Guidelines

Safe practice of total intravenous anaesthesia (TIVA) 2018

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Guidelines

Guidelines for the safe practice of total intravenous anaesthesia (TIVA)

Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia

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Summary

Guidelines are presented for safe practice in the use of intravenous drug infusions for general anaesthesia. When maintenance of general anaesthesia is by intravenous infusion, this is referred to as total intravenous anaesthesia. Although total intravenous anaesthesia has advantages for some patients, the commonest technique used for maintenance of anaesthesia in the UK and Ireland remains the administration of an inhaled volatile anaesthetic. However, the use of an inhalational technique is sometimes not possible, and in some situations, inhalational anaesthesia is contraindicated. Therefore, all anaesthetists should be able to deliver total intravenous anaesthesia competently and safely. For the purposes of simplicity, these guidelines will use the term total intravenous anaesthesia but also encompass techniques involving a combination of intravenous infusion and inhalational anaesthesia. This document is intended as a guideline for safe practice when total intravenous anaesthesia is being used, and not as a review of the pros and cons of total intravenous anaesthesia vs. inhalational anaesthesia in situations where both techniques are possible.

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This is a consensus document produced by expert members of a Working Party established by the Association of Anaesthetists and the Society for Intravenous Anaesthesia. It has been seen and approved by the Board of Directors of the Association of Anaesthetists and the Society for Intravenous Anaesthesia.
It has been endorsed by the Royal College of Anaesthetists,the College of Anaesthesiologists of Ireland, the Intensive Care Society, the Faculty of Intensive Care Medicine, and the Association of Paediatric Anaesthetists of Great Britain and Ireland.

What other guidelines are available on this topic?

At the time of writing, there were no nationally or internationally agreed guidelines on the use of total intravenous anaesthesia (TIVA).

Why were these guidelines developed?

Surveys of anaesthetists working in the UK and Ireland have concluded that training in TIVA is currently inconsistent and often inadequate and that many anaesthetists do not feel confident when using the technique. The 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia found that self-reported cases of awareness were more common when TIVA was used, but that most of the cases were preventable and that the commonest contributory factor was inadequate education and training [1]. The report recommended that *'the relevant anaesthetic organisations should establish a set of standards and recommendations for best practice in the use of TIVA'*. These guidelines have been produced by the Society for Intravenous Anaesthesia (SIVA) and the Association of Anaesthetists in response to that recommendation.

Recommendations

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, co-administered 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 minimise 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.

Introduction

When maintenance of general anaesthesia is by intravenous (i.v.) infusion, this is referred to as TIVA. Although TIVA has advantages for some patients, and is the preferred technique of some anaesthetists, the commonest technique used for maintenance of anaesthesia in the UK and Ireland remains the administration of an inhaled volatile anaesthetic. However, the use of an inhalational technique is sometimes not possible, for example, anaesthesia delivered outside the operating room, during transfer or for some operations on the airway. Furthermore, in some situations inhalational anaesthesia is contraindicated, for example, in patients with malignant hyperthermia, or TIVA may be advantageous, for example, in patients at high risk of postoperative nausea and vomiting (PONV) or when intra-operative monitoring of somatosensory or motor-evoked potentials is required. Therefore, all anaesthetists should be able to deliver TIVA competently and safely.

The knowledge required by an anaesthetist using TIVA includes:

1. the principles behind achieving and maintaining an appropriate plasma and brain concentration of the i.v. anaesthetic drug;
2. the factors determining the appropriate target drug concentration to aim for, and how to adjust this in the light of the patient's response;
3. practical aspects involved in ensuring that the intended dose of drug is delivered to the patient;
4. monitoring of the patient receiving TIVA including the use and interpretation of pEEG monitors.

Achieving a desired drug concentration in the patient

All anaesthetists need to know the pharmacokinetic principles underpinning TIVA to be able to achieve and maintain an appropriate concentration of an i.v. anaesthetic or analgesic drug in the patient's plasma and brain. Achieving a stable plasma concentration of a drug requires varying drug infusion rates. For example, during induction and maintenance of anaesthesia, a bolus or rapid infusion should be followed by a decreasing infusion rate [2, 3]. The drug concentration achieved in the plasma and brain can be predicted from pharmacokinetic models (Appendix 1). Anaesthesia may be induced and maintained either using manual dosing, where the anaesthetist determines the bolus dose(s) and infusion rate(s) used, or using a TCI pump where the anaesthetist enters the desired 'target' concentration to be achieved in the patient's plasma or brain.

Target-controlled infusions

A TCI pump contains a microprocessor programmed with pharmacokinetic models for relevant drugs. The user selects the drug and pharmacokinetic model to be used by that TCI pump and inputs the patient characteristics (covariates) such as body weight and age, and the target plasma or 'brain' (effect-site) concentration, with the pump determining the initial bolus and subsequent infusion rates. The two most commonly used adult propofol models are Marsh [4] and Schnider [5, 6].

How relevant is the pharmacokinetic model to my patient?

A pharmacokinetic model is likely to be applicable to patients with similar characteristics to the subjects in which it was developed. Most pharmacokinetic models were developed in young, healthy, non-obese subjects [7]; caution is required when using models in patients whose characteristics are different (e.g. ASA physical status 3–5, older patients, obese patients). The Marsh and Schnider models are most applicable to healthy adults, and the Kataria [8] and Paedfusor [9] models only to children. The Eleveld propofol model [10] was developed from a wider variety of patients, and is suitable for use in children, the elderly and the obese, but has not yet been incorporated into commercially available TCI pumps.

Plasma drug concentrations in individual patients are unlikely to be identical to those predicted by the pharmacokinetic model and displayed by the TCI pump. The mean difference between estimated and measured concentrations is usually less than 25% [10], but, if the patient differs from the population in which the model was developed, the difference may be considerably greater. In such circumstances, TCI pumps can be a useful tool for titrating a propofol infusion to effect (clinical effect or the desired effect on the EEG as measured by a pEEG monitor), but the predicted propofol concentration cannot be assumed to be accurate.

The Association of Anaesthetists and the Society for Obesity and Bariatric Anaesthesia (SOBA) have published a guideline which includes discussion of TIVA use in the obese surgical patient [11]. There is a lack of evidence on whether it is better to use total body weight or another scalar such as adjusted body weight when using a TCI pump with these models in the obese. The Marsh and Schnider pharmacokinetic models and the calculated plasma

propofol concentrations may not be accurate in the obese. The maximum body weight accepted by Marsh TCI pumps is 150 kg and pumps using the Schnider model only accept variables that result in a body mass index (BMI) < 35 $kg.m^{-2}$ for women or < 42 $kg.m^{-2}$ for men. When using TIVA in the obese, titration to clinical effect and pEEG monitoring is recommended.

Manual infusions

When TIVA is administered manually (i.e. without a TCI pump), a thorough understanding of the pharmacokinetics of the drugs being used is necessary. A fixed infusion rate may cause rising, declining or stable concentrations, depending on prior administration rate and duration of infusion, leading to a risk of under- or overdosage. It should be remembered that even when using drugs with the fastest pharmacokinetic profiles, a simple change in an infusion rate is associated with a significant delay before plasma concentrations change appreciably; this lag is even greater for effect-site concentrations and clinical effect.

On starting a propofol infusion at a fixed rate without an initial bolus, concentrations rise very slowly and only reach near steady-state conditions after several hours (Fig. 1). If no loading dose is given, then administration by fixed infusion rate will be initially associated with inadequate concentrations. On the other hand, after some time at a fixed infusion rate, the concentrations may rise to excessive levels. Likewise, if the infusion rate is decreased, plasma concentrations will change slowly. In contrast, remifentanil achieves around 75% of steady-state concentration after 5 min, with 100% reached after 15–20 min. Examples of manual infusion protocols for propofol and remifentanil can be found in Appendix 1.

Choosing an appropriate target drug concentration for a patient

A clinical calibration of the individual patient's response to propofol is recommended during induction and maintenance of anaesthesia. The drug concentration achieved should be sufficient to produce loss of consciousness and prevent movement in response to noxious stimuli. However, the concentration should not be excessive, as this may cause marked hypotension and delayed recovery from anaesthesia. There is no plasma or effect-site concentration that is appropriate for all patients. Rather, the concentration required will depend on inter-individual patient variation, other drugs administered and the degree of surgical stimulus.

Inter-individual variation

There is considerable variation between patients in the brain propofol concentration required for anaesthesia, as is also the case for volatile anaesthetics [12]. The brain concentration required cannot be predicted in advance, but observation of the patient's response during induction of anaesthesia can give an indication of the approximate propofol concentration that is likely to be required for maintenance. In general, older patients require a lower brain anaesthetic drug concentration than younger patients [6], but there is considerable variation between individuals of the same age and overlap between patients of different ages. Patients who are ASA physical status 3–5 require

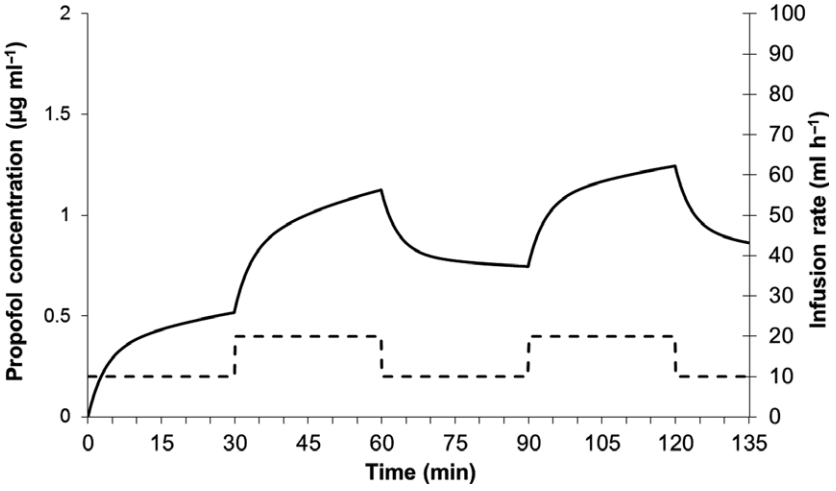

Figure 1 Estimated plasma concentrations (solid line) achieved with alternating infusion rates (dashed line) of 10 and 20 $ml.h^{-1}$ 1% propofol, in a 70 kg adult without a bolus dose (Marsh model). The concentrations change slowly and do not reach concentrations usually associated with general anaesthesia.

particularly careful management. They may require a lower concentration to produce anaesthesia and may become hypotensive during and after the induction period.

Other drugs administered

The administration of opioids, benzodiazepines, ketamine, α_2-adrenoceptor agonists, magnesium and nitrous oxide result in a marked reduction in the required brain propofol concentration [13, 14]. Synergy of effect occurs between propofol and opioids. Opioids reduce the propofol dose required to produce loss of consciousness and, in particular, to obtund movement and haemodynamic responses to noxious stimuli [15]. A remifentanil infusion is often used in conjunction with propofol infusion. The rapid offset of effect after stopping remifentanil enables doses to be given that reduce propofol requirements by approximately 50% (Table 1) without causing prolonged respiratory depression after surgery. However, intra-operative remifentanil does not provide postoperative analgesia. Higher dose remifentanil infusions (target concentration above 5 $ng.ml^{-1}$ or infusions above 0.2 $\mu g.kg^{-1}.min^{-1}$) may cause acute opioid tolerance or opioid-induced hyperalgesia but the clinical significance of this is uncertain [16].

Degree of surgical stimulus

The brain propofol concentration required for adequate anaesthesia during surgery is influenced by the magnitude of the surgical stimulus. An effective regional anaesthetic block will reduce the propofol concentration required.

Typical target concentrations in routine practice

Target concentrations should be individually determined based on patient characteristics, other drugs administered and the expected magnitude of surgical stimulus. If a relatively rapid induction of anaesthesia is required, initial plasma (Marsh model) or effect-site (Schnider model) propofol target concentrations of 4–6 $\mu g.ml^{-1}$ are typically used in healthy young or middle-aged patients. During maintenance of anaesthesia, target concentrations of 3.0–6.0 $\mu g.ml^{-1}$ (without opioids) or 2.5–4.0 $\mu g.ml^{-1}$ (with opioids) are typical. Higher initial targets may be required for anxious and 'robust' individuals, whereas lower targets are appropriate for older, frail or unwell patients.

Alternatively, a slower induction of anaesthesia may be achieved by setting a lower initial target propofol concentration (e.g. 1 $\mu g.ml^{-1}$) and making repeated 0.5–1.0 $\mu g.ml^{-1}$ incremental increases in the target concentration. This technique can be particularly useful for older, frail or unwell patients because it is associated with a less severe, and less rapid, fall in blood pressure. A slower induction also makes it easier for the anaesthetist to observe the estimated effect-site concentration at which the patient stops responding to stimuli.

It is recommended that such a clinical calibration of the individual patient's response to propofol routinely takes place during induction of anaesthesia using TCI. This can be achieved by noting the effect-site concentrations at which there is: a. loss of response to speech; and, b. loss of movement in response to a noxious stimulus (e.g. very firm pressure on the angle of the mandible). The latter concentration may be used as a guide to the approximate concentration likely to be required during maintenance of anaesthesia.

Where TCI remifentanil is administered with propofol, target remifentanil concentrations of 2–6 $ng.ml^{-1}$ are commonly used (equivalent to manual infusion rates of approximately of 0.08–0.25 $\mu g.kg^{-1}.min^{-1}$) and will usually necessitate ventilation of the patient's lungs, as spontaneous ventilation is uncommon with concentrations > 1.5 $ng.ml^{-1}$ in adults. During maintenance of anaesthesia, the target propofol concentration and opioid administration should be adjusted, using clinical judgement supported by the observation of clinical signs, and supplemented by the use of a pEEG device if the patient has received a neuromuscular blocking drug.

Table 1 Influence of differing remifentanil effect-site concentrations on the propofol effect-site concentration required for loss of response to different stimuli. Figures shown are the effect-site propofol concentrations that have a 50% (ED_{50}) and 95% (ED_{95}) probability of absence of a response. Data are adapted from a study of female patients (ASA physical status 1, aged 18–60 years) [14].

	Remifentail effect-site concentration ($ng.ml^{-1}$)					
	0		**2**		**4**	
	ED_{50}	**ED_{95}**	**ED_{50}**	**ED_{95}**	**ED_{50}**	**ED_{95}**
Verbal stimulus	2.9	3.8	2.4	3.1	2.0	2.7
Eyelash reflex	2.8	3.4	1.8	2.6	1.7	2.5
Tetanic (electric) stimulus	4.1	6.6	1.8	3.8	1.3	3.3

Practical aspects of the safe use of TIVA

Errors during TIVA can lead to the failure to deliver the intended drug, underdosing, overdosing or other complications. In NAP5, the two commonest causes of accidental awareness during TIVA were failure to deliver the intended dose of drug and poor understanding of the underlying pharmacological principles [1].

Drug concentrations, pumps, models and syringes

Within an anaesthetic department it is preferable to stock only one concentration of propofol; the availability of both 1% and 2% propofol creates the potential for error. For the same reason, remifentanil should be diluted to a single, standard concentration. If more than one concentration of drug is used, robust mechanisms should be in place to minimise the risk of drug error.

Adequate numbers of TCI pumps should be available in areas where propofol infusions are used for maintenance of anaesthesia. It is preferable to use a single model of TCI pump, which should contain a locally approved set of pharmacokinetic models.

Syringes of the same capacity from different manufacturers have varying internal diameters so that for the same travel of the syringe plunger, different volumes of drug are delivered. Therefore, it is necessary for the infusion pump to be programmed with the brand of syringe used. It is preferable for a single brand of syringe to be used within a department. Syringes used for TIVA should have Luer-lock connectors to reduce the risk of accidental disconnection.

The choices available when programming a TCI pump should be restricted to the agreed drug concentrations, pharmacokinetic model(s) and syringe type to reduce the risk of selecting the wrong concentration, model or syringe type.

Pumps for both TCI infusions and fixed-rate infusions should have audible alarms enabled by default. Alarms should include high pressure, stopped infusion, empty syringe, disconnection from the mains electricity supply and low battery. Some pumps also have an alarm for a drop in pressure which may permit some disconnections to be detected. Infusion pumps that automatically decrease the infusion rate to a low 'keep vein open' ('KVO') rate when the syringe is nearly empty, should not be used for infusions of propofol or remifentanil. There should be a visual display to indicate that the infusion is in progress.

Pump dysfunction or failure is uncommon; however, should equipment malfunction or fail in use, and where potential or actual harm occurs, this should be reported locally in line with hospital policy and to the Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card scheme for medical devices.

Mixing of drugs for infusion

Mixing of propofol and remifentanil in a single syringe is not recommended because it has a number of disadvantages: it is not possible to separately adjust the hypnotic and analgesic components of the anaesthetic; when a TCI model for propofol is used, the rapid infusion at induction or when increasing the target concentration is likely to result in administration of an excessive dose of remifentanil; if a low concentration of remifentanil (e.g. 5 $\mu g.ml^{-1}$) is used in the mixture, the remifentanil becomes unstable and breaks down in the syringe [17]; and remifentanil and propofol undergo separation and layering when mixed in a syringe resulting in varying remifentanil concentrations in different regions of the syringe [18].

Drug infusion administration sets and i.v. cannulae

The infusion set through which TIVA is delivered should have a Luer-lock connector at each end to reduce the risk of accidental disconnection and an antisyphon valve on the drug delivery line(s) to prevent uncontrolled infusion from a damaged syringe. Where more than one infusion is given through a single i.v. cannula (or central venous catheter lumen) an anti-reflux valve should be present to prevent backward flow of drug up the infusion tubing. It is particularly important that this is present on an i.v. fluid administration line. Drug and fluid lines should join together as close to the patient as possible to minimise dead space in which a drug may accumulate rather than entering the vein [19, 20] (Fig. 2). The infusion line through which TIVA is delivered should have as few potential sites for leakage as possible. A continuous line from syringe to cannula is ideal, without additional connections or three-way taps. Administration sets specifically designed for TIVA are more likely to meet the above requirements than self-assembled sets and for this reason are recommended. It is essential that the i.v. cannula through which TIVA is administered is securely sited in a vein. Particular caution should be exercised if a cannula is inserted in a vein in the antecubital fossa, where accidental subcutaneous administration may be difficult to detect. Accidental awareness in patients having TIVA is commonly due to the failure to deliver the drug(s) due to a problem with the i.v. cannula. Previous guidance has recommended that the i.v. cannula, through which TIVA is delivered, should be 'visible at all times' [20],

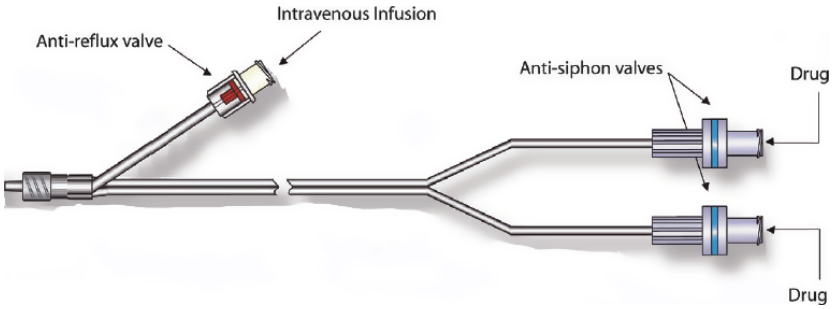

Figure 2 Diagram demonstrating the arrangement of a multi-lumen connector including an anti-reflux valve for intravenous fluid and anti-siphon valves for intravenous drugs.

although this has been modified in more recent publications to specify 'visible whenever practical' [1, 21]. It is acknowledged that during some operations constant observation of the i.v. cannula may not be practical. In these circumstances anaesthetists should have a higher index of suspicion for problems with the infusion and periodically inspect the cannula site, if possible. The threshold for using pEEG should be reduced in these circumstances. The cannula site should be inspected immediately if the patient's response to the infused drug(s) appears less than would be expected.

Preparation for TIVA

Pumps should be charged before use and, where practical, mains powered during use to prevent failure due to battery depletion. Infusion pumps should only be programmed after a syringe containing the drug to be infused has been placed in the pump. Cases of awareness have occurred when a propofol syringe was placed in a pump that had been already programmed to give an infusion of remifentanil. Such errors may also be reduced by having a consistent lay-out of pumps, for example, placing the propofol infusion pump at the top of any stack of pumps.

Syringes should be labelled with the drug name and concentration. To avoid drawing up drugs into an incorrectly labelled syringe, and to avoid administering diluent without active drug, drug labels should be attached to syringes only when the intended drug is drawn up.

Most propofol formulations available in Europe support bacterial growth and postoperative infection has resulted from contaminated propofol [22, 23]. Propofol should be drawn up using precautions to reduce the risk of contamination. Before use, the ampoule neck or rubber stopper should be disinfected using medicinal alcohol, and a new sterile syringe and drawing up device should be used each time. All syringes should be prepared shortly before use and those not used immediately should be sealed with a cap.

Conduct of TIVA

The drugs to be administered, the programming of the pump, the infusion set and the i.v. cannula should be checked before starting TIVA. At induction, the dose of drug administered by the pump and the infusion rates should be observed periodically as a check that the system is operating as expected. If a neuromuscular blocking drug is to be administered, this should be given only after loss of consciousness has been confirmed.

When TCI anaesthesia is used, additional 'manual' boluses are usually not required and the target concentration should be increased to deepen anaesthesia. If a manual bolus is administered, the displayed drug concentrations will be inaccurate for several minutes.

The infusion pump should be visible throughout anaesthesia. The anaesthetist should observe the infusion rate (e.g. $ml.h^{-1}$ or $mg.kg^{-1}.h^{-1}$) every few minutes. If, during maintenance of anaesthesia, a TCI pump shuts down due to a depleted battery or has to be restarted due to a malfunction, it is not appropriate to restart TCI anaesthesia using the previous target concentration. If this was done, the pump's calculations would not take into account the drug previously administered and it would give another induction dose by rapid infusion, resulting in an excessively high drug concentration. If a pump does shut down accidently, then it is appropriate to restart it in the manual mode and programme an infusion rate similar to that being delivered at the time of failure.

All vascular access devices used for TIVA should be flushed with at least twice the dead space volume of the device at the end of the procedure. If this is not done, potent anaesthetic drugs (e.g. remifentanil or neuromuscular blocking drugs) may remain in the dead space of a vascular

access device and may be accidently administered to the patient postoperatively [24–26].

Consent for anaesthesia

As with all medical interventions, the use of TIVA requires an analysis of the risks and benefits for the patient to whom it will be administered. Some observational studies have found an association between TIVA and an increased incidence of accidental awareness during general anaesthesia [1], whereas others have not [27]. An observational study found an association between TIVA and improved outcome after cancer surgery [28], but the results of randomised trials are awaited. The anaesthetist should consider what information the patient would wish to know about the technique chosen. However, unbundling all aspects of anaesthetic technique in the consent process may be undesirable and impractical [29]. Balancing uncertain differences in the incidence of complications (e.g. awareness) or benefits (e.g. cancer outcome) against a proven frequent impact (e.g. reduced sickness) is complex. The Working Party does not consider that use of TIVA per se is an aspect of anaesthetic technique that routinely requires specific formal consent, provided best practice is observed. Whether consent is required should be assessed on a case by case basis [30].

Monitoring the patient during TIVA

Monitoring of the patient during TIVA should be in accordance with the Association of Anaesthetists recommendations for standards of monitoring during anaesthesia and recovery [21]. Use of a pEEG monitor is recommended when a neuromuscular blocking drug is used with TIVA. The large majority of cases of self-reported awareness that were identified in NAP5 occurred in patients who had received a neuromuscular blocking drug [1]. Efforts to prevent awareness should, therefore, focus on patients who receive a neuromuscular blocking drug. About half of the reports of awareness in NAP5 occurred around the time of induction of anaesthesia and transfer from the anaesthetic room to the operating theatre. Processed EEG monitoring should commence before administration of the neuromuscular blocking drug.

During the maintenance phase of anaesthesia with an inhaled agent, it is possible to use the end-tidal anaesthetic gas concentration as an indication that the anaesthetic drug is being delivered as intended; this is not possible during TIVA. Monitoring of the effect of the anaesthetic drug on the cerebral cortex with a pEEG monitor can reduce the likelihood of awareness [31]. The isolated forearm technique can also be used to assess conscious state in paralysed patients [32–34]; however, its use to date has largely been confined to research studies. Almost 20% of the NAP5 reports of awareness occurred after the end of surgery and these were commonly caused by neuromuscular blockade still being present when the patient regained consciousness [1]. Processed EEG monitoring should, therefore, be continued until full recovery from the effects of the neuromuscular blockade has been confirmed by monitoring with a nerve stimulator.

Processed EEG monitors provide much more information to the anaesthetist than just a derived index value. For example, the EEG waveform may be displayed together with measures of the EEG signal quality, EMG activity and degree of burst suppression. Optimal use of a pEEG monitor involves using all the information it provides together with the information from other patient monitors, clinical judgement and experience. A pEEG index value may be a useful extra piece of information, but it should be considered along with all the other available information before making a judgement about whether anaesthetic dose should be adjusted. Anaesthetists require training and experience in the use of pEEG monitors as part of training in TIVA. Adequate numbers of pEEG monitors should be available in areas where propofol infusions may be used for maintenance of anaesthesia.

TIVA in particular circumstances

Rapid sequence induction

Rapid sequence induction may be undertaken before the maintenance of anaesthesia with an i.v. infusion of propofol. If TCI propofol is used for the induction of anaesthesia, this can be achieved by setting an initial high target concentration so the induction 'bolus' dose of propofol is delivered as a rapid infusion (e.g. 1200 $ml.h^{-1}$), and then reducing the target concentration once the desired dose has been administered. (Many pumps will display the bolus dose to be given for a set target concentration before the start button is pressed). Some newer TCI pumps can run bolus infusion rates of 1800–2200 $ml.h^{-1}$. When using a TCI propofol pump for rapid sequence induction, the induction dose of propofol is typically delivered more slowly than a manual bolus. The time to loss of consciousness may be reduced by co-administration of other drugs with a rapid onset such as remifentanil or alfentanil. If the induction propofol bolus is given manually rather than by the TCI pump, then the estimated plasma propofol concentration displayed by the pump will not be accurate in the early phase of the anaesthetic. An alternative approach is to use a bolus of a

different drug such as thiopentone or etomidate for the rapid sequence induction and then use TCI propofol for maintenance of anaesthesia. If ketamine is given, then paradoxical increases in pEEG index value may occur [35].

Switching from inhalational anaesthesia to TIVA

When switching from inhalational anaesthesia to TIVA, it is important to ensure that an adequate brain concentration of the i.v. anaesthetic agent is achieved as the concentration of volatile anaesthetic agent falls, in order to ensure continued anaesthesia. Several reports of awareness have occurred when changing from maintenance with an inhaled anaesthetic to i.v. propofol, for example, to facilitate postoperative transfer to the ICU. All patients identified in NAP5 who had suffered awareness in this manner had received a neuromuscular blocking drug [1]. The commonest cause appeared to be the use of inappropriately low doses of propofol by fixed-rate infusions so that when the anaesthetic effect of the volatile anaesthetic wore off, insufficient propofol had been administered to maintain anaesthesia. This may be avoided by using a TCI pump and increasing the target concentration as the end-tidal concentration of volatile anaesthetic agent falls. If a manual infusion is used, then it will be necessary to give an initial bolus or rapid infusion followed by a decreasing infusion rate. Processed EEG monitoring should be used whenever maintenance of general anaesthesia is changed from an inhaled anaesthetic agent to TIVA in a patient who has received a neuromuscular blocking drug, and should start before the switch is made.

TIVA outside the operating theatre and during transfers

When TIVA is delivered outside the operating theatre, for example, in the radiology or emergency department, the same standards of practice and monitoring should apply as for TIVA given in theatre. Several reports of awareness in NAP5 were from patients who had received propofol infusions outside the operating theatre or during transfer, and the commonest cause of awareness was the use of inappropriately low doses of propofol by fixed-rate infusion. The use of TCI pumps and pEEG monitoring may reduce the risk of awareness in this situation. Monitoring depth of anaesthesia is desirable during the transfer of patients using TIVA who have received a neuromuscular blocking drug. If a portable battery-powered pEEG monitor is not available, then pEEG monitoring during the period leading up to the transfer may assist with the choice of target concentration/infusion rate to be used during transfer.

Magnetic resonance imaging

All anaesthetists administering TIVA during magnetic resonance imaging (MRI) scanning should be competent in the use of this technique within this environment. Anaesthesia for MRI can be maintained by TIVA or inhalational anaesthesia. Some patients requiring MRI scanning will be transferred to the scanner with anaesthesia already maintained with i.v. infusions. In these situations, the options for the maintenance of anaesthesia during scanning include continuing with TIVA or switching to an inhalational anaesthetic; however, extra vigilance is necessary to minimise the attendant risks, such as awareness during the transition period between maintenance agents. Only a few infusion pumps are MRI compatible and this may necessitate using a pump situated outside of the scanning room. Some infusion pumps may be placed within a specially designed radiofrequency shield enclosure (Faraday cage). However, there is a risk of the door of the enclosure occluding infusion lines. The pump display(s) should be visible all times, wherever the pump is situated. The majority of infusion pumps are not allowed to cross the 50 Gauss field strength line.

Specific safety issues of using infusion anaesthesia during scanning are:

1. The i.v. cannula site is not visible. There should be a high index of suspicion for problems with infusions. Where possible the anaesthetist should check the cannula site, infusion tubing and connections between scanning sequences.
2. The anaesthetist may not be able to hear pump alarms, either from the viewing room or from inside the scanning room.
3. Long infusion lines are usually necessary. It is preferable to use a single, long infusion line than to connect multiple shorter lines together. Failure to connect i.v. extensions correctly may cause drug leakages that are not detected by the pump. Serially connected extensions may cause excessive resistance, which when detected by the pump, will result in cessation of the infusion. Long infusion sets specifically designed for TIVA in a MRI scanner are available, and their use is recommended. The high-pressure alarm limit on infusion pumps may be adjustable. The anaesthetist should ensure that an appropriate combination of infusion lines, pump(s) and pump settings is used so that infusions do not stop due to undesired high-pressure alarms caused by the resistance of the infusion tubing.

4 Processed EEG monitoring during anaesthesia in the MRI scanner is not practical as currently available monitors are not MRI compatible.

Obstetrics

This guideline makes no recommendation on the routine use of TIVA in obstetric anaesthesia. This is an area which requires further research. In situations where TIVA is required (e.g. the transfer of an anaesthetised patient to the ICU), the principles in this guideline apply.

General anaesthesia in the intensive care unit (ICU)

These guidelines are not intended to apply to sedation of patients in the ICU.

When general anaesthesia is required in the ICU, for the performance of a surgical or diagnostic procedure, then TIVA is almost invariably used. Similar considerations should apply as for the use of TIVA in the operating theatre. Total intravenous anaesthesia may be administered using either a manual propofol infusion or a TCI pump. However, the propofol pharmacokinetic models in TCI pumps were developed from studies involving healthy patients or subjects. These models are unlikely to accurately predict the plasma propofol concentration in critically ill patients with organ dysfunction. Furthermore, the calculation of predicted concentration will not take account of any propofol administered for ICU sedation before the TCI pump is used. Therefore, titration to clinical effect rather than relying on the estimated drug concentration displayed on the pump is likely to be appropriate. Processed EEG monitoring may be useful in ICU patients receiving TIVA although data on its use are limited.

TIVA in paediatric practice

Anaesthetists providing infusion anaesthesia to children require specific knowledge, recognising the pharmacological and practical differences in this age range.

The two widely used and validated paediatric TCI programmes which target plasma propofol concentration are the Kataria [8] and Paedfusor [9] models. The Kataria model can be used in children aged 3–16 years and weighing 15–61 kg, and the Paedfusor in children aged 1–16 years and weighing 5–61 kg. Teenage children weighing > 61 kg can be managed using the Marsh adult model. Details of the pharmacokinetics and TCI models relevant to paediatrics can be found in Appendix 1.

Pain on induction is common and can be reduced by prior administration of i.v. lidocaine, opioids or nitrous oxide. A target of 5–6 $\mu g.ml^{-1}$ will usually be sufficient for rapid induction of anaesthesia. When switching to TIVA following a gaseous induction it is important to avoid an inadequate effect-site concentration. This may be achieved by setting an initial propofol target of 4 $\mu g.ml^{-1}$ and decreasing the target after the pump indicates that a 2–3 $mg.kg^{-1}$ bolus has been delivered (which typically takes 60–120 s). When using an analgesic adjunct such as remifentanil or a regional block, the propofol target concentration during maintenance can be reduced by up to 50% [34]. This is important in children aged < 12 years, as a target concentration of 5–6 $\mu g.ml^{-1}$ soon leads to accumulation of propofol, resulting in delayed recovery after anaesthesia. A target propofol concentration of 2.5–4 $\mu g.ml^{-1}$ is generally adequate during the maintenance of anaesthesia for cases lasting > 30 min when an opioid is also given. In some circumstances the required target concentrations may fall outside of this range. Titration to effect and clinical judgement are always necessary.

Remifentanil is commonly used with propofol infusions. Children aged < 8 years tend to be less sensitive to its effects, tolerating larger doses when breathing spontaneously and requiring higher doses to produce a given antinociceptive effect [36, 37]. Target-controlled infusion of remifentanil can be administered using adult targets and the Minto model for patients aged ≥ 12 years and weighing ≥ 30 kg. For smaller children, it is necessary to use a manual infusion, for example, 0.2–0.5 $\mu g.kg^{-1}.min^{-1}$ as a TCI model is not yet available.

Propofol-related infusion syndrome (PRIS) is a very rare, but potentially fatal, condition associated with propofol infusion. Interference with mitochondrial energy production leads to rhabdomyolysis, acidaemia and multi-organ failure. Risk factors include: prolonged infusion; high propofol delivery rate (> 6 $mg.kg^{-1}.h^{-1}$); critical illness; low sugar intake; and co-administration of catecholamines and steroids [38]. It is even rarer in the context of TIVA for general anaesthesia. There are several uncommon metabolic conditions, such as mitochondrial disease, fatty acid oxidation disorders and co-enzyme Q deficiency, which cause an increased risk of developing PRIS if propofol infusions are administered. Guidelines for the safe administration of anaesthesia in adults with mitochondrial disease have been published (http://www.newcastle-mitochondria.com/wp-content/uploads/2016/03/Anaesthesia-Peri-Operative-Care-Guidelines.pdf).

Processed EEG monitoring may be used to guide TIVA administration in children. However, the effects of anaesthetic agents on the EEG in children under the age of 1 year differ from those in older children and adults [39]. Processed EEG monitoring is recommended when a neuromuscular blocking drug is administered in children aged > 1 year.

Training and competency in TIVA

All anaesthetists need to be able to deliver TIVA competently as they may encounter situations where administration of an inhaled anaesthetic is not possible. However, surveys have found that not all anaesthetists in the UK and Ireland are gaining adequate knowledge and experience in the use of TIVA [1, 40–42].

Schools of Anaesthesia and training bodies should provide teaching, training and practical experience of TIVA to all Anaesthetic and Intensive Care Medicine trainees. Training in TIVA should be part of core anaesthetic training. Trainee anaesthetists should be competent in the use of TIVA before they are left unsupervised to care for a patient receiving TIVA, including patients anaesthetised by an i.v. propofol infusion for transfer or for anaesthesia outside the operating theatre. Resources are available to help support this learning (http://www.siva.ac.uk/ accessed 25/02/2018).

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. This should form part of their ongoing career-long learning.

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Appendix

Pharmacokinetic principles and models for total intravenous anaesthesia (TIVA)

A pharmacokinetic model is a mathematical description of the distribution, metabolism and elimination of a drug in the body. The pharmacokinetic behaviour of most anaesthetic drugs used for TIVA can be predicted with a three-compartment model (Fig. S1). The drug is administered into the central compartment (V_1), which represents the initial volume of distribution. The second (V_2) and third (V_3) compartments are mathematical constructs explaining rapid and slow redistribution of drug from V_1 into highly perfused and less well perfused tissues, respectively. Rate constants describe the proportion of drug moving between compartments, for example, k_{12} indicates the movement from V_1 to V_2, and k_{21} the movement from V_2 to V_1. A metabolic rate constant (k_{10}) describes the proportion of drug in V_1 that is metabolised or eliminated in any unit of time. Finally, a rate constant k_{e0} describes the transfer from the central compartment to the effect-site (brain). The k_{e0} describes the speed of equilibration between plasma and brain; a higher k_{e0} equates to more rapid equilibration.

These volumes and rate constants are determined from studies in which the drug is administered to volunteers or patients by bolus, infusion or both, following which timed blood samples are taken to assay drug concentrations. In some studies, propofol concentration was measured in whole blood whereas in others it was measured in plasma. There is a slight difference between whole blood and plasma concentrations but for simplicity we have used the term plasma concentration throughout this document. Mathematical modelling software is used to estimate these pharmacokinetic variables in individual subjects, and then to estimate the influence of potential covariates such as body weight and age on these variables. Finally, a population model is developed, incorporating significant covariates. Importantly, different pharmacokinetic models use quite different covariates and pharmacokinetic variables.

Anaesthesia may be induced and maintained either using manual dosing where the anaesthetist determines the bolus dose(s) and infusion rates to be used or using a target controlled infusion (TCI) pump. A TCI pump contains a microprocessor programmed with pharmacokinetic models for relevant drugs.

How does a TCI pump achieve and maintain the programmed plasma concentration?

The user selects the drug and pharmacokinetic model to be used by that TCI pump, and inputs the patient characteristics (covariates) and the desired ('target') initial blood concentration. Once started, the system delivers a bolus as a fast infusion (600–1200 $ml.h^{-1}$) to achieve the target concentration in V_1 (Fig. S2a). During use, the pump software calculates the estimated amount of drug in each compartment every 10 s. It calculates the net amount of drug required over the following 10 s which depends on the target concentration, estimated drug metabolised and the net movement of drug between V_1 and V_2, and between V_1 and V_3. For a stable plasma concentration, the amount of drug metabolised per minute is constant, while the net movement of drug between compartments gradually decreases as gradients equalise. If the target concentration is unchanged, the pump will thus slowly decrease the infusion rate. If the target concentration is increased by the anaesthetist, a new bolus will be administered and the infusion rate increased. If the target concentration is decreased, drug infusion will pause until the plasma concentration is estimated to have fallen to the new target, taking into account metabolism and flux of drug between compartments, at which time the infusion will restart at a lower rate.

What is effect-site targeting?

Effect-site targeting is a TCI mode in which the user inputs a target effect-site (brain) concentration (Fig. S2b). When the effect-site target concentration is increased a bolus of drug is administered, raising the plasma concentration higher than the effect-site target, to hasten the increase in effect-site concentration. However, when plasma concentration targeting is used, a similar effect can be achieved on induction by setting a higher initial plasma target which is reduced after the patient has lost consciousness.

With effect-site targeting, the size of the bolus and the 'overshoot' in plasma concentration depends considerably on the V_1, V_2 and k_{e0} in the pharmacokinetic model. When the effect-site target concentration is decreased, the system stops infusing drug until the estimated effect-site concentration has decreased to the new target.

Key differences between common propofol models

The two most commonly used adult propofol models are Marsh [1] and Schnider [2, 3] models. Both were derived from studies involving healthy adults and did not include obese or older patients [4]. The Marsh model is the simplest. Compartment volumes are scaled to body weight only, and rate constants are fixed. The original model had no k_{e0}. This model is used in the Diprifusor (AstraZeneca Limited, Macclesfield, UK) devices, which only offer plasma targeting, although later versions of the Diprifusor used the Marsh model together with a k_{e0} of 0.26 min^{-1} to calculate and display an estimated effect-site concentration for information purposes. Most newer 'open TCI' pumps that offer effect-site targeting with the Marsh model use a more rapid k_{e0} (e.g. 1.2 min^{-1}) to avoid excessively large loading doses.

The Schnider model includes age, gender, total body weight and height as covariates. V_1 and V_3 are fixed, and thus so are k_{13} and k_{31}. V_2 is influenced by age, and thus so are k_{12} and k_{21}. The metabolic rate constant, k_{10} is influenced by total weight, height and lean body mass (which is turn depends on gender, height and total weight). The Schnider model should routinely be used in effect-site targeting mode. Despite the use of effect-site targeting, for a given target concentration, in most patients, induction doses are similar to those provided by the Marsh model in plasma targeting mode because a smaller V_1 is used in the Schnider model. Thereafter, for the same target concentration, in most patients infusion rates will be somewhat higher with the Marsh model than when the Schnider model is used.

Manual infusion for propofol

For general anaesthesia, the 'Roberts' (or Bristol) regimen for propofol has been commonly used [5]. It involves a loading bolus of 1 $mg.kg^{-1}$ followed by a step-down infusion scheme (10 $mg.kg^{-1}.h^{-1}$ for the first 10 min, 8 $mg.kg^{-1}.h^{-1}$ for the next 10 min, and then 6 $mg.kg^{-1}.h^{-1}$ thereafter). For an average healthy young adult of normal proportions, this scheme will achieve a plasma concentration of approximately 3 $\mu g.ml^{-1}$. However, that concentration is not appropriate for all patients and may be inadequate for some but excessive for others. The concentration required is affected by other drugs given and in the study by Roberts et al., temazepam premedication, intravenous fentanyl and inhaled nitrous oxide were all given in addition to propofol [5].

If the anaesthetist using a manual infusion wishes to achieve a higher plasma propofol concentration, an additional bolus is administered and the infusion rate increased. To reduce the plasma propofol concentration, the infusion is paused for a period and then recommenced at a lower rate. However, determining the size of an additional bolus or the duration of a pause in an infusion, and the subsequent infusion rates is difficult.

TCI and manual infusion for remifentanil

The Minto model is a validated model for remifentanil, and can be used for plasma or effect-site targeted TCI in patients aged $\geq$ 12 yr, and weighing $\geq$ 30 kg [6, 7]. Covariates incorporated in this model include age, weight, height and sex. From the latter three covariates, lean body mass is calculated, but the calculation is only valid in patients who have a BMI $<$ 35 $kg.m^{-2}$ in females and $<$ 42 $kg.m^{-2}$ in males.

Typical maintenance doses of remifentanil are in the order of 0.08–0.25 $\mu g.kg^{-1}.min^{-1}$ which are equivalent to plasma concentrations of approx. 2–6 $ng.ml^{-1}$ (Table S1). In older patients, the plasma concentration resulting from a given infusion rate is higher, whilst in children it is lower. In young or middle-aged healthy adults of normal proportions, a plasma concentration appropriate for tracheal intubation (approximately 6 $ng.ml^{-1}$) can be achieved reasonably quickly by giving a loading dose in the form of an initial rapid infusion of 0.5 $\mu g.kg^{-1}.min^{-1}$ with a step down to 0.25 $\mu g.kg^{-1}.min^{-1}$ after 3 min. Giving a bolus loading dose manually from a syringe is not recommended because that technique may result in an excessively high peak remifentanil concentration leading to severe bradycardia and chest wall rigidity.

Paediatric considerations

Compartment volumes in children are about twice the size of those in adults in comparison with their body weight. This difference gradually reduces from around 12 years of age, reaching adult values at 16 year. Thus, to achieve a given

plasma concentration, children require larger propofol bolus doses and initial infusion rates relative to body weight than adults.

During prolonged infusion of propofol in children aged < 12 year, drug accumulation in the peripheral compartment occurs to a greater extent than in adults. Therefore, when the infusion is stopped, it typically takes longer in a child for the propofol concentration to decline to a level at which consciousness is regained than in an adult [8, 9]. Propofol requirements can be reduced, and speed of emergence improved, by remifentanil (or other opioid) co-administration, and the use of other drugs such as nitrous oxide, ketamine and α_2 agonists. Most children regain consciousness at an estimated propofol plasma concentration of approximately 2 $\mu g.ml^{-1}$, but this can vary considerably from 1 to 3 $\mu g.ml^{-1}$ depending on inter-individual differences and the use of adjunctive drugs [10].

The two widely available and validated paediatric models which target plasma propofol concentration are Kataria [11] for ages 3–16 years and Paedfusor [12] for ages 1–16 years. Kataria can be used in children weighing 15–61 kg and Paedfusor 5–61 kg. Effect-site targeting has not been implemented in paediatric TCI systems. For an average length procedure in a young child, both models administer approximately 50% more propofol than in an adult using the Marsh model, which is why adult models should not be used in this age group. If a propofol manual infusion is used in children the initial bolus and subsequent infusion rates need to be higher than in adults [13].

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Remifentanil plasma concentrations ($ng.ml^{-1}$) achieved at steady state, estimated by the Minto model in a 70-kg, 170-cm, 40-yr-old male patient for various fixed infusion rates. In older patients, the plasma concentration resulting from a given infusion rate is higher, whereas in children it is lower.

Figure S1. Schematic illustration of a three-compartment model, with an added effect-site compartment. Constants k_{xx} represent the proportion of drug that diffuses from one compartment into another, per unit of time.

Figure S2. Illustration of plasma (a) and effect-site (b) TCI-targeting modes when the Marsh model is used with 1% propofol and a k_{e0} of 1.2 min^{-1}. In both figures, the target concentration is set to 3 $\mu g.ml^{-1}$ at time 0, increased to 6 $\mu g.ml^{-1}$ at 5 min, and then decreased to 3 $\mu g.ml^{-1}$ at 10 min. Plasma concentrations are represented by the solid lines, effect-site (brain) concentrations by dotted lines and infusion rates by dashed lines. With effect-site targeting, over- and undershoot of the plasma concentration, above and below the target (effect-site) concentration, is used to achieve more rapid changes in the effect-site concentration. k_{e0}, constant relating to the speed of equilibration between plasma and effect-site drug concentrations; TCI, target-controlled infusion.

Guidelines

Safe practice of total intravenous anaesthesia (TIVA) 2018

The Society for Intravenous Anaesthesia

Association of Anaesthetists

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