Adjuvant Medications for Use With Propofol-Based Total Intravenous Anaesthesia

Lauren M. Hughes[1†], Michael G. Irwin[2], Claire C. Nestor[3]

[1]Specialist Registrar in Anaesthesia, Beaumont Hospital, Ireland
[2]Daniel CK Yu Professor of Anaesthesiology, Department of Anaesthesiology, University of Hong Kong, Hong Kong Special Administrative Region, China
[3]Consultant Anaesthetist, Tallaght University Hospital, Ireland

Edited by: Dr Maytinee Lilaonitkul, Assistant Professor, University of California, San Francisco, USA

[†]Corresponding author email: hugheslauren23@gmail.com

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KEY POINTS

- The use of total intravenous anaesthesia (TIVA) is increasing and has demonstrated many potential benefits.
- Analgesic medications combined with propofol-based TIVA can greatly reduce the propofol dose required, providing a multimodal balanced anaesthetic.
- An understanding of the pharmacokinetic profiles of opioids and nonopioid adjuvant agents is essential for the safe practice of TIVA.
- Target drug concentrations for target-controlled infusions are dependent on the magnitude of the surgical stimulus, patient characteristics, and different adjunctive agents used.
- Several adjunctive agents have been described and can augment TIVA-based anaesthetics.

INTRODUCTION

While the most commonly used method for the maintenance of anaesthesia remains the inhalation of a volatile agent, the use of total intravenous anaesthesia (TIVA) had increased in a recent audit of anaesthetic practice in the United Kingdom. This demonstrated an increase in TIVA use from 8% to 26% between the years 2013 and 2021.[1] The NAP5 study from the United Kingdom and Ireland highlighted that many anaesthetists lack appropriate training and education in TIVA.[2] Since NAP5's publication in 2015, there remains a lack of formal training and education in TIVA use according to international surveys.[3] These findings emphasise the importance of training and education in administering TIVA safely and effectively.

Propofol-based TIVA has been widely used in anaesthetic practice for many years. While propofol is a very effective hypnotic agent, it is a poor analgesic. Consequently, very large doses of propofol are required to provide an effective loss of response to noxious stimuli.[3] As a result, an analgesic agent, which is most often an opioid, is used alongside propofol. This combination provides surgical anaesthesia and reduces the propofol dose required.[4] Introduction of the ultrashort-acting opioid remifentanil into practice in 1996 revolutionised TIVA practice, and it remains one of the most commonly used analgesic adjuncts to propofol-based anaesthesia due to its favourable pharmacokinetic profile.[5] However, a number of different opioid- and nonopioid-based drugs can

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also be used to provide the analgesic component of TIVA. This tutorial will provide an overview of some of the different agents that can be used in clinical practice to provide the analgesic component of TIVA and deliver a 'balanced anaesthetic.'[6]

WHY CONSIDER ALTERNATIVES TO PROPOFOL-REMIFENTANIL-BASED TIVA?

The safe and effective administration of TIVA is an essential skill for trainee anaesthetists to practice and master. TIVA is not only advantageous in certain situations but also indicated in specific clinical scenarios where the use of a volatile agent is not recommended (Table 1). Although the advantageous pharmacokinetic profile of remifentanil cannot be ignored, the use of remifentanil for TIVA does have some limitations. Remifentanil does not provide postoperative analgesia and can cause hyperalgesia if used at high doses without other adjunctive agents.[7] Its use may not be appropriate as the sole analgesic agent in certain surgeries (eg, multilevel spine fusion) or in opioid-tolerant patients. In addition, the recent drug shortages affecting the supply of remifentanil also further highlight the need to diversify our TIVA practice and incorporate less commonly used alternatives.

An understanding of the pharmacokinetic principles that underpin TIVA's use is essential so that appropriate concentrations of anaesthetic and analgesic agents are targeted in the patient's plasma and effect site. In clinical practice, the synergy between propofol and an opioid-based agent has proven highly effective at providing adequate surgical anaesthesia, with the administration of other adjuncts (α-agonists, ketamine, magnesium, and lidocaine) demonstrating a further propofol-sparing effect. Where appropriate, regional techniques or local anaesthetic infiltration should also be considered to provide a balanced multimodal anaesthetic technique.

BASIC PHARMACOLOGY FOR THE OPIOID COMPONENT OF TIVA

Synthetic opioids can be administered alongside propofol-based TIVA by manual or target-controlled infusions (TCIs). The use of sufentanil, alfentanil, or fentanyl alongside propofol has been described as an alternative to remifentanil. The major challenge with intravenous anaesthesia is the control of drug concentrations and the corresponding depth of anaesthesia. The aim of any regimen is to titrate the dose to clinical effect for the individual patient while minimising potential drug adverse effects. The recently published NAP7 report examining perioperative cardiac arrest found that drug choice or dosing was a contributory factor in a substantial proportion of perioperative cardiac arrests.[8] In cases using TIVA, excessive or too rapid dosing during induction was judged to be a factor as well as the use of intermittent boluses and manual infusions. Manual infusion and bolus regimens can be used for the administration of TIVA, but their primary drawback is a lack of real-time knowledge of the predicted blood concentration. TCI automates drug titration using complex pharmacokinetic models to maintain stable predicted concentrations and level of anaesthesia. The pharmacokinetics behind the use of these devices are further described in a separate *Anaesthesia Tutorial of the Week* 75, Target Controlled Infusions in Anaesthetic Practice.[8] Correctly inputting patient data into the infusion pump and selecting the correct pharmacokinetic model are essential for the safe use of TCI. Although TCIs are more accurate and less labour intensive than manual infusions, adjustments are still required. Individual patients' pharmacokinetics and pharmacodynamics may vary from the population that the model was designed with. NAP7 further highlighted that cardiac arrests following the induction of anaesthesia using TIVA were overrepresented in older, frail, and unwell patients undergoing nonelective surgery.[8] These findings further emphasise the importance of training and education to ensure the safe and educated administration of TIVA.

The synthetic opioids remifentanil, sufentanil, alfentanil, and fentanyl all bind to G-protein-coupled receptors. An overview of the pharmacokinetics of each opioid is provided in Table 2. How long it will take the plasma concentration of the drug to decrease is dependent on the pharmacokinetic profile of the drug and the duration of the infusion. Context-sensitive half-time (CSHT) is defined as the time it takes for the plasma concentration to reduce by 50% after stopping an infusion of a specified duration. A wide range of CSHTs exists between the different opioids, as discussed further below. TCI pumps have an inbuilt decrement function that displays the estimated time it would take, after stopping the infusion, for the current plasma

Advantages	Indications
Reduced postoperative nausea and vomiting	Malignant hyperthermia risk
Avoid use of neuromuscular blocking agents (eg, myasthenia gravis and neuromuscular disorders)	Use of intraoperative monitoring of somatosensory or motor evoked potentials
Trainee exposure and training in TIVA use	Anaesthesia in nontheatre environments
Avoids atmospheric pollution associated with volatile agents and nitrous oxide	Transfer of anaesthetised patients
Lower incidence of emergence phenomena in children	Operations on the airway
	Long QT syndrome

Table 1. Advantages and Specific Indications For Using Total Intravenous Anaesthesia (TIVA)

	Remifentanil	Alfentanil	Sufentanil	Fentanyl
Volume of distribution, l kg^{-1}	0.3–0.4	0.25–0.75	2.5–3	3–5
Clearance, ml kg min^{-1}	40–60	3–8	10–15	10–20
CSHT after 1-hour infusion, min	3.8	30	25	20
CSHT after 3-hour infusion, min	3.8	40	30	70
CSHT after 8-hour infusion, min	3.8	60	40	260
Protein binding, %	70%	92%	91%	84%
TCI models	Minto	Maitre Scott	Gepts	McClain* Shafer*

Table 2. Overview of the Pharmacokinetics of Short-Acting Opioids Used In Total Intravenous Anaesthesia. CSHT, context-sensitive half-time; TCI, target-controlled infusion.
*Not commercially available

concentration to decline to a chosen plasma concentration (Figure). This can be useful when titrating infusions at the end of a case to aid in a timely emergence from anaesthesia. A 50% decrement time is equal to CSHT.

Remifentanil

Remifentanil is an ultrashort-acting opioid analgesic with a CSHT of around 3 minutes due to its rapid metabolism by plasma esterases. Given its favourable and consistent pharmacokinetic profile, it is widely combined as a target-controlled or manual infusion with propofol-based TIVA. When used together, propofol and remifentanil behave synergistically. Minto is the most popular pharmacokinetic model; the variables used for programming are age, weight, height, and sex.[10] Given that the offset of remifentanil is so predictable, regardless of the infusion rate and duration, a manual infusion of μg kg^{-1} min^{-1} is an effective and safe alternative.[11] The short-acting nature of remifentanil means that additional analgesia is required.

Alfentanil

The pharmacokinetic and pharmacodynamic parameters of alfentanil have proven useful for TIVA in combination with propofol,[12] with coadministration of alfentanil with propofol for TIVA allowing for a reduction in the propofol requirement. Alfentanil is a pure mu receptor opioid agonist that has one-fourth the potency of fentanyl, has a brief duration of action, and is readily titratable. Alfentanil has a pKa of 6.5, which explains its rapid onset due to a large proportion remaining unionised at physiological pH. Its lower lipid solubility means that it is less likely to accumulate than fentanyl. Its CSHT is reasonably predictable but does rise significantly with time (see Figure 1). Down titration toward the end of surgery with alfentanil is required before propofol given its longer CSHT. This sequence is opposite to propofol-remifentanil-based TIVA, where propofol infusion is reduced first.[11] The Maitre[13] and Scott[14] models for alfentanil are available on commercial TCI pumps. The Maitre model requires the covariates of weight, age, and sex for

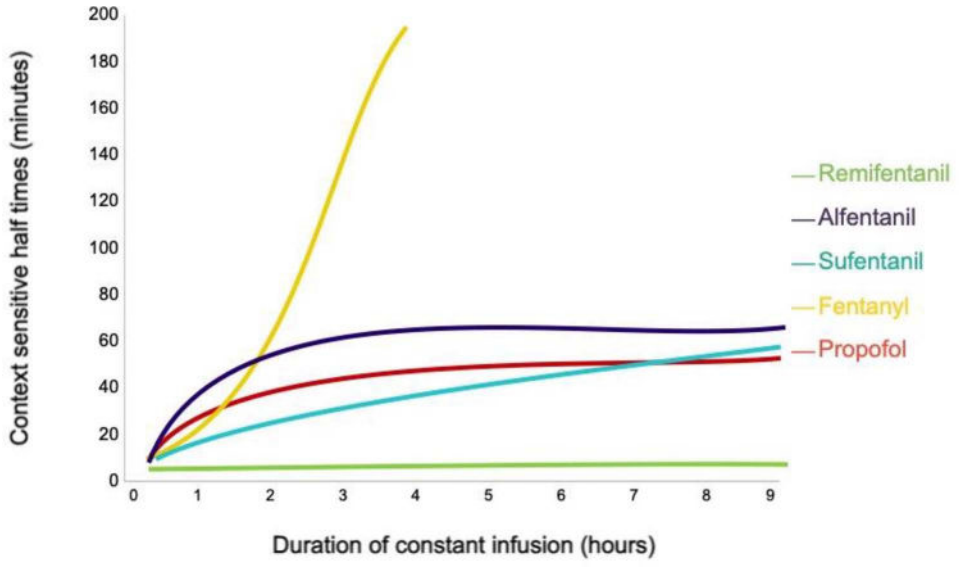

Figure. Context-sensitive half-times: the time required to achieve a 50% reduction in concentration following the cessation of a continuous infusion. (Used with permission).[9]

the calculation of infusion rates and seems to be the best model[11] compared with the Scott model, which has no covariates, meaning that the same dose of drug will be infused regardless of age/weight/sex.

Sufentanil

Sufentanil is a potent fentanyl derivative with a potency of 5 to 10 times that of fentanyl. It has a slower onset than alfentanil. When comparing the CSHT of sufentanil with that of alfentanil, sufentanil has a CSHT shorter than alfentanil.[11] Sufentanil takes longer to wear off, with a duration of action from 30 to 60 minutes, which is longer than that of both remifentanil and alfentanil. The real benefit of sufentanil for use in TIVA is seen when severe postoperative pain is expected, as its use allows more time for titration of opioids in the postanaesthesia care unit.[15] The use of the Gepts[16] TCI mode has been described for administration via TCI pumps.

Fentanyl

Pharmacokinetic models for the administration of fentanyl TCI are described in the literature, but commercial TCI pumps are often not configured for the administration of a TCI of fentanyl.[17] As a result, recipes for the administration of fentanyl using a manual infusion have been described. Fentanyl has a CSHT that rises rapidly after just 1 hour of infusion, meaning that its use for the analgesic component of TIVA requires careful titration to provide the most favourable recovery profile. Its use can be helpful in situations where rapid emergence is not a priority and, like sufentanil, where significant postoperative pain is anticipated. The longer half-life of fentanyl means that transition opioids may not be required in the postanaesthetic care unit.

Table 3 provides an overview of suggested TCI and manual infusion dosing regimens for the administration of alfentanil, sufentanil, and fentanyl for the adult population. Similar to any anaesthetic or analgesic agent, dosing should be individualised to the patient, American Society of Anaesthesiologists grade, and cardiovascular status of the patient. Further information regarding TIVA for the paediatric population can be found in *Anaesthesia Tutorial of the Week* 392.

THE ROLE OF OTHER ADJUVANTS

Apart from opioids, many other drugs can be used as adjuncts to propofol-opioid-based TIVA. The administration of these adjuncts can help further lower propofol requirements and improve operating conditions and haemodynamic stability. The roles of the different nonopioid analgesic adjuvants commonly used in TIVA are described below (Table 4).

α-2 Agonists

Clonidine and dexmedetomidine are the most widely used α-2 agonist drugs. They work by inhibiting the release of epinephrine and norepinephrine by binding to α-2 receptors. Clonidine has a longer half-life; therefore, it may have more of a role in the postoperative period.

Opioid	Typical TCI Dosing	Manual Infusions[18]	Points to Note at the End of the Procedure	When to Consider Its Use
Alfentanil	TCI Maitre: 30–150 ng ml^{-1}	Bolus: 25–35 μg kg^{-1} Continuous infusion: 50–75 μg kg^{-1} h^{-1} for 30 min and 30–42.5 μg kg^{-1} h^{-1} thereafter	Down titration at the end of surgery depends on length of surgery, usually before propofol; remember the longer CSHT	Rapid onset but much less potent than remifentanil
Sufentanil	TCI Gepts: 0.2–1 ng ml^{-1}	Bolus: 0.15–0.25 μg kg^{-1} Continuous infusion: 0.15–0.22 μg kg^{-1} h^{-1}	Down titration at the end of surgery, usually before propofol. Typically terminated 30 minutes before extubation	Shorter CSHT than alfentanil may make it a more suitable remifentanil alternative; may be less likely to induce acute tolerance
Fentanyl	TCI Shafer 2–4 ng ml^{-1}	Bolus: 3 μg kg^{-1} Continuous infusion: 2 μg kg^{-1} h^{-1} for 30 min 1.5 μg kg^{-1} h^{-1} from 31 to 150 min 1 μg kg^{-1} h^{-1} until 30 min before skin closure	Aim for an effect site concentration of 1.4–2 ng ml^{-1} to minimise postoperative respiratory depression	Rapid emergence not a priority, significant postoperative pain anticipated

Table 3. Suggested Dosing Regimens For Manual and Target Controlled Infusions of Opioid Analgesics For The Administration of Total Intravenous Anaesthesia. CSHT, context-sensitive half-time; TCI, target-controlled infusion

Adjunct	Percent Reduction in Propofol-Maintained Anaesthesia Requirements	Suggested Dosing Regimens	Points to Note at the End of the Procedure
Dexmedetomidine	20–50%	IV loading dose of 1 mcg kg^{-1} over 5–10 minutes ± infusion of 0.2–0.7 mcg kg^{-1} h^{-1}	When using an infusion for longer procedures, it should be discontinued 30–60 minutes before completion of surgery to avoid delays in recovery
Ketamine	20–40%	IV loading doses of 0.1–1 mg kg^{-1} ± infusion of 0.1–0.2 mg kg^{-1} h^{-1}or repeat doses of 0.1–0.2 mg kg^{-1} at 1-hour intervals	To minimise adverse psychiatric effects, it is advisable to stop a continuous infusion at least 30 minutes before the end of the procedure
Magnesium	15–20%	IV loading dose of 20–50 mg kg^{-1} given over 15–20 minutes ± IV maintenance of 6–20 mg kg^{-1} h^{-1}	Can potentiate the effects of neuromuscular blocking agents; monitoring of neuromuscular block is recommended
Lidocaine	10–20%	IV loading dose of 1.5 mg kg^{-1} ± infusion of 1–2 mg kg^{-1} h^{-1}	Continuing the infusion into the postoperative period is possible but may increase the risk of drug accumulation and toxicity

Table 4. Summary of Nonopioid Analgesic Adjuvants. IV, intravenous

Dexmedetomidine is a highly selective α-2 agonist that has a shorter half-life than clonidine.[18] Its onset of action is less than 5 minutes, with its peak effect occurring within 15 minutes. Its use intraoperatively can reduce propofol-maintained anaesthesia requirements and delay postoperative opioid requirements.[19] It produces dose-dependent analgesia, sedation, and anxiolysis and has been shown to help smooth emergence from anaesthesia.[20] Caution is required as it can produce a 20% decrease in heart rate and blood pressure. An initial loading dose followed by an intraoperative infusion can be used. However, its sedative effects can prolong recovery after anaesthesia when used as an adjuvant drug. A reduction in the infusion rate is advised before the end of a procedure due to its CSHT of up to 250 minutes after an 8-hour infusion (Table 4).

Ketamine

Ketamine is a noncompetitive NMDA receptor antagonist, potent analgesic, and dissociative anaesthetic agent.[21] Unlike most analgesic agents, ketamine is an effective cardiovascular stimulant that can result in an increase in heart rate, blood pressure, and cardiac output. In terms of sedation, a synergistic relationship exists between propofol and ketamine, making sedation more effective and reducing adverse effects.[22] A systematic review showed that low-dose ketamine can reduce total opioid consumption and provide better overall pain control,[23] with evidence also existing for reduced hyperalgesia secondary to opioid use.[24] Side effects of ketamine include increased airway secretions, nausea, and hallucinations.

Magnesium

Magnesium, the fourth most abundant cation in the body, is a noncompetitive antagonist at the NMDA receptor with antinociceptive effects. Magnesium administration has been shown to reduce analgesic consumption in the intraoperative and postoperative periods.[25,26] Magnesium administration has also been shown to have a propofol-sparing effect, reducing propofol-maintained TIVA maintenance infusions by 15 to 20%. Magnesium can be administered as a bolus, bolus and infusion, or infusion, with no current consensus on the optimal dosing strategy.[27]

Lidocaine

Lidocaine is a widely available and commonly used amide local anaesthetic. When given intravenously, it has antihyperalgesic and antinociceptive properties that help with postoperative pain management.[28,29] Its addition to propofol-maintained TIVA can reduce requirements by 10 to 20%. A loading dose can be administered intraoperatively, followed by intraoperative ± postoperative infusions. An infusion of no greater than 1.5 mg kg^{-1} h^{-1} for no longer than 24 hours is recommended and requires close supervision in a monitored bed due to its narrow therapeutic index.[30]

SUMMARY

Knowledge of the pharmacological differences between opioid and nonopioid TIVA adjuncts is essential for providing safe and effective TIVA. Although opioids play a large role in providing the analgesic component of TIVA, nonopioid adjuncts should also be considered. Selected concentrations of TCI infusions should be individualised to the patient, extent of surgery, and other drugs administered. It is essential to calibrate the TCI to the patient's response at all times. These basic principles reiterate the recommendations from the international guidelines for TIVA administration[31] and remain true regardless of the different agents used.

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