Total intravenous anaesthesia

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Abstract
Total intravenous anaesthesia (TIVA) is the induction and maintenance of general anaesthesia exclusively via intravenous anaesthetic agents. TIVA provides an anaesthetic alternative when inhalational agents are relatively or absolutely contraindicated and is also used in a number of practical situations where delivery of inhalational anaesthetic is not feasible, such as during patient transfers. It is essential that all anaesthetists understand the pharmacokinetic principles involved with TIVA and are confident in their ability to deliver TIVA safely. This article describes the key pharmacokinetic principles and models used for TIVA with additional focus on practical and safety aspects during its use.

Keywords: Marsh model; Minto model; pharmacokinetics; propofol; remifentanil; Schnider model; target-controlled infusions (TCI); total intravenous anaesthesia (TIVA)

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Total intravenous anaesthesia
The properties of an ideal TIVA agent include a fast onset/offset time with predictable pharmacokinetic behaviour when used as a continuous infusion with fluctuating target concentrations. Propofol possesses all these qualities and its introduction into clinical practice in 1986 revolutionized the use of TIVA. The addition of remifentanil as a synergistic adjunct has further increased its practical uses. Modern target-controlled infusion (TCI) systems enable the delivery of short-acting, potent hypnotic and analgesic drugs that can be easily titrated to clinical need. This has made the process of administering TIVA a practical alternative to inhalational anaesthesia and there are now various indications for its use (see Table 1).

The Fifth National Audit Project (NAP5) identified that TIVA had been associated with 28 cases of accidental awareness during general anaesthesia (AAGA), with the majority deemed to have been preventable and secondary to a lack of understanding of the underlying pharmacokinetic principles. This resulted in the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the Society of Intravenous Anaesthesia (SIVA) producing guidelines for the safe practice of TIVA in 2018 (see Table 2). The first recommendation is that all anaesthetists should be trained and competent to set up and administer TIVA safely. Having a sound knowledge and understanding of its pharmacokinetic principles is therefore pivotal.

Pharmacokinetic principles
Maintenance of anaesthesia relies on an adequate concentration of anaesthetic agent at the effect site (the brain). TIVA uses models that produce a desired steady state concentration both at the effect site ($C_{eq}$) and within the plasma ($C_{pl}$). Immediately after IV administration, a drug undergoes simultaneous distribution, metabolism and elimination. Understanding these processes produced a theoretical model, predicting the response of a drug given. An initial bolus dose will result in a peak plasma concentration that will rapidly decline as it is undergoing redistribution, metabolism and elimination from the plasma. In order to maintain a constant plasma concentration of drug it needs to equilibrate with both the distribution to peripheral tissue and elimination rate from the body. This can be achieved via a continuous infusion. The delivery of drug at a fixed infusion rate will produce a steady-state plasma concentration but is likely to take a considerable amount of time (propofol may require up to 24 hours). Therefore, an initial bolus is delivered to achieve equilibrium at a quicker rate, with an infusion continued at a slower rate. Theoretically, once equilibrium is achieved, a steady-state concentration can be maintained by simply matching the rate of infusion with the rate of elimination. Continuous infusions of a drug will lead to increased amounts being taken up in the peripheral tissue. An issue with this is that on cessation of the infusion, the drug will redistribute from the peripheries back into the plasma and then undergo elimination, causing prolonged anaesthesia. The time taken for the plasma concentration of drug to reduce by half following a steady-state infusion is referred to as the context-sensitive half-time (CSHT). Drugs with a lower CSHT allow for a quicker and more predictable offset and are therefore advantageous for use during surgery/procedures. Figure 1 compares the CSHT for commonly used anaesthetic agents and illustrates the advantage of using propofol and remifentanil.

Three-compartment model
The three-compartment model is a mathematical description of the redistribution and elimination of a drug in the body. It comprises three theoretical compartments with plasma forming the central compartment ($V_1$). This gives us our initial plasma volume of blood or volume of distribution. From here the drug undergoes distribution into two further compartments. These two compartments equilibrate at different rates with compartment 2 ($V_2$)

Learning objectives
After reading this article, you should be able to:
• explain the indications for TIVA
• describe the pharmacokinetic principles of TIVA
• compare the available TCI pharmacokinetic models
• summarize the key safety components when delivering TIVA
Indications for TIVA

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Table 1

Recommendations from the guidelines for the safe practice of TIVA 2018

1. All anaesthetists should be trained and competent in the delivery of TIVA. Schools of Anaesthesia and training bodies should provide teaching, training and practical experience of TIVA to all anaesthetic and intensive care medicine trainees. Consultant and staff grade, associate specialist and specialty doctor (SAS) anaesthetists have a responsibility to ensure that they have the knowledge and skills required to deliver TIVA competently and safely.

2. When general anaesthesia is to be maintained by propofol infusion, use of a target-controlled infusion (TCI) is recommended.

3. Starting target concentrations should be chosen depending on the characteristics of the patient, coadministered drugs and clinical situation. Older, frail or unwell patients may benefit from setting a low initial target propofol concentration, and making repeated small incremental increases.

4. Within an anaesthetic department, it is preferable to stock only one concentration of propofol and to dilute remifentanil to a single, standard concentration.

5. The infusion set through which TIVA is delivered should have a Luer-lock connector at each end, an antisyphon valve on the drug delivery line(s) and an anti-reflux valve on any fluid administration line. Drug and fluid lines should join as close to the patient as possible to minimize dead space. The use of administration sets specifically designed for TIVA is recommended.

6. Infusion pumps should be programmed only after the syringe containing the drug to be infused has been placed in the pump.

7. The intravenous cannula or central venous catheter through which the infusion is being delivered should, whenever practical, be visible throughout anaesthesia.

8. Anaesthetists should be familiar with the principles, interpretation and limitations of processed electroencephalogram (EEG) monitoring. Observation of the EEG trace and electromyography activity is likely to improve the clinical utility of the monitoring.

9. Use of a processed EEG (pEEG) monitor is recommended when a neuromuscular blocking drug is used with TIVA.

10. When TIVA is administered outside the operating room, the same standards of practice and monitoring should apply as for anaesthesia in the operating room.

Table 2

Comparison of context-sensitive half-time of common anaesthetic drugs

![Figure 1](image-url)
representing highly perfused tissue, allowing for a quicker rate of redistribution, and compartment 3 \((V_3)\) representing lower perfused tissue (see Figure 2).

As previously mentioned, the drug will also undergo immediate elimination from the central compartment. The constant dynamic movement of drug between each of the compartments is represented with rate constants, with \(K_{12}\) signifying the movement from \(V_1\) to \(V_2\) and \(K_{21}\) signifying the movement from \(V_2\) to \(V_1\). The metabolism and elimination of drug from \(V_1\) is represented with the metabolic rate constant \(K_{10}\) and the amount of drug diffusing to the effect site (the brain) is represented with \(K_{e0}\). Incorporating the effect site produces a pharmacokinetic-pharmacodynamic model and allows one to predict the time for a clinical effect to be achieved. The theoretical volume of the effect-site compartment is insignificant and therefore has no bearing on the overall pharmacokinetic model.

**Target-controlled infusions (TCIs)**

There are multiple methods one can use to deliver TIVA with the choice often dictated by the indication for the TIVA itself. Intermittent boluses may be used for rapid procedures such as electroconvulsive therapy or cardioversions. Fixed-rate infusions are commonly used when delivering TIVA outside of theatre such as on transfers or in critical care. TCI is the most commonly used method for TIVA in theatre but infusions based on manual algorithms, such as the Bristol regimen, can be used.

All methods involve titrating the dose of drug to achieve the desired level of anaesthesia and this can lead to a number of safety implications. Due to frequent inter-patient variability in drug response, it is easy to administer an inappropriate dose. This may result in the patient receiving too much anaesthetic, potentially leading to haemodynamic instability, or too little anaesthetic, risking awareness. To help reduce the human error associated with dosing TIVA regimes we commonly use dedicated TCI pumps. These pumps adopt the three-compartment model to form complex algorithms in order to calculate the distribution of a drug based on entered patient demographics. There are now multiple device manufacturers since the ‘Diprifusor’ pump was released in 1998 as the first commercially available TCI system, but all must possess the same key components: a user interface, microprocessors with pharmacokinetic software, infusion pump with ability to deliver up to 1200ml/h, and visual and audible safety systems.

The majority of TCI pumps can be programmed to target either the plasma concentration \((C_{pl})\) or the effect-site (brain) concentration \((C_{et})\). Plasma targeting involves the infusion of a bolus into \(V_1\) followed by a continually slowing infusion to achieve the desired steady state concentration in \(V_1\). The TCI pump calculates the bolus dose and ongoing infusion rate to maintain a steady plasma drug concentration \((C_{pl})\). These calculations are based on the demographics entered and are constantly reviewed by the TCI system (approximately every 10 seconds). The initial bolus leads to an initial exponential uptake of drug from the plasma to the brain with equilibrium achieved in 4–5 half-times. A key issue with plasma targeting is that the TCI pump delivers the drug to the targeted concentration and will not exceed this. The effect-site concentration (and pharmacodynamic response) then increases passively and therefore a delay is seen with both the induction of anaesthesia and when changing...
target concentrations. Effect-site targeting delivers a bolus dose to increase the plasma concentration to above that of the desired effect-site target concentration. This produces a greater concentration difference between $V_1$ and the effect site, resulting in quicker equilibration and quicker clinical effect. When reducing the effect-site target concentration, the pump will stop the infusion, allowing the plasma concentration to fall and generate a new concentration gradient that results in the effect-site concentration reducing to the new target.

**Pharmacokinetic models**

TCI pumps possess multiple pharmacokinetic models with no agreed consensus on which model best represents the closest match between calculated propofol concentrations and the actual concentrations within the plasma and brain. All models used have proved clinically effective and reliable allowing the clinician to choose the model that they feel most comfortable using. Current models have similar limitations in accuracy due to the inter-individual variability between the young, healthy, non-obese subjects that were used during development and the often older, obese and acutely unwell patients in clinical practice. It is therefore important that the anaesthetist takes the clinical presentation into consideration when using TIVA and adheres to close clinical monitoring throughout.

The two most commonly used adult propofol pharmacokinetic models are Marsh and Schnider. The Marsh model is a simpler model that assumes that $V_1$ is directly proportional to a patient’s actual body weight. When programming the TCI the anaesthetist is asked to enter the patient’s age but this is not used in the calculation. It can be used in patients who are 16 years or older. The Diprifusor device initially only allowed plasma targeting; however, later versions offered effect-site targeting by incorporating a $K_{eo}$ of 0.26 min$^{-1}$. Newer ‘open TCI’ devices offer Marsh models with both plasma and effect-site targeting and most utilize a $K_{eo}$ of 1.2 min$^{-1}$ to avoid excessively large loading doses.

The Schnider model incorporates multiple patient demographics (age, height, weight and gender) into its calculations. The patient’s age influences $V_2$ and therefore the Schnider model takes into consideration the reduced clearance rates seen in the older population. Height, weight and gender produce a gender-specific lean body mass that is then used to calculate the metabolic rate constant.

The Schnider model uses a smaller, fixed volume for $V_1$ (4.27 litre) when compared to the Marsh model where $V_1$ is determined by actual body weight (15.9 litre for a 70 kg man). This results in a much smaller initial bolus when using plasma targeting and therefore a slower onset of anaesthesia. It is therefore recommended that when using the Schnider model an effect-site target is used. This will produce an initial bolus similar to the Marsh model but will then often result in a lower ongoing infusion rate to achieve the same target concentration. It is also for this reason that it is advised that when using the Marsh model in a frail or critically unwell patient, that a lower target concentration is initially used and then titrated to effect.

**Remifentanil**

Opioids are a vital component in delivering a balanced TIVA technique. They obtund movement and improve tube tolerance, reducing the need for muscle relaxant, and blunt the haemodynamic response to noxious stimuli. The synergistic effect between opioids and propofol reduces the amount of propofol required to produce loss of consciousness, again improving haemodynamic stability. Remifentanil has a rapid onset and offset with a negligible context sensitive half-time and can reduce propofol requirements by approximately 50%. It is therefore recognized as an ideal co-agent to propofol during TIVA. Excessively high peak concentrations can cause bradycardias and chest wall rigidity; therefore it is recommended not to administer manual bolus doses and to start infusions at a lower target concentration that can be titrated up. High dose remifentanil may also cause opioid-induced hyperalgesia, but this is of uncertain clinical significance. The rapid offset of remifentanil reduces the risk of prolonged respiratory depression but also means it has no long-term analgesic properties. It is therefore recommended that a longer-acting opioid is administered prior to the cessation of the infusion.

The Minto model is a validated model for remifentanil TCI in patients over 12 years old and weighing over 30 kg. Both plasma and effect-site targeted TCI can be used. The Minto model is similar to Schnider in that it uses height, weight and gender to derive lean body mass for use in its calculations. Age is also used to calculate pharmacokinetic parameters but has little effect on pharmacodynamics. The Minto model shares the same limitations in accuracy as other pharmacokinetic models and calculations are only valid in female patients with a BMI $<35$ kg/m$^2$ and males with a BMI $<42$ kg/m$^2$. Effect-site targeting results in a bolus dose three to four times larger than with plasma targeting and therefore additional care must be taken when using this mode in the frail population.

**Common target concentrations**

Multiple factors must be considered when choosing target concentrations. The patient’s individual characteristics, the current clinical condition, drugs that are co-administered and also the magnitude of the surgical stimulus will help determine an appropriate target concentration. For rapid induction with propofol in healthy middle-aged patient then an initial plasma (Marsh model) or effect-site (Schnider model) target concentration of 4–6 µg/ml is used, with maintenance target concentrations of 3–6 µg/ml. If an opioid is used then the synergistic effect reduces the maintenance target concentrations to 2.5–4 µg/ml. Lower initial target concentrations are usually suitable in elderly, frail or acutely unwell patients whereas higher targets may be required in those who are anxious, have a higher muscle mass and a history of substance misuse. In patients where there is particular concern regarding potential haemodynamic instability then an incremental increase from a lower initial target concentration can be used. A typical example would be starting the target concentration at 1 µg/ml and gradually increasing the target concentration by 0.5 µg/ml until loss of consciousness is achieved. This will result in the slower onset of anaesthesia but is hoped to reduce the severity of any associated hypotension. It is recommended that clinical effect is routinely monitored during induction and the $C_{crit}$ is noted at the point at which the patient becomes unresponsive to speech and noxious stimuli as this will help guide maintenance target concentrations during surgery.
Concomitant administration of remifentanil typically requires a maintenance dose of 2–6 ng/ml (equivalent to 0.08–0.25 μg/kg/min). Target concentrations >1.5 ng/ml will often obtund spontaneous ventilation; therefore, the majority of patients will require mechanical ventilation.

Throughout the anaesthetic, the propofol and remifentanil target concentrations can be titrated based on clinical effect, supplemented by the use of processed EEG (pEEG) monitoring.

**Safe use of TIVA**

TIVA involves multiple processes and components and therefore lends itself to potential error. These errors can result in overdosing, underdosing or a failure to deliver the intended drug. NAP5 identified that failure to deliver the intended dose of drug and poor understanding of the underlying pharmacological principles were the leading causes for accidental awareness during TIVA. To help reduce this error, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) in conjunction with the Society for Intravenous Anaesthesia (SIVA) have produced guidelines for the safe use of TIVA (see Table 2).

There is no standardized approach for the delivery of TIVA, specifically whether to use plasma or effect-site targeting. It is fairly common practice to use remifentanil effect-site targeting and commence this prior to the propofol infusion, monitoring for both apnoea and bradycardia. The synergy between remifentanil and propofol then allows for lower propofol levels to be used, resulting in a quicker offset of anaesthesia. If effect-site targeting is chosen for both, then they can be started simultaneously. Using plasma targeting for both increases the risk of apnoea and bradycardia due to remifentanil’s rapid onset and using effect-site for propofol and plasma targets for remifentanil will negate the synergistic effect and lead to higher propofol concentrations required, therefore increasing the risk of haemodynamic instability. TCI propofol can be used for rapid sequence induction by selecting a high initial target concentration and then reducing this following the initial bolus dose. Time to loss of consciousness is typically slower when compared to a manual bolus but co-administration of an opioid can increase the speed of onset. If a manual bolus dose is used followed by TCI infusion, then the system estimations of propofol concentration will be inaccurate and may lead to haemodynamic instability. Use of an alternative induction agent followed by a maintenance infusion can be used as an alternative. TCI infusions can be stopped simultaneously; however, remifentanil may be continued at a lower target infusion to aid emergence and reduce the risk of airway irritability and coughing.

All TCI pumps must be connected to the main power supply when not being used for transfers. Power or battery failure leads to a loss of all information including the programmed data and amount of drug delivered. If pump failure occurs intraoperatively then options include restarting the TCI infusion, but this will cause boluses of drug to be given, switching to a manual infusion, or switching to inhalational agents. All options risk haemodynamic instability or inadequate level of anaesthesia if not managed swiftly and carefully.

**Patient monitoring during TIVA**

Monitoring of patients receiving TIVA should comply with the Association of Anaesthetists recommendations for standards of monitoring during anaesthesia and recovery. This includes the use of pEEG monitoring in all patients who have received neuromuscular blocking agents. In NAP5, the majority of AAGA cases during TIVA occurred in patients who had received neuromuscular blockade with subsequent underdosing of anaesthetic agent. Unlike end-tidal concentrations with inhalational agents, there is no practical way of continuously measuring propofol plasma concentrations to ensure delivery of our anaesthetic. pEEG monitoring allows us to monitor the effect of our anaesthetic at the target site by interpreting waveforms from the cerebral cortex. The derived index value as seen with the use of bispectral (BIS) index monitors has formed a validated method for quantifying clinical anaesthesia levels. pEEG also provides the EEG waveforms, signal quality, EMG activity and degree of burst suppression, all of which can be used by the anaesthetist in correlation with standard monitoring and clinical experience to guide any adjustments in dosing. During NAP5, almost 50% of awareness cases were reported around induction with 20% reported on emergence. It is recommended that pEEG monitoring is started prior to induction of anaesthesia and continued until full recovery from neuromuscular blockade has been confirmed.

**TIVA in paediatric practice**

TIVA in paediatrics remains a growing concept and provides a number of advantages including reduced postoperative nausea and vomiting, decreased emergence delirium and reduced airway reactivity. TIVA is difficult to standardize when compared to adults due to the pharmacokinetic and pharmacodynamic variation and practical differences across the various age ranges, and requires specific knowledge and training to allow its safe use.

Compartment volumes in children are approximately twice the size of those in adults when compared to their respective body weight. This, along with having an increased clearance rate, means children receive a much larger initial bolus and maintenance infusion rate of propofol, relative to their body weight when compared to adults. This difference gradually reduces from around 12 years of age and matches adult values at 16 years. Prolonged infusion results in greater accumulation in peripheral compartments when compared to adults, leading to a prolonged time for emergence from anaesthesia. pEEG monitoring may be useful in helping titrate and reduce the amount of anaesthetic delivered in patients over 1 year.

Propofol infusion syndrome (PRIS) is a rare but potentially fatal condition that causes impaired mitochondrial energy production leading to rhabdomyolysis and multi-organ failure. It is associated with prolonged propofol infusion in the paediatric population. Risk factors include inborn errors of metabolism, prolonged propofol infusion time, infusion rates above 4mg/kg/h, low carbohydrate intake, critical illness, sepsis, co-administration of catecholamines and steroids.

The two most widely used and validated paediatric TCI programmes are the Paedfusor and Kataria models. The Paedfusor is suitable for children aged 1–16 years old who weigh between 5 and 61 kg. It is a variant of the Marsh model; therefore children
over the age of 12 who weigh more than 61 kg can be safely managed using the Marsh adult model. The Kataria model is suitable for use in children aged 3–16 years who weigh between 15 and 61 kg. Both models target plasma propofol concentration with an initial target of 5–6 μg/ml normally adequate for rapid induction of anaesthesia. Concomitant use of an opioid, ketamine, α2-agonists, nitrous oxide or regional block can significantly reduce propofol requirements. A target of 2.5–4 μg/ml is usually sufficient for maintenance of anaesthesia when an opioid is used. Both models deliver approximately 50% more propofol than in adults utilizing the Marsh model, this explains why adult models cannot be used in children.

Pain is a common and potentially very distressing issue during induction of TIVA. The use of intravenous lidocaine, opioids or nitrous oxide can alleviate this symptom.

Remifentanil TCI using the adult Minto model can be used in children over the age of 12 and weighing over 30 kg. There is currently no TCI model available for children below this age and weight, therefore a manual infusion of 0.2–0.5 μg/kg/min can be used.

TIVA in the obese patient
Available pharmacokinetic models are likely to be inaccurate in the obese patient. The Marsh model can only be programmed up to a weight of 150 kg, whereas the Schnider model will only accept a BMI of <35 kg/m² in females and <42 kg/m² in males. There remains a lack of evidence on whether one should use actual or ideal body weight. Current advice has been produced in accordance with the Society for Obesity and Bariatric Anaesthesia (SOBA) which recommends careful titration to clinical effect, with supplemental pEEG monitoring to reduce the risk of over/underdosing.

TIVA outside of theatre
TIVA administered outside of theatre should adopt the same level of monitoring used in theatre. Ideally, a TCI pump should be used; however the majority of transfers are performed on fixed-rate infusions without pEEG monitoring. NAP5 identified that TIVA use outside of the theatre setting led to a higher risk of accidental awareness, particularly when a neuromuscular blocking agent was used. The most common causes were a failure to deliver a suitable initial bolus dose and an inappropriately low fixed-rate infusion. When switching a patient from inhalational agents to TIVA it is vital that a bolus dose is given to ensure adequate effect-site concentration. If the patient has received a muscle relaxant, then adequate anaesthesia should be confirmed and monitored with pEEG prior to switching off the inhalational agent and before embarking on transfers where depth of anaesthesia monitoring may not be available.

Fixed-rate infusions are commonly used for sedation in critical care. There are occasions when general anaesthesia is required, such as during bedside procedures or if a neuromuscular blocking agent is given to aid ventilation. Critically ill patients with organ dysfunction can make the TCI models inaccurate and increase the risk of haemodynamic instability. There is therefore a tendency for cautious administration of TIVA which raises the risk of awareness. Guidelines suggest titrating TIVA to clinical effect with pEEG monitoring to guide dosing.

Conclusion
TIVA is an essential technique that is indicated for a number of common clinical scenarios. All anaesthetists are required to be competent in delivering TIVA. A lack of knowledge and training in using TIVA have been highlighted as major factors in AAGA. Anaesthetists therefore have a responsibility to gain an understanding of the underlying pharmacokinetic principles, be familiar with the practical aspects of TIVA, along with its limitations, to ensure it is used safely and effectively.

FURTHER READING
1 Nimmo AF, Cook TM. 5th national Audit Project (NAP5). Accidental awareness during general anaesthesia in the United Kingdom and Ireland report and findings - chapter 18. Total intravenous anaesthesia. The Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland, September 2014.