVA set which incorporates
   - anti-siphon valves on the drug administration lines
   - non-return valve on any i.v. fluid line
   - minimal dead space distal to the point of agent and/or i.v. fluid mixing
5. Use only Luer lock syringes for administering drugs
6. Do not label the remifentanil syringe until the drug has been added to the diluent
7. Always check the infusion site if a pump alarms (except 'syringe empty', 'infusion paused', or 'mains failure')
8. Flush TIVA drugs from the dead space of a three-way administration set before connection to the patient cannula, and out of the cannula at the end of the case

Setting up and using TIVA equipment

The RCoA's Safe Anaesthesia Liaison Group and the NAP5 investigators reported that technical failure accounts for most cases of anaesthetic awareness using TIVA. The recommendations in Tables 4 and 5 incorporate and extend the lessons from their publications. It is vital that TCI infusion devices are checked as thoroughly as the anaesthetic machine.

Failure of pump programming

Most commercial TCI devices 'forget' their programming with complete failure of both mains and battery power. In this situation, the clinician has three options with similar disadvantages;

- Default to a volatile-based technique with the likelihood of an exaggerated haemodynamic response due to synergism between propofol, remifentanil, and volatile molecules at the effect-site.
- Re-start the pump in manual mode using the millilitres per hour rates exhibited on the device display just before power failure. If a rapid increase in target is subsequently required, the clinician must calculate an additional bolus before increasing the infusion rate or an inadequate effect-site concentration would result.
- Re-start the pump in TCI mode. The device will be naïve to the drug already present at the effect-site and an exaggerated haemodynamic response is highly likely to occur unless the chosen target is titrated upwards incrementally.

Terminating the infusions

It is reasonable to decrease TCI targets near the end of surgery, but closure of some wounds produces intense noxious stimulation in the absence of locoregional techniques. Targets should not be reduced inappropriately just to promote a more rapid recovery (Fig. 1). Generally, the infusions are more safely stopped once the final sutures are applied. The remifentanil infusion can be continued at a target of 1–2 ng ml^{-1} to smooth extubation if desired. Delayed recovery after TIVA may be seen in patients who have received morphine at the higher end of the dose range or when the Marsh model is used in obese subjects. Patients are often content to receive assisted ventilation at subanaesthetic concentrations of TIVA drugs and may need active encouragement to open their eyes and take spontaneous breaths. Post-extubation apnoea remains a risk until remifentanil is completely cleared from the effect-site.

Potential problems with TIVA

Awareness

Clinicians often quote awareness as the reason for avoiding TIVA, although evidence to support this view is very limited. Interpretation of outcome data from some large studies[5 6] is confounded by heterogeneity in drug combinations and techniques included as 'TIVA' (Errando and Zhang, personal communications). By analogy, an 'oxygen/nitrous oxide/no volatile' technique would not reasonably be included in studies of awareness with inhalation anaesthesia. Highly controlled studies on awareness during TIVA are few in number but have failed to demonstrate an increased incidence.[7–9] Studies using an isolated forearm technique have shown equivalent rates of responsiveness in subjects receiving TIVA or volatile anaesthesia titrated to bispectral index.[10 11] Technical errors and poor application of knowledge were highlighted in the NAP5 report as the major cause of awareness during TIVA, and 75% of these cases would have been prevented by suitable education and training. Conversely, interruption in delivery of volatile anaesthesia was highlighted in NAP5 as the key factor in generating accidental awareness. The use of 'ideal' TIVA free from technical errors would have prevented nearly all of these cases by avoiding the 'gap' phenomenon which occurs with volatile agent administration. NICE has recommended deployment of a processed EEG device when administering TIVA and NAP5 emphasized that this is particularly necessary in patients who require neuromuscular paralysis. However, prevention of excessive hypnosis is probably the most beneficial outcome of using such devices during TIVA.[12]

Morbid obesity

TIVA for the morbidly obese is challenging but regularly practiced, although the current TCI models are not formally validated for use in such patients. Pump manufacturers limit the input weight to the Marsh model at 150 kg, although this can usually be increased with their proprietary software. However, a bolus dose calculated on actual body weight is likely to represent a significant overdose and attract unwanted cardiovascular side-effects at induction.

A different problem arises in the Schnider and Minto kinetics because these models use the 'James equation' to derive lean body mass (LBM). This equation generates a paradoxically diminishing value of LBM as BMI exceeds 42 in men and 35 in women. Manufacturers prevent input of anthropomorphic data exceeding these sex-specific BMI values as the derived LBM is important in the pharmacokinetic calculations.

For the Schnider model, the rate constant for drug elimination from the central compartment (K_{10}) is corrected for LBM and this limits the infusion rate applied as actual body weight increases. If BMI exceeded the critical value, the infusion rate would be insufficiently corrected and the high rate of drug administration might generate exaggerated haemodynamic effects. The converse is true of the Minto model where the central and rapidly equilibrating compartment volumes and the K_{10} rate constant increase proportionately with LBM. At BMIs above the critical value, the pump would progressively reduce bolus dose and infusion rate and an inadequate analgesic effect would be provided.

The 'correct' body mass to use with TIVA has been investigated and currently Servin's formula for calculating an input mass for TCI infusions seems most useful.

$$\text{Input mass} = (\text{ideal body weight}) + 0.4 \times (\text{actual} - \text{ideal})$$

where

$$\text{ideal body weight} = \text{ideal BMI}\ (\text{male } 22,\ \text{female } 26) \times \text{height}^2\ (\text{m})$$

However, propofol is highly lipid-soluble and excess fat in the morbidly obese provides a sink into which the agent diffuses from the plasma. Theoretically, the patient's actual body weight is required for calculation of an infusion rate which maintains the targeted plasma or effect-site concentration; under-prediction has been demonstrated in some studies using 'ideal mass' derivatives.[13] Recently, an allometric propofol TCI model for patients with actual body weights of 5–160 kg has been described and may allow uneventful TIVA for the morbidly obese in the future.

At present, caution must be exercised when providing TIVA to the morbidly obese who appear to be particularly at risk of accidental awareness when neuromuscular blocking drugs are used. Continuous clinical assessment of the obese patient is particularly important, and use of processed EEG monitoring in the morbidly obese is recommended by both NAP5 and NICE.

Analgesia and hyperalgesia

Several studies have emphasised that morphine must be administered at least 30–40 min before stopping a remifentanil infusion, and the need for doses between 0.15 and 0.3 mg kg^{-1}. The

phenomenon of acute opioid tolerance after remifentanil has been addressed in a recent meta-analysis which concluded that the use of high intraoperative concentrations is associated with small but significant increases in acute pain after surgery.[14] The use of adjunctive non-opioid analgesics and locoregional techniques are of particular benefit with TIVA, as is fentanyl 'rescue' in the immediate postoperative period.

Propofol-related infusion syndrome

Propofol-related infusion syndrome (PRIS) presents as acute metabolic acidosis and cardiac dysfunction in combination with one or more of the following features: rhabdomyolysis, hypertriglyceridaemia, or renal failure. Currently, there are no published case reports of PRIS occurring in association with TIVA. There are three cases reports where clinicians abandoned an adult TIVA technique due to discovery of an unexplained metabolic acidosis. However, these patients subsequently failed to exhibit other features of PRIS. The use of TIVA in paediatric practice is considered safe and possibly an ideal technique,[15] even though PRIS is more likely to occur when this age group is exposed to propofol sedation in a critical care setting.

Conclusion

TIVA is the default solution for a patient with malignant hyperthermia risk who requires general anaesthesia. Poor education and training in the use of this technique is likely to result in a significant risk of awareness. The use of propofol and remifentanil by TCI and adherence to simple recommendations will obviate most of this risk.

Declaration of interest

D.M. is a member of the Committee of SIVA, the UK Society for Intravenous Anaesthesia (www.siva.ac.uk).

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at http://www.oxfordjournals.org/podcasts/bjaed_total_intravenous_anaesthesia_vol_16_issue_8.mp3.

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