CHAPTER
18

Total intravenous anaesthesia

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HEADLINE

18.1. There were 28 Certain/probable or Possible reports of AAGA involving intravenous anaesthesia. In 21 of them total intravenous anaesthesia (TIVA) was used for induction and maintenance of anaesthesia, and in seven the patient received both a volatile anaesthetic and an IV infusion of propofol. Twenty four cases occurred in theatre and an important cause was failure to deliver the intended dose of propofol. One quarter of cases occurred when anaesthesia was initiated or continued outside the operating theatre (where volatile anaesthesia would have been impossible). In these cases the commonest cause of AAGA was the administration to a paralysed patient of an inappropriately low dose infusion, usually as a fixed-rate infusion. More than three-quarters of the 28 cases of AAGA were considered to have been 'preventable'. All anaesthetists need to be skilled in the administration of intravenous anaesthesia, and these results suggest that is not currently the case.

BACKGROUND

18.2 In the UK and Ireland general anaesthesia for procedures in the operating theatre is most commonly induced by administering a bolus of an intravenous anaesthetic drug, and then maintained with an inhaled anaesthetic agent. An alternative technique is to use an intravenous drug for both induction and maintenance of anaesthesia (total intravenous anaesthesia). Propofol is preferred because there is usually a relatively rapid and clear-headed recovery even after prolonged infusion, and for the purposes of this chapter the term TIVA indicates anaesthesia maintained by propofol infusion unless stated otherwise. During some surgical procedures (e.g. on the airway) administration of an inhaled anaesthetic is not practical and TIVA is required.

18.3 In addition when general anaesthesia is administered during patient transfer or in an area which does not have the equipment required to deliver inhaled anaesthesia, TIVA must be used as there is no practical alternative.

18.4 The blood (and therefore brain) propofol concentration required for anaesthesia varies between individuals and cannot be predicted in advance. However, some patterns are evident. Older patients on average require a lower propofol concentration than younger patients, while other anaesthetic, sedative and opioid analgesic drugs reduce drug requirement during surgery (Reves et al., 2007). A co-infusion of remifentanil may be administered and at higher doses markedly reduces the propofol concentration needed for anaesthesia (Milne et al., 2003). More major or stimulating surgery increases the propofol concentration required while effective regional anaesthesia reduces it. The propofol (blood or brain) concentration required for maintenance of anaesthesia

will usually be between 1.5 and 6.0 µg/ml (Reves et al., 2007).

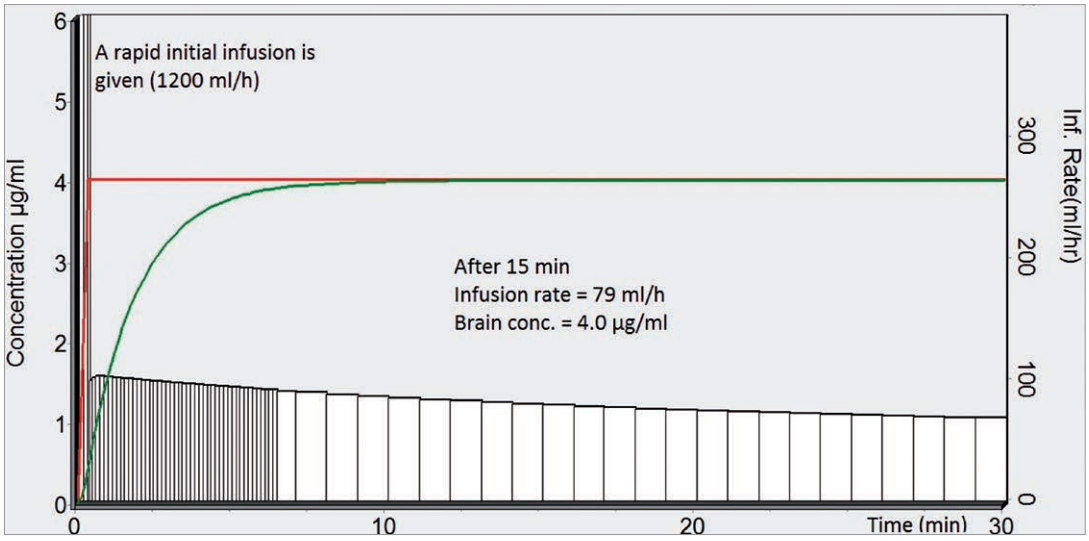
18.5 TIVA may be administered by giving an initial bolus followed by a continuous infusion at a set rate in ml/h or mg/kg/h. Regimens have been designed to maintain a constant blood propofol concentration. For example, Roberts et al. (1988) described a manual infusion scheme for a target blood propofol concentration of 3 µg/ml, consisting of a loading dose of 1 mg/kg followed immediately by an infusion of 10 mg/kg/hour for 10 minutes, 8 mg/kg/hour for the next 10 minutes and 6 mg/kg/hour thereafter. An overall mean blood propofol concentration of 3.67 µg /ml was achieved within two minutes and maintained stable for the subsequent 80–90 minutes of surgery.

18.6 However in practice, adjustments to vary the blood propofol concentration are often necessary in response to clinical signs and/or the output of a depth of anaesthesia (DOA) monitor. Making such adjustments is awkward when a manual infusion regimen such as that of Roberts et al. (1988) is used. To increase the blood propofol concentration an additional bolus is required followed by a higher infusion rate. However, it can be difficult to calculate the necessary size of bolus and new infusion rate. To decrease the blood propofol concentration the infusion is paused for a period and then resumed at a lower infusion rate. Again, calculating how long to stop the infusion for and how much to reduce the rate by can be difficult.

18.7 The first commercially available target controlled infusion (TCI) system, the 'Diprifusor' (Glen, 1998), was introduced in 1996 for the induction and maintenance of anaesthesia in adults. TCI pumps incorporate a pharmacokinetic model of the distribution of propofol in the body and its elimination from the body. The anaesthetist enters patient variables such as the body weight and the required blood concentration 'target'. The software in the pump then calculates the size of the bolus (delivered as a rapid infusion) and the infusion rates required to achieve and maintain this. The actual blood propofol concentration typically differs somewhat from the calculated concentration displayed by the pump, but raising or lowering the blood concentration is easier than with a manual infusion regimen. The anaesthetist simply increases or decreases the target blood concentration. Administration of propofol by TCI pump has become a commonly used technique for TIVA in the operating theatre in the UK and Ireland.

18.8 TCI pumps also display the brain or effect site concentration of propofol, and in some pumps a target effect site may be chosen rather than a target blood concentration. Different pharmacokinetic models may be incorporated in the pumps, and there is debate about which achieves the closest match between the calculated and actual propofol concentrations. Figure 18.1 shows a simulation of the blood and effect site concentrations over the first 30 minutes of an anaesthetic.

Figure 18.1. Pharmokinetic simulation of an anaesthetic in which the target blood propofol concentration in a 70 kg patient is set to 4 µg/ml and then left unchanged. Time in minutes is on the x-axis and propofol concentration on the y-axis. The red line is the calculated blood concentration and the green line the calculated brain or effect-site concentration. The white blocks show the infusion rate of 1% propofol in ml/h as indicated on the y-axis on the right (TIVAtrainer Marsh pharmacokinetic model with a blood-brain equilibration rate constant of 0.6/min)



18.9 There are several methods by which TIVA anaesthesia may be administered (intermittent bolus, fixed rate infusion, infusion based on a manual algorithm, TCI and mixtures of these). This means that TIVA-anaesthesia may encompass several heterogeneous techniques, which might not be equivalent in efficacy or safety, and may hamper understanding of the technique. We are not aware of any robust recommendations that make one of these techniques the 'standard'.

18.10 There has been debate about whether or not the use of TIVA is associated with a higher incidence of AAGA than an intravenous induction/volatile maintenance technique. Sandin and co-workers reported similar incidences of AAGA with both techniques in their studies (Sandin et al., 2000; Nordström et al., 1997). However, other studies have suggested that the incidence of AAGA may be higher with TIVA (Errando et al., 2008, Morimoto et al., 2011)

18.11 Whereas with inhaled anaesthetic drugs the end tidal anaesthetic gas (ETAG) concentration may be continuously measured and displayed, similar monitoring is not available for TIVA. If the delivery of propofol to the patient is interrupted for example by disconnection between the infusion tubing and intravenous cannula, then this may go undetected as the infusion pump will continue to display adequate delivery, and alarm systems do not recognise this problem (Safe Anaesthesia Liaison Group, 2009). Table 18.1 lists some of the possible problems that can arise with delivery of the IV anaesthetic.

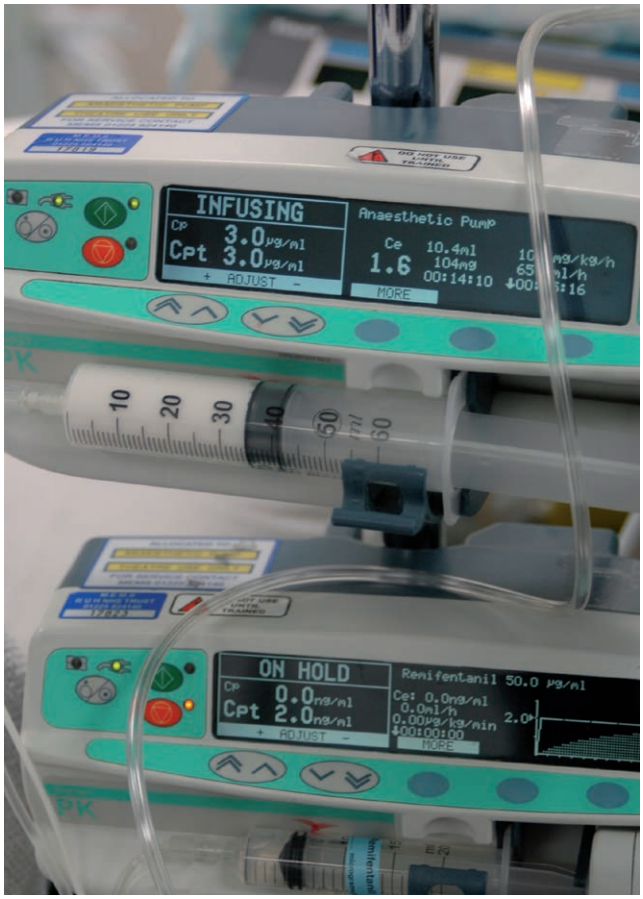
18.12 One potential advantage of TIVA is that it ensures a continuous delivery of anaesthetic from the moment of induction. In contrast, a technique of intravenous induction followed by volatile anaesthetic maintenance necessarily involves a period when the former is switched to the latter. The concentration of intravenous agent declines while the concentration of volatile anaesthetic rises but there is potential for a 'gap' during which inadequate anaesthetic is administered. This is more likely if there is a delay in starting the volatile agent (e.g. a delay in turning on the vaporiser) or a delay in the agent reaching the patient (e.g. prolonged airway management). A similar gap may occur on changing from a volatile to an intravenous anaesthetic for instance for transfer at the end of surgery.

18.13 Because of the problems inherent in monitoring TIVA delivery, discussed above, the use of specific DOA monitoring is often recommended when TIVA is used. The National Institute for Health and Care Excellence (NICE) expressed the view that patients receiving TIVA were not at higher risk of AAGA, but recommended that the use of DOA monitors should be an option in these patients (NICE, 2012).

Table 18.1. Potential problems with drug delivery from intravenous anaesthesia pumps

Problem	Prevention / Detection / Solution
IV cannula disconnection or 'tissuing' (i.e. subcutaneous rather than IV infusion)	Cannula or central venous catheter visible and accessible during procedure
Disconnection of infusion tubing from pump or at an intermediate connection point	Pump and tubing connections visible; use of Luer lock syringes
Low battery / pump paused	Modern pumps usually have an audible alarm
Occlusion of IV cannula; tap or clamp closed	Pump high infusion pressure alarm
'False' occlusion alarm because of small cannula or long infusion tubing	Adjustable high infusion pressure alarm and users trained in their adjustment
'Backtracking' of propofol into intravenous fluid infusion tubing when the infusions are given through the same cannula/catheter lumen	One-way valves to prevent back-tracking
Use of 1% propofol in a pump which has been programmed for the use of 2% protocol or vice versa	Stocking of only one concentration of propofol
When using infusions of both propofol and remifentanil, insertion of the propofol syringe into the pump programmed for remifentanil and vice versa.	Prominent pump displays with the drug name and perhaps colour-coding of the pump LCD displays to match the colour of the syringe labels

Pump programming errors may lead to failure to deliver intended anaesthesia during TIVA and risk AAGA



NAP5 CASE REVIEW AND NUMERICAL ANALYSIS

18.14 The distribution of reports of AAGA by anaesthetic technique (volatile vs TIVA +/- neuromuscular blockade +/- processed EEG monitoring) is discussed in detail in Chapter 20, DOA and is not repeated here.

18.15 In the Activity Survey (Sury et al., 2014), 5.8% of general anaesthetics were by propofol infusion. In theatres 90% of these were TCI techniques, while in radiology, intensive care units (ICU) and emergency departments (ED) only 18% were.

18.16 In Class A and B there were 28 reports of AAGA associated with TIVA or mixed volatile/intravenous techniques. Twenty-four were in the operating theatre setting: 19 Certain/probable AAGA and 5 Possible AAGA (all the possible AAGA cases were TCI infusions).

18.17 One report of AAGA described intermittent thiopental and suxamethonium, but as this is a technique of only historical interest it is not included in the analysis in this chapter

18.18 Table 18.2 presents the distributions of TIVA techniques in the Activity Survey and in Certain/probable and Possible reports of AGAA. Here we compare only cases and Activity Survey data to the theatre setting, as denominator data may be less reliable outside theatres. Comparing these

Table 18.2. Techniques used to maintain anaesthesia in those UK Activity Survey cases (actual results) where general anaesthesia was induced in theatres, and Certain/probable and Possible cases of AAGA. *counted as TIVA (952; 6.6%)

	AAS		AAGA		Ratio AAGA: Activity Survey
	n	%	n	%	
Volatile agent	13,479	93.1 %	112	82.4%	0.89
Propofol infusion TCI*	764	5.3%	14	10.3 %	1.94
Propofol infusion not TCI*	82	0.6 %	2	1.5 %	2.50
Intermittent boluses*	106	0.7 %	1	0.7%	1.00
Both volatile agent and propofol infusion	48	0.3 %	7	5.1%	17.00
Total	14,479	100%	136	100%	–

distributions enables a ratio to be calculated as a crude indicator of whether a particular technique is 'over-represented' (i.e. a higher risk technique).

18.19 Excluding cases where intermittent bolus propofol was used, of the 27 cases who received TIVA, or volatile anaesthesia followed by TIVA 25 (93%) received a neuromuscular blocking drug. In the single case involving intermittent boluses of propofol no NMB was given.

18.20 Notwithstanding the small number of AAGA cases in some categories, Table 18.2 indicates an approximate two-fold over-representation of cases where a propofol infusion was used for maintenance, as compared with the Activity Survey. However the most striking over-representation is for cases where there was a mix of volatile and TIVA technique.

18.21 Anaesthetics comprising a mixture of volatile and intravenous technique were most commonly cases where patients were transferred using a propofol infusion after maintenance with volatile. In one case (not shown in Table 18.2) no agent at all was used for transfer, leading to an experience of awake paralysis on arrival in ICU.

18.22 In eight cases, maintenance of anaesthesia with a volatile agent would not have been possible for all or part of the case. These were one case of bronchoscopy in theatre, three cases of maintaining anaesthesia after surgery and four cases of anaesthesia outside theatre.

Anaesthesia in theatre

18.23 There were 11 Certain/probable cases involving propofol infusions alone. Certain/probable reports are those with the greatest case detail and for which causation is clearest. These cases are important in the discussion of increased risk of AAGA and TIVA and therefore are all briefly described here.

18.24 In these cases the causes of AAGA were: (i) failure to deliver the intended dose of propofol (four cases), (ii) mistiming of propofol administration in a paralysed patient (four cases), and (iii) under-dosing of propofol when mixing remifentanil with propofol in the TCI infusion (i.e. a 'non-standard' regime (three cases).

(i) Two cases were as a result of the 'tissuing' or 'failure' of the IV cannula and in at least one of these the cannula was not visible during surgery; in a third case the anaesthetist was using TCI propofol and remifentanil, and mistakenly reversed the syringes; in the fourth case the anaesthetist completely forgot to connect the propofol infusion to the IV cannula before 'induction' and administration of an NMB.

(ii) There were two cases in which an NMB had been administered and paralysis produced before loss of consciousness at induction, and two in which the patient experienced awake paralysis because the NMB was still acting when they woke up after surgery.

(iii) In one case propofol and remifentanil were mixed in the same syringe and in another both were given as boluses followed by a manual infusion; in the final case a spinal-epidural was combined with a fixed rate propofol infusion (in ml/h with no bolus recorded) where the patient breathed spontaneously via a 'Hudson' type mask.

18.25 The modified NPSA score for patient harm was none in six of the cases, moderate in two and severe in three. Eight of the eleven cases were judged preventable.

18.26 The other eight Certain/probable reports in theatre comprised: one case of intermittent boluses of propofol and seven cases with a combination of intravenous and volatile agents (two administered concurrently and five sequentially). This latter group included three patients who had received a volatile anaesthetic in theatre which was turned off towards or at the end of surgery and replaced with a continuous fixed rate infusion of propofol for transfer elsewhere. In one case the cause of AAGA was thought to be a 'tissued' IV cannula while in the others it was thought that inadequate doses of propofol were given to maintain anaesthesia in patients who were still paralysed by NMBs (see below – anaesthesia outside theatre).

18.27 All five possible cases used TCI TIVA.

Anaesthesia outside theatre

18.28 Four Certain/probable reports were of patients who received a propofol infusion for intended general anaesthesia in the ICU, radiology department or the ED. The cause of the awareness in most of these cases appeared to be propofol doses that were too low. A further three similar cases, classified as ICU cases, are discussed in Chapter 17, (ICU), and there is considerable overlap of the results and messages.

18.29 The Activity Survey indicates that 4% of all general anaesthetics and 12% of all TIVA general anaesthetics were induced outside theatres. As seven (23%) of the AAGA cases involving TIVA were induced outside theatre (four Certain/probable cases and three ICU cases) this suggests that TIVA general anaesthesia outside theatre is of higher risk for AAGA than TIVA in theatres.

18.30 In contrast to the cases where TIVA was used during operations in theatre, when it was used for anaesthesia outside theatre (and for transfer after theatre) non-TCI fixed rate infusions were used in all cases and in some of these cases no bolus 'loading dose' was given.

TIVA may need to be administered in areas outside the normal operating theatre environment. In NAP5 this setting was a risk factor for AAGA during TIVA

After an emergency procedure in theatre, a patient was transferred to ICU for post-operative ventilation. The following day the patient reported recollection of voices ('needs to go to ICU') and being unable to move but no pain. Anaesthesia had been maintained in theatre with desflurane in oxygen/air, and then a propofol infusion (with no initial bolus documented) had been started for transfer to ICU. An NMB had been given and not reversed. It was thought that the awareness probably resulted from rapid elimination of desflurane and an insufficient dose of propofol to maintain anaesthesia.

18.31 In two of the reports, patients experienced awareness during general anaesthesia for an MRI scan. Not only were low doses of propofol infused but the propofol infusion pumps alarmed and stopped infusing, probably because of the extra resistance of additional infusion tubing required to reach from the pumps to the patient in the scanner. In each case some additional boluses of propofol were given but were not sufficient to prevent AAGA. Management would likely have been affected by the anaesthetist not being beside the patient during the scans.

DISCUSSION

18.32 Failure to ensure delivery of the intended anaesthetic dose was an important cause of AAGA during TIVA in theatre, in one case in the recovery room and two outside theatre. This has been reported previously (Sandin & Norström, 1993). Several of the potential causes of interruption of delivery of TIVA to patients described by SALG and shown in Table 18.1 – were seen in reports to NAP5. Specific training and attention to detail in the practical aspects of ensuring drug delivery during intravenous anaesthesia is required.

18.33 Other cases occurred when TIVA was initiated too late or stopped too early in patients affected by NMB drugs. Similar cases were also seen when intravenous induction agents were used prior to volatile maintenance (see Chapter 19, NMB and Chapter 8, Induction) so this problem is not exclusive to TIVA.

18.34 There were relatively few reports of AAGA in theatre associated with inadequate dosing while using a TIVA TCI technique – except as a result of cannula problems and errors in the use of infusion pumps. The Activity Survey confirms that a TCI is the commonest TIVA technique in theatre. Taken together, this suggests there is not a frequent problem with the TCI pharmacokinetic models leading to underdosing. In contrast, a number of cases of AAGA were reported with non-TCI infusions, despite these being used as intended by the operator.

18.35 Reports of AAGA in association with TIVA infusions often involved 'mixed' intravenous and volatile techniques, either sequentially or concurrently. Overall there appeared to be a 17-fold over-representation. However, we cannot be certain how reliably the Activity Survey captured conversion of a volatile anaesthetic to an intravenous one, so this finding might be interpreted cautiously.

18.36 One quarter of Certain/probable and possible reports described intravenous anaesthesia initiated outside the theatre or initiation of intravenous anaesthesia after surgery for transfer and treatment elsewhere. In these cases administration of volatile anaesthesia would have been difficult or impossible. Three similar cases were included in the ICU section (see Chapter 17, ICU). Taken together this highlights 'out of theatre' use of TIVA as a higher risk setting for AAGA.

18.37 In these cases the commonest cause of AAGA was inadequate dosing: both due to failure to administer a loading dose of propofol and/or

administration of a notably low dose fixed rate infusion. Propofol was routinely administered using a non-TCI method and often as fixed-rate infusion: infusions of 10ml/hr were seen in several cases. The Activity Survey confirms that TCI infusions are rarely used during TIVA outside theatres (see para 18.15). None of these patients received DOA monitoring.

18.38 Figures 18.3 and 18.4 show pharmacokinetic simulations of the predicted blood and brain propofol concentrations following doses such as those seen in AAGA cases during transfer or anaesthesia outside theatre. The predicted brain concentrations achieved are well below the range usually required for adequate anaesthesia in theatre (i.e. 1.5–6 µg/ml). The use of manual rather than TCI infusions in these cases may have made administration of an appropriate dose more difficult.

18.39 Because it is necessary to use intravenous anaesthesia during (sometimes unplanned) transfers and in locations where the facilities for volatile-based anaesthesia are not available, it is important for all anaesthetists to be trained in the administration of TIVA. However, surveys of anaesthetic trainees in the UK suggest that most consider their training in the technique to be inadequate and that they lack confidence in using TIVA (Madhivathanan et al., 2010).

18.40 Preventability was assessed by the Panel in 25 of the 28 Certain/probable, and possible reports involving TIVA: 19 (75%) were considered to have been preventable. The commonest contributory factor identified was education and training.

18.41 The use of processed EEG DOA monitors, in the context of intravenous techniques, is discussed further in Chapter 20, DOA.

18.42 In summary: observed crudely the data from NAP5 might be interpreted as indicating an excess of reports of AAGA when anaesthesia is maintained with TIVA. However deeper analysis indicates that such cases often occur in situations when there is no alternative to maintenance of anaesthesia with TIVA; when mixed volatile/TIVA techniques or non-TCI techniques are used; when the result of poor technique in the use of TIVA, or when there are frank errors. Intravenous anaesthesia initiated outside theatre was over-represented. There is less evidence to suggest an excess of reports of AAGA when TIVA is used correctly and with a target controlled infusion.

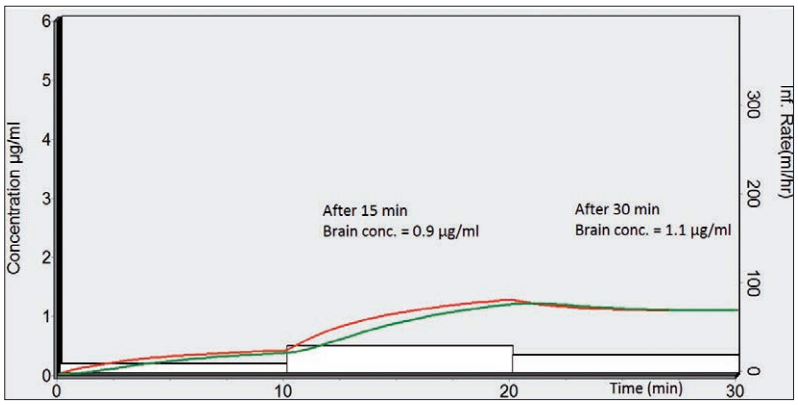


Figure 18.3. Pharmokinetic simulation of an anaesthetic in a 70 kg patient in which there is no propofol bolus dose, an infusion of 1% propofol at 10 ml/h for 10 min then 30 ml/h for 10 min then 20 ml/h for 10 min. Time in minutes is on the x-axis and propofol concentration on the y-axis. The red line is the calculated blood concentration and the green line the calculated brain or effect-site concentration. The white blocks show the infusion rate of 1% propofol in ml/h as indicated on the Y-axis on the right. (TIVAtrainer Marsh pharmacokinetic model with a blood-brain equilibration rate constant of 0.6/min)

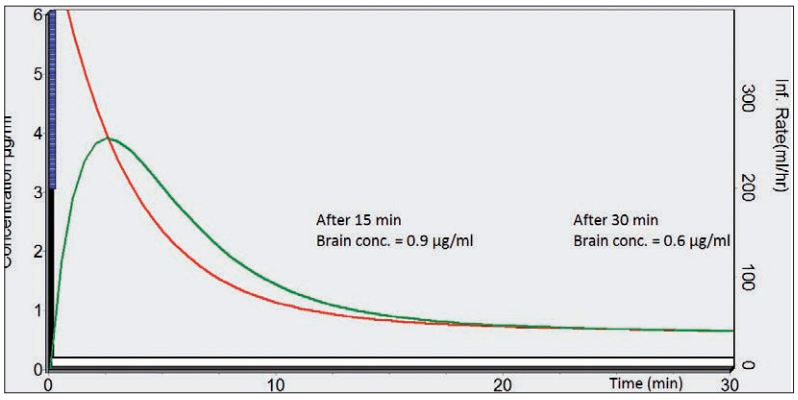


Figure 18.4. Pharmokinetic simulation of an anaesthetic in a 120 kg patient in which a bolus of 200 mg of propofol is followed immediately by a continuous infusion of 10 ml/h of 1% propofol. Time in minutes is on the x-axis and propofol concentration on the y-axis. The red line is the calculated blood concentration and the green line the calculated brain or effect-site concentration. The white blocks show the infusion rate of 1% propofol in ml/h as indicated on the y-axis on the right. (TIVAtrainer Software Version 9-B; Marsh pharmacokinetic model with a blood-brain equilibration rate constant of 0.6)

IMPLICATIONS FOR RESEARCH

Research Implication 18.1
Research should compare the performance and outcomes from target-controlled infusions vs manual infusion regimens when TIVA is used during patient transfers and for anaesthesia outside the operating theatre.

Research Implication 18.2
Research should identify suitable protocols for maintaining adequate anaesthesia when changing from volatile to TIVA during an anaesthetic.

RECOMMENDATIONS

RECOMMENDATION 18.1
All anaesthetists should be trained in the maintenance of anaesthesia with intravenous infusions.

RECOMMENDATION 18.2
When using total intravenous anaesthesia, wherever practical, anaesthetists should ensure that the cannula used for drug delivery is visible and patient at all times.

RECOMMENDATION 18.3
Depth of anaesthesia monitoring should be considered in circumstances where patients undergoing TIVA may be at higher risk of AAGA. These include use of neuromuscular blockade, at conversion of volatile anaesthesia to TIVA and during use of TIVA for transfer of patients.

RECOMMENDATION 18.4
The relevant anaesthetic organisations should establish a set of standards and recommendations for best practice in the use of TIVA.

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