



Target Controlled Infusion (TCI) in anaesthetic practice

New edition






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Convenience and control
of intravenous anaesthesia with 'Diprivan'

Diprivan
propofol

New edition 1999



‘Diprifusor’ (TCI Software/Subsystem/System) has been developed to further enhance the convenience and control of intravenous anaesthesia with ‘Diprivan’. ‘Diprifusor’ is incorporated in anaesthesia syringe pumps manufactured by SIMS Graseby, Fresenius Vial and ALARIS Medical Systems.

Further information about anaesthesia syringe pumps incorporating ‘Diprifusor’ is available from the manufacturers

SIMS Graseby Limited

Colonial Way
Watford
Herts, UK

Fresenius Vial SA

Le Grand Chemin
38590 Brézins
France

ALARIS Medical Systems

The Crescent, Jays Close
Basingstoke
Hants, UK

‘Diprivan’, ‘Diprifusor’ and the stylized D with arrow logo are trade marks of the AstraZeneca group of companies.

Further information about ‘Diprivan’ and clinical aspects of ‘Diprifusor’ TCI is available on request

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Introduction

Many advances in anaesthesia have arisen from developments in pharmacology (e.g. improved drugs) or technology (e.g. improved mode of administration). The introduction of a new drug has often been the stimulus for the gradual development of more precise delivery systems.

Historically, inhalational anaesthesia developed from intermittent administration using a Schimmelbusch mask to continuous administration using a vaporizer so as to provide a steady depth of anaesthesia. Further refinements included the introduction of vaporizers with automatic compensation for changes in pressure and temperature. Measurement of end-tidal partial pressure of volatile drugs is an example of drug delivery based on an estimate of target concentration. The basic principle is that the vaporizer setting – and target concentration – is adjusted on clinical grounds to provide optimum control of anaesthesia.

Similarly with intravenous anaesthesia, the development of delivery systems has lagged behind that of drug development. Intermittent administration of bolus doses is still common. Infusion pumps do allow the administration of a wide range of infusion rates as well as bolus delivery. But maintenance of optimum anaesthetic conditions is difficult whenever drug is titrated according to the changing needs of the patient. Frequent recalculations of infusion rate may be required with corresponding “manual” alterations to the pump controls.

‘Diprivan’ (propofol) was introduced in 1986 as an intravenous anaesthetic agent for the induction and maintenance of general anaesthesia. Widespread clinical experience with ‘Diprivan’ has established the benefits relating to the quality of control of anaesthesia and the quality of recovery. Onset and offset of anaesthetic effects are rapid and reliable. ‘Diprivan’ offers rapid emergence, a low incidence of postoperative nausea and vomiting (PONV) and a potential reduction in time to discharge. Total intravenous anaesthesia (TIVA) based on ‘Diprivan’ has the general advantage of avoiding occupational exposure to inhalational agents.

Manual control of ‘Diprivan’ infusion for maintenance of anaesthesia is sometimes viewed as “not as easy” as using a vaporizer with an inhalational agent. There is, therefore, a general need for a more convenient method for infusing intravenous agents.

Target Controlled Infusion (TCI) systems have been developed to provide improved convenience and control during intravenous anaesthesia. The basic principle is that the anaesthetist sets and adjusts the target blood concentration – and depth of anaesthesia – as required on clinical grounds. Infusion rates are altered automatically according to a validated pharmacokinetic model.

‘Diprifusor’ (TCI Software/Subsystem/System) for ‘Diprivan’ is such a development. ‘Diprifusor’ is the first commercially available TCI system and is incorporated in syringe pumps from major manufacturers. ‘Diprifusor’ is designed to be as convenient to use as a vaporizer; the skills required in varying target blood concentration according to response have been learned during administration of volatile agents from a calibrated vaporizer.

This monograph reviews aspects of ‘Diprivan’ relevant to TCI as well as outlining the principles of TCI before summarising practical information and clinical studies of ‘Diprifusor’ TCI for induction and maintenance of anaesthesia in adult patients.

The terms manually-controlled infusion, manual infusion and manual control are used to designate manual adjustment of infusion rates for anaesthesia syringe pumps administering ‘Diprivan’.

'Diprivan'

The distinct pharmacokinetic profile and clinical benefits of 'Diprivan' were major factors in the development of 'Diprifusor' as an improved delivery system over manual control of infusion. This section summarises these aspects of 'Diprivan'.

Pharmacokinetic properties

Target Controlled Infusion (TCI) is a logical approach to the development of improved administration techniques for an intravenous anaesthetic agent. TCI is based on an understanding of the agent's pharmacokinetic properties.

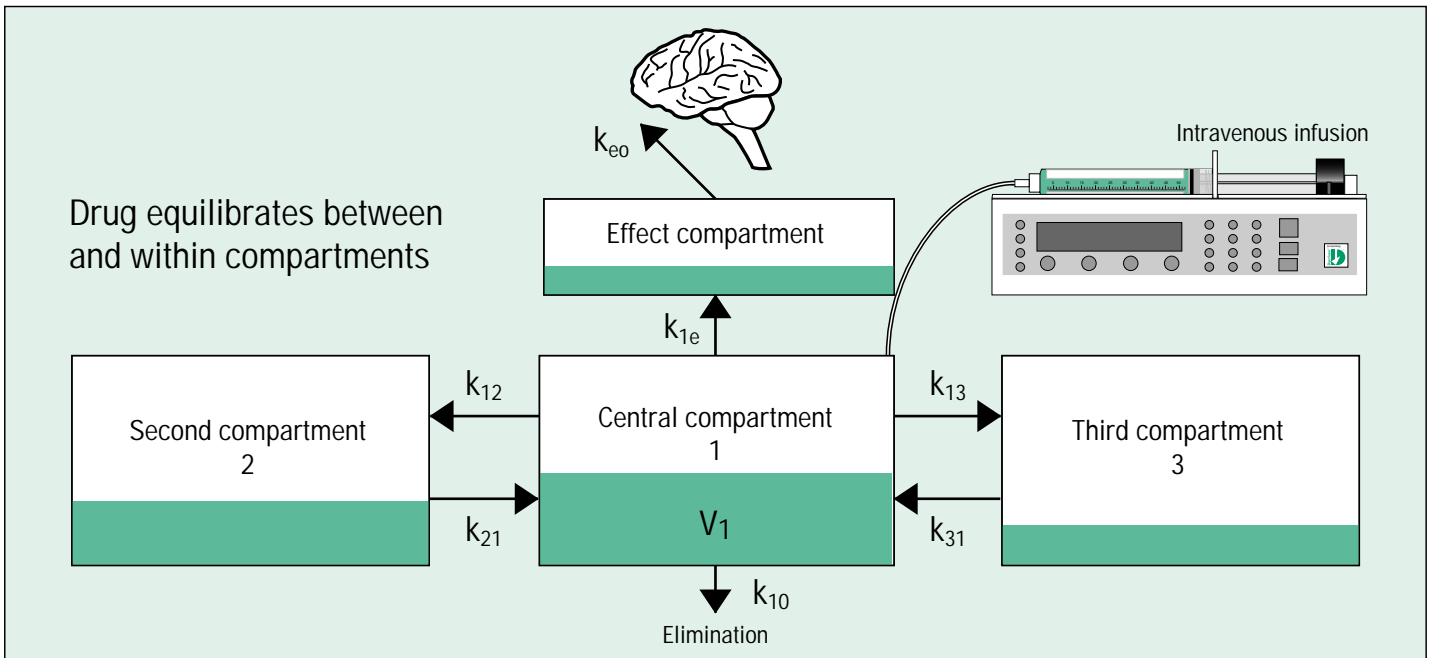
The pharmacokinetics of 'Diprivan' have been evaluated extensively in a variety of disease states and patient groups after either bolus doses or continuous infusions.¹

'Diprivan' undergoes rapid and extensive distribution – and rapid metabolic clearance.

After a bolus dose, there is a rapid, initial distribution phase which represents distribution to highly perfused organs such as the brain (effect site). This is followed by a slower, second phase representing redistribution to less well perfused tissues such as muscle. Significant metabolism occurs during the second phase. Recovery from anaesthesia is due to extensive redistribution from the brain and to metabolic clearance.

The decline of blood concentrations after a bolus dose or termination of infusion can best be described by an open, three-

Figure 1. Open, three-compartment pharmacokinetic model: schematic representation



Central compartment represents blood or plasma

Second compartment could represent the highly perfused tissues

Third compartment could represent the poorly perfused tissues

k_{21} , k_{12} , k_{31} , k_{13} and k_{1e} are intercompartmental distribution rate constants i.e. they describe the proportions of drug exchanged between compartments per unit time

k_{10} is the elimination rate constant from the central compartment

k_{eo} is the rate constant describing drug elimination from the effect site.

Pharmacokinetic properties

Table 1. Pharmacokinetic parameters for 'Diprivan' (propofol) incorporated in 'Diprifusor' TCI Software*

V_1 Volume of central compartment	228 ml kg ⁻¹
k_{10} Elimination rate constant from the central compartment	0.119 min ⁻¹
k_{e0} Elimination rate constant from the effect compartment	0.26 min ⁻¹
Intercompartmental distribution rate constants	
k_{12}	0.114 min ⁻¹
k_{21}	0.055 min ⁻¹
k_{13}	0.0419 min ⁻¹
k_{31}	0.0033 min ⁻¹

* © University of Glasgow.

compartment model² (Figure 1). Such a model is utilised for 'Diprifusor' TCI. Based on specific pharmacokinetic parameters, a microprocessor calculates the changing drug distribution and elimination and the amount of drug needed to achieve and maintain the desired blood concentration.

Various models for 'Diprivan' with differing sets of pharmacokinetic parameters have been published by independent research groups. Standardisation and validation of pharmacokinetic parameters are essential for the clinical application of a TCI system.

Three models³⁻⁵ were examined in consultation with principal academic groups. Based on computer simulation⁶ and a direct

comparison of predicted values with measured values obtained from a study in which the same infusion profile was used in all patients,⁷ the "Marsh" model³ was selected for the development of 'Diprifusor'. A subsequent comparative study⁸ endorsed the accuracy of the "Marsh" model for TCI using a validated method⁹ to compare the accuracy of different models. The pharmacokinetic parameters incorporated in software (© University of Glasgow) used in 'Diprifusor' are listed in Table 1.

Clinical benefits

The rapid onset and short duration of action of 'Diprivan' enable good control of the depth of anaesthesia and good quality of recovery.

Quality of induction

Induction of anaesthesia with 'Diprivan' is characteristically smooth, rapid and reliable. Induction time is related to the speed of injection. For instance, with a fixed dose of 2.5 mg/kg, mean induction time was 30.8 seconds with an injection time of 20 seconds and 58.4 seconds with an injection time of 80 seconds.¹⁰ The overall quality of induction was rated as good or adequate in about 90% of patients who received 'Diprivan' 2.0 mg/kg or 2.5 mg/kg.¹¹ Patients over 55 years of age may require lower doses of 'Diprivan'.

The additive or synergistic hypnotic effects of 'Diprivan' with benzodiazepines or opioids is well documented.¹

There is interindividual variability with respect to plasma or blood concentration and response during induction with 'Diprivan'. The anaesthetic endpoint of loss of consciousness (loss of response to verbal or tactile stimuli) occurred in 50% of patients with plasma concentrations ($C_{p_{50}}$ or EC_{50}) ranging from 2.7 to 3.4 µg/ml.¹²⁻¹⁴ Lower plasma concentrations were required to achieve loss of eyelash reflex¹² whereas higher plasma concentrations were required to prevent movement on skin incision.¹⁴

Quality of maintenance

Maintenance of anaesthesia with 'Diprivan' is characterised by smooth, easy control of the depth of anaesthesia and good haemodynamic stability. 'Diprivan' has been used to maintain anaesthesia during a wide variety of surgical procedures ranging from short procedures lasting only 10 minutes to major procedures lasting several hours.

Numerous empirically-designed bolus or infusion administration schemes have been reported for 'Diprivan'. Infusion rates have been adjusted manually within a typical range of 4 to 12 mg/kg/h.

The pharmacokinetic profile enables blood concentration – and hence depth of anaesthesia – to respond rapidly to changes in the infusion rate of 'Diprivan'. When fixed-rate infusion of 'Diprivan' commences, there is a rapid increase in blood concentration followed by a more gradual increase. A linear relationship between the infusion rate of 'Diprivan' and steady-state blood concentrations has been demonstrated; with continuous infusions of 3, 6 or 9 mg/kg/h for at least 2 hours, blood concentrations were 2.1, 3.6 and 5.9 µg/ml.¹⁵

In practice, infusion rates of 'Diprivan' are titrated against the clinical response of the individual patient because of interpatient variability as well as differences in the degree of surgical stimulation and the use of supplementary analgesics.

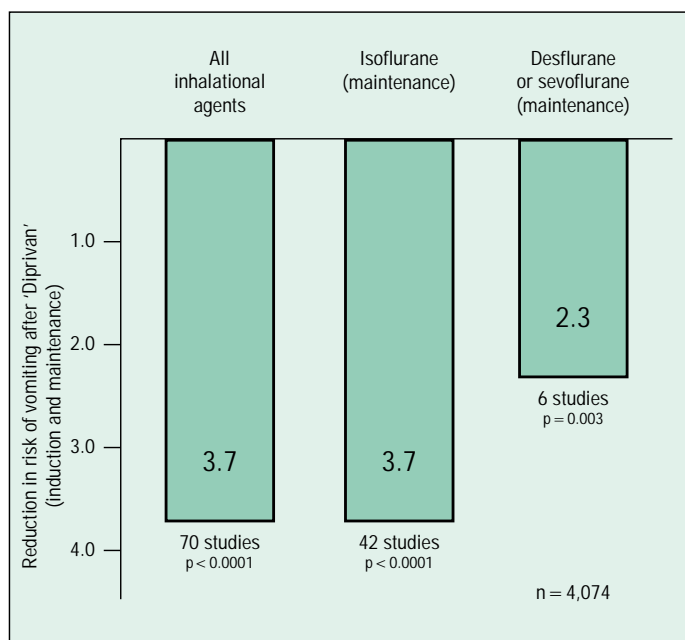
Quality of recovery

Extensive clinical experience has established that anaesthesia with 'Diprivan' is characterised by a prompt, clear-headed recovery.

All stages of recovery have been evaluated, especially in investigations of 'Diprivan' in the induction and maintenance of anaesthesia for day-case surgery (see reviews^{1,16}). Early recovery (or emergence), as defined by time to eye-opening and orientation, is rapid and predictable after 'Diprivan'.¹⁷⁻²⁰ Fast intermediate recovery, including the early return of cognitive and psychomotor function and early time to discharge,¹⁷⁻²⁰ has been demonstrated after 'Diprivan'. Features of the late stage of recovery (i.e. complete return to the preoperative state and resumption of normal activities) have also been studied after 'Diprivan'.

Clinical benefits

Figure 2. Reduced risk of postoperative vomiting after anaesthesia with 'Diprivan' compared to inhalational agents²¹

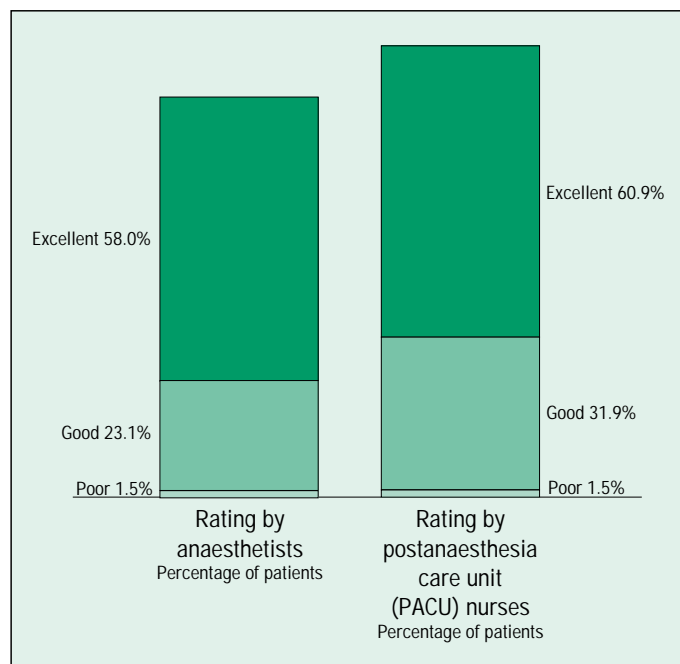


Meta-analyses of studies that recorded the incidence of vomiting (total of 70 studies comprising 4,074 patients). Log-odds ratios and confidence limits were calculated and presented in the paper together with the represented values for reduction in risk.

The occurrence of adverse events such as postoperative nausea and vomiting (PONV) has a major influence on the quality of recovery – and on the duration of postoperative stay.

Importantly, there is a low incidence of PONV associated with 'Diprivan' anaesthesia.^{17–20} A recent meta-analysis²¹ of randomised controlled studies of anaesthetic agents showed that there was a 2.7-fold reduction in the risk of nausea and/or vomiting for patients who were induced and maintained with 'Diprivan' compared with those maintained with inhalational agents ($p < 0.0001$). Patients were 3.7 times less likely to vomit postoperatively after anaesthesia with

Figure 3. Quality of recovery after 'Diprivan'²²



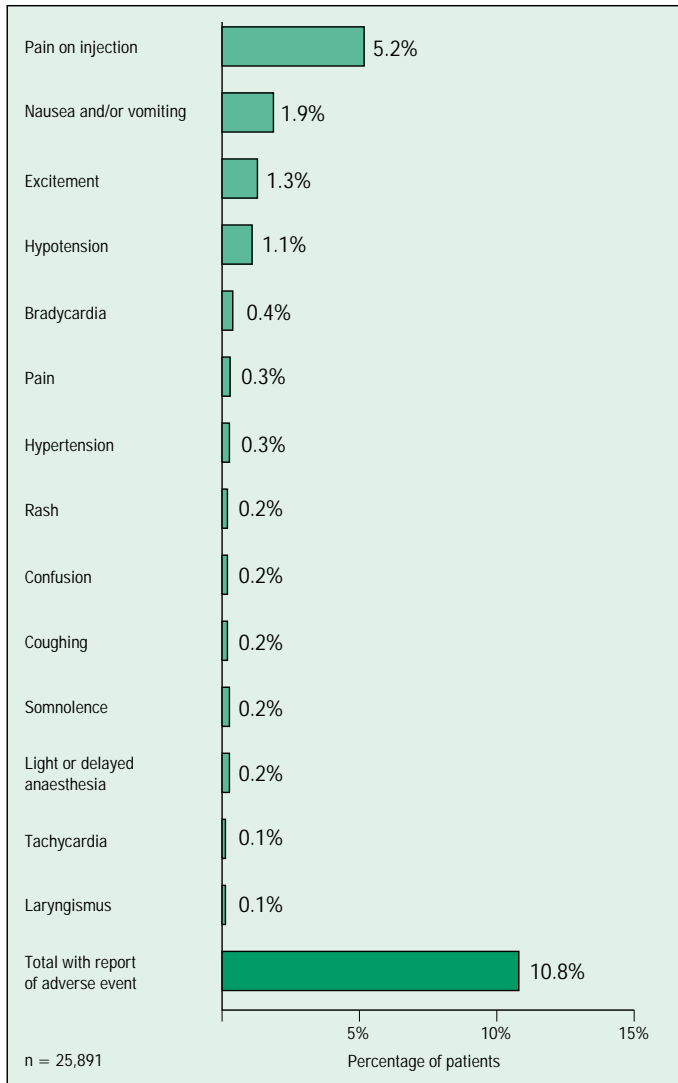
Total population of 25,981 surgical patients (age range 18–80 years) and 1,819 anaesthetists (from 1,722 institutions in USA). Recovery information was missing from 17.4% of data collection forms completed by anaesthetists and from 5.7% of forms completed by PACU nurses.

'Diprivan' than after an inhalational agent (Figure 2); the difference was evident ($p < 0.0001$) for adults (57 studies, 3.5-fold risk reduction) and for children (13 studies, 5.7-fold risk reduction).²¹ Also, the risk of vomiting was significantly reduced after 'Diprivan' compared with isoflurane (Figure 2) or the newer agents, desflurane or sevoflurane (Figure 2).²¹

An American post-marketing survey²² of over 25,000 patients who received 'Diprivan' included a global evaluation by anaesthetists and nurses of patient recovery (Figure 3). Quality of recovery was rated as excellent or good for the vast majority of the patient

'Diprivan'

Figure 4. Most commonly reported adverse events associated with administration of 'Diprivan'²²



population (Figure 3). Anaesthetists were more likely to rate recovery as poor when emergence from anaesthesia was delayed or there was postoperative confusion.

Nurses were more likely to rate recovery as poor when nausea and/or vomiting occurred or there was postoperative pain. Rating of recovery as poor by both anaesthetist and nurse was noted for only 0.6% of patients.

The survey²² also confirmed low frequencies of adverse events (Figure 4) often associated with rating of recovery as poor; examples included nausea and/or vomiting (1.9%), light or delayed anaesthesia (0.2%), postoperative confusion (0.2%), somnolence (0.2%) and excitement (1.3%) associated with 'Diprivan'.

The clinical and economic benefits resulting from the favourable recovery profile of 'Diprivan' are summarised (Table 2) with particular reference to anaesthesia for day-case surgery.

Measurements of blood concentrations during recovery after 'Diprivan' infusion have demonstrated that patients awoken when concentrations are in the region of 1 to 2 µg/ml.^{27,28}

Table 2. Clinical and economic benefits resulting from recovery profile of 'Diprivan' for anaesthesia in day-case surgery

Clinical benefits of 'Diprivan'

- Short time to recovery¹⁷⁻²⁰
- Low incidence of PONV¹⁷⁻²⁰
- Short time to discharge¹⁷⁻²⁰

Economic benefits

- Saves nursing time in the recovery room^{20,23,24}
- Limits the need for anti-emetic therapy^{25,26}
- Allows patients an early return to work²⁴

Target Controlled Infusion (TCI)

The basic rationale for Target Controlled Infusion (TCI) of an intravenous anaesthetic agent is to enable the anaesthetist to alter the depth of anaesthesia in as simple a manner as using standard volatile anaesthetics delivered via calibrated vaporizers. With TCI, induction and maintenance are a continuous process with a single agent unlike the separate use of an intravenous agent for induction and an inhalational agent for maintenance.

A TCI system should improve both the convenience of administration and ease of control of anaesthesia compared with conventional infusion techniques.

This section reviews the scientific principles and research background to TCI in anaesthesia.

Development of concept and terminology

The concept of pharmacokinetic models with mathematical equations to describe infusion schedules to provide a target concentration in blood of an intravenous drug originated in 1968.²⁹ By the early 1980s, a group in Bonn, Germany, had suggested and demonstrated that a computer-controlled infusion pump could deliver complex infusion schedules of intravenous anaesthetic agents.³⁰ Subsequently, numerous investigators in Europe and the USA reported experimental systems linking computer software and hardware to the operation of an infusion pump for delivery of intravenous drugs to the patient.

Acronyms

Researchers have referred to the basic concept of utilising a pharmacokinetic model and microprocessor (= computer) to control an infusion pump, by the following acronyms:

- CATIA – Computer Assisted Total Intravenous Anaesthesia
- TIAC – Titration of Intravenous Agents by Computer
- CACI – Computer Assisted Continuous Infusion
- CCIP – Computer Controlled Infusion Pump.

The acronym TCI (Target Controlled Infusion) is now used as a broader term to describe the technique for the continuous control of the concentration in blood or plasma of infused drug.³¹ TCI involves the use of a microprocessor to manage the pump. Instead of setting an infusion rate in terms of mg/kg/h, the anaesthetist enters the following:

- Body weight of the patient
- Age of the patient
- Required blood concentration of the drug (= target blood concentration in $\mu\text{g/ml}$).

Key components

Software and hardware are required to achieve and maintain a target blood concentration of an anaesthetic by balancing the rate

Table 3. The key components of a TCI system and considerations for commercial development

Key components – basic software and hardware

- Pharmacokinetics – a validated model with specific parameters for drug
- Algorithm(s) to control infusion rate
- “Control unit” i.e. software and microprocessors for above
- Infusion pump
- “Communication” system between “control unit” and infusion pump
- User interface for input of patient data and target blood concentration

Considerations for development of a commercial system

- Standardisation of the pharmacokinetic model for a particular drug
- Validation of the system software and production processes
- Safety mechanisms in the unlikely event of malfunction of components
- Integration of basic software and hardware with infusion pump to provide a reliable and portable unit
- User interface to be as simple to operate as the controls of a vaporizer
- Convenient syringe presentation of drug
- Documentation (e.g. prescribing information, user guides) for drug and device
- Automatic recognition device for correct drug identification and usage

Development of concept and terminology

of infusion with the processes of distribution and elimination. This requires information about the pharmacokinetic properties of the drug in appropriate patients.

Software in the microprocessor incorporates a pharmacokinetic model and a specific set of parameters for the drug to be infused. The microprocessor continuously calculates the variable infusion rates required to achieve a predicted blood concentration. An algorithm controls the operation of the infusion pump so that infusion rates are altered automatically to achieve this blood concentration. The TCI system maintains the blood concentration until a new target is set by the anaesthetist.

The choice of pharmacokinetic model and infusion control algorithm are major determinants of the performance of a TCI system. Different models and algorithms produce different actual blood concentrations even if the same target blood concentration is selected.

These key components of any TCI system in terms of software and hardware are summarised (Table 3).

Considerations for commercial development

Aspects of safety, reliability and user convenience are foremost considerations for the development of a commercial TCI system (Table 3).

Standardisation of the amount of drug delivered at a particular target setting (i.e. the pharmacokinetic model) for all systems used with a given drug is an important requirement. The system software and production processes must be validated. A basic safety mechanism will shut the system down in the unlikely event of malfunction of software or hardware. Integration of the basic hardware and software with the infusion pump is important for a commercial system; an integrated system should be more reliable and portable than configurations used for research purposes.

The user interface should, ideally, be as simple to operate as the controls of a vaporizer. Obviously, a suitable syringe presentation of the drug with documentation such as amended prescribing information and user guides for drug and pump are required for a commercial TCI system. Finally, an automatic recognition device for identification of the correct drug and concentration would provide an important safety feature.

Defining TCI for anaesthesia

TCI is **not** a system for the complete computer control of anaesthesia. When using TCI, the anaesthetist adjusts the target blood concentration of drug and titrates to clinical effect. A TCI system is a convenient tool to assist the anaesthetist in adjusting the depth of anaesthesia. Control still rests with the anaesthetist, who uses clinical signs or more sophisticated means of monitoring. As such, a rigorous definition of TCI, as applied to anaesthesia, is as follows:

Definition of Target Controlled Infusion (TCI)

When applied to anaesthesia, TCI is an infusion system which allows the anaesthetist to select the target blood concentration required for a particular effect, and then to control depth of anaesthesia by adjusting the requested target concentration.

Benefits of TCI

Several potential benefits of TCI over manually controlled infusion (Table 4) have been summarised in authoritative reviews^{32,33} and textbooks.^{34,35} Benefits can be considered mainly in terms of convenience in use and control of anaesthesia.³²

Convenience in use

The simplicity of operation and ease of titration to anaesthetic effect with a TCI system mean that it can be likened to an “intravenous vaporizer”.³⁶

Simple to operate

With TCI, the anaesthetist simply sets the initial target blood concentration required for an intravenous drug in a similar way to setting the percentage concentration of an inhalational agent with a vaporizer. The target concentration is achieved and maintained with no further intervention required by the user.

Easy to titrate the level of anaesthesia

Titration of the target concentration and therefore the depth of anaesthesia is rapid and predictable with a TCI system. Setting a new target concentration produces a proportional change in the depth of anaesthesia. This is unlike the situation with inhalational anaesthetics where “overpressure” is often used to titrate rapidly to deeper levels of anaesthesia.

TCI facilitates the direct transfer of fundamental skills learnt with inhalational agents. Target concentration is readily increased in anticipation of stimulating events (e.g. placement of laryngeal mask airway or surgical incision). Similarly, target concentration can be readily decreased to tailor the level of anaesthesia needed towards the end of surgery.

A TCI system is easier to operate than a manually controlled infusion pump. The required target value can be achieved accurately and rapidly – and then maintained. In contrast, manual control with

Table 4. Benefits of TCI

<p>Convenience in use</p> <p>Practical aspects</p> <ul style="list-style-type: none"> ● Simple to operate ● Easy to titrate the level of anaesthesia ● Displays calculated blood or plasma concentrations ● Compensates for interrupted infusion ● Avoids the need for time-consuming calculations ● Continuous process from induction through to maintenance
<p>Control of anaesthesia</p> <p>Theoretical aspects</p> <ul style="list-style-type: none"> ● Good control of depth of anaesthesia ● Gives stable anaesthesia ● Improved control of cardiovascular and respiratory parameters ● Induction phase can be used to predict maintenance effects

Compiled from references 32–35

a constant infusion rate produces fluctuations in blood concentration in relation to distribution and elimination of drug. Also, manual control with variable infusion rates can often require calculations for alterations. Supplementary bolus doses may be needed to increase the depth of anaesthesia.

Displays calculated blood concentration

With TCI, there is a constantly changing display of calculated (or predicted) blood concentration. The system may also provide information on the time required to reach the desired target concentration. This advisory information from a TCI system, in conjunction with clinical signs, enables the anaesthetist to assess

Benefits of TCI

progress and whether further changes are required i.e. the anaesthetist “knows where he/she is up to.”

Displays calculated effect-site concentration

Some systems have the facility to display the propofol concentration calculated to exist at the effect-site in the brain. This concentration tends to lag behind the blood concentration when the target concentration is increased, and provides an indication of the degree of equilibration which exists at a given time between blood and brain concentrations of propofol.

Pharmacodynamic effects are likely to be more closely related to effect-site concentrations but guidance in ‘Diprivan’ prescribing information on setting of target concentration refers only to target blood concentrations. However, the provision of advisory information on effect-site concentration should assist the anaesthetist in making more rational adjustments to the blood target setting e.g. delaying an increase in target if the effect-site concentration indicates only partial equilibration.

Predicts patient waking time

Some TCI systems have the facility to display predictive information about the time required to achieve a lower calculated concentration if the infusion were to be stopped (decrement time). The anaesthetist can then easily modify drug administration to optimise the speed of recovery. The decrement time displayed is influenced by the expected waking concentration which can be adjusted by the anaesthetist.

Compensates for interrupted infusion

When an infusion is interrupted (e.g. for a change of syringe), a TCI system may make automatic compensation. When infusion stops, the system continues to predict the blood concentration. When infusion restarts, the rate is adjusted automatically to maintain the desired

target concentration. With manually controlled infusion, such a procedure requires skill and experience to manage with a similar degree of precision.

Avoids the need for time-consuming calculations

Infusion rates do not need to be calculated when using a TCI system. The anaesthetist simply selects a target blood concentration. The system makes continuous calculations and controls the rate of drug infusion so as to achieve and maintain the requested target concentration – and the desired level of anaesthesia. With manual control of an infusion pump, calculations are needed for the initial infusion rate and subsequent adjustments so as to maintain a stable level of anaesthesia.

Potential benefits that arise from the above aspects of ease of use of a TCI system include:

- TCI might allow the anaesthetist more time to focus on monitoring the patient
- TCI might avoid errors in dosage sometimes associated with manual control of complex infusion regimens.

Control of anaesthesia

There are some theoretical or potential clinical benefits of TCI over conventional intravenous drug administration techniques that stem from the predictability of anaesthetic effects during induction and maintenance.

Good control of depth of anaesthesia

TCI may assist precise control of the depth of anaesthesia by allowing the anaesthetist to make rapid and predictable changes simply by setting a new target blood concentration. It is easy to make proportional changes in target concentration so that the level of anaesthesia can be readily titrated as necessary to suit individual patients and varying degrees of stimulation.

Target Controlled Infusion (TCI)

The initial target concentration required to induce anaesthesia is selected according to age, ASA status, premedication and supplementary analgesic administration. Response to the initial target concentration may be used as a guide to subsequent requirements, including during the maintenance phase.

TCI allows the anaesthetist to make small (e.g. 0.1 µg/ml) as well as large changes (e.g. 1 µg/ml) to target concentration at any time. Stimulating events (e.g. surgical incision) may be anticipated by increasing the target concentration. Decreases in target concentrations may be required in response to events such as a fall in blood pressure. Target concentrations can also be reduced as the operation progresses in anticipation of the end of surgery.

Stability of anaesthesia

Theoretically, a more stable blood concentration of drug – and more precise control of the depth of anaesthesia – may be obtained with TCI than with manual methods of administration. The response of the patient to surgical stimulation may be countered rapidly and in a well-controlled manner with TCI. As mentioned, the anaesthetist titrates to effect. The facility to make small increments and decrements to target concentration is useful should the anaesthetist have to “fine tune” the depth of anaesthesia in “difficult” patients e.g. those with respiratory or cardiovascular disease.

Control of cardiovascular and respiratory parameters

The careful control of blood concentrations of drug with TCI could, in theory, improve haemodynamic and/or respiratory stability – and help to avoid dose-dependent events such as apnoea or hypotension.

Conventional bolus administration of an induction dose of an intravenous anaesthetic agent may produce an “overshoot” of blood concentration; with some agents, there is a high attendant risk of apnoea or an undue reduction in blood pressure. Similarly, during

maintenance of anaesthesia, blood concentrations could rise higher or fall lower than intended with manual alteration of the rate of drug administration; there could be a corresponding loss of control of haemodynamic variables. A TCI system provides more predictable blood concentrations. There is automatic reduction of drug administration when the predicted concentration is reached. Manual administration of supplementary bolus doses is not required with TCI. Overall, a TCI technique may provide smoother control of anaesthetic, haemodynamic and respiratory effects than manually adjusted administration techniques.

Other benefits

When an intravenous anaesthetic agent is administered by a TCI technique, induction and maintenance can be viewed as a continuous process.

TCI facilitates TIVA. There is the general advantage with TIVA of avoiding the use of, and therefore occupational exposure to, inhalational agents.

A TCI system makes the administration of an intravenous agent, especially for maintenance, analogous to the use of a vaporizer.

The features of the syringe pumps and microprocessors that form part of a TCI system for anaesthesia may confer additional advantages such as:

- Portability
- Data storage and retrieval capability
- Creation of documentary record at the time of the anaesthetic procedure (e.g. for clinical audit).

The general benefits of TCI as outlined in this section are obtainable with many prototype TCI systems. ‘Diprifusor’ takes these benefits and adds features such as an improved user interface and improved portability, details of which are given in the next section.

TCI systems for 'Diprivan'

Several academic centres, including the University of Glasgow,³⁷ have developed independently and published clinical results^{4, 37-41} on a variety of prototype systems for the administration of 'Diprivan' by TCI (Table 5).

These systems cannot be regarded as equivalent; they utilise different pharmacokinetic parameters and/or different infusion control algorithms.

Prototype 'Diprifusor' TCI systems

The system^{37,42} developed by the University of Glasgow contains a pharmacokinetic model and parameters together with infusion control algorithms that are identical to those incorporated in 'Diprifusor' TCI Software (see also pages 5 and 22). This Software (© University of Glasgow) has been licensed to the manufacturers of 'Diprivan' and was incorporated in the 'Diprifusor' TCI System used in the programme of clinical trials (see pages 35 to 53).

Published studies on the University of Glasgow system refer to a variety of hardware configurations. The software was identical but differing computers and user interfaces evolved. The reported versions of the basic system can be regarded as *prototype 'Diprifusor' TCI systems*. Published experience with 'Diprifusor' or prototype 'Diprifusor' TCI systems extends to over 1,500 anaesthetised adults.*

Other prototype TCI systems for 'Diprivan'

At least six systems other than from the University of Glasgow have been reported and are listed (Table 5). These systems cannot be regarded as equivalent to 'Diprifusor' TCI because of differing pharmacokinetic parameters and/or control software. Published reports describe a total of over 1,000 patients who have been anaesthetised with such prototype TCI systems for 'Diprivan'.*

Extensive experience

Extensive published experience* with prototype 'Diprifusor' and other TCI systems for 'Diprivan' has helped to establish the scientific principles and methods for clinical testing and validation of a commercial system. Relevant publications are summarised in subsequent sections of this review.

* A bibliography of published reports is available on request from AstraZeneca

Table 5. Prototype systems for the administration of 'Diprivan' by TCI

Prototype 'Diprifusor' TCI system <ul style="list-style-type: none"> ● University of Glasgow, UK (GNC Kenny and colleagues)³⁷
Other prototype TCI systems for 'Diprivan' <ul style="list-style-type: none"> ● CACI (computer-assisted continuous infusion, Duke University, USA)³⁸ ● STANPUMP (S Shafer, Stanford, USA)³⁹ ● STELPUMP (JF Coetzee, University of Stellenbosch, South Africa) ● J Schüttler (Bonn, Germany)⁴⁰ ● RM Tackley (Bristol, UK)⁴ ● FHM Engbers (Leiden, Holland)⁴¹

'Diprifusor' TCI – practical aspects

'Diprifusor' (TCI Software/Subsystem/System for 'Diprivan') is the first commercially available TCI system and is incorporated in syringe pumps from leading manufacturers. This section summarises practical aspects including user requirements.

The term '*Diprifusor*' is used when referring to the infusion system whereas '*Diprifusor* TCI' is used to describe the technique of anaesthetising a patient with 'Diprivan' using a 'Diprifusor' system (see also Glossary on page 58). 'Diprifusor' TCI is only indicated for anaesthesia in adult patients (see also Prescribing Information for 'Diprivan').

General requirements for use of 'Diprifusor' TCI

The basic requirements for anaesthetising a patient with 'Diprifusor' TCI are:

- Documentation – information from the pump manufacturer (e.g. Instruction Manual) and from AstraZeneca (current Prescribing Information for 'Diprivan' and Guide for Anaesthetists on administration by 'Diprifusor' TCI)
- Drug – 'Diprivan' Pre-Filled Syringe (PFS) with recognition tag
- Delivery system – commercially-available syringe pump incorporating 'Diprifusor'.

'Diprivan' Pre-Filled Syringe (PFS)

A range of Pre-Filled Syringe (PFS) presentations of 'Diprivan' has been developed. Your local AstraZeneca representative or office will be pleased to advise on available presentations, whether 'Diprivan' 1% or 2% and syringe sizes.

For administration by TCI, a 'Diprivan' PFS first needs to be assembled before loading into a syringe pump that incorporates 'Diprifusor'.

The 'Diprivan' PFS can be used for the following methods of administration:

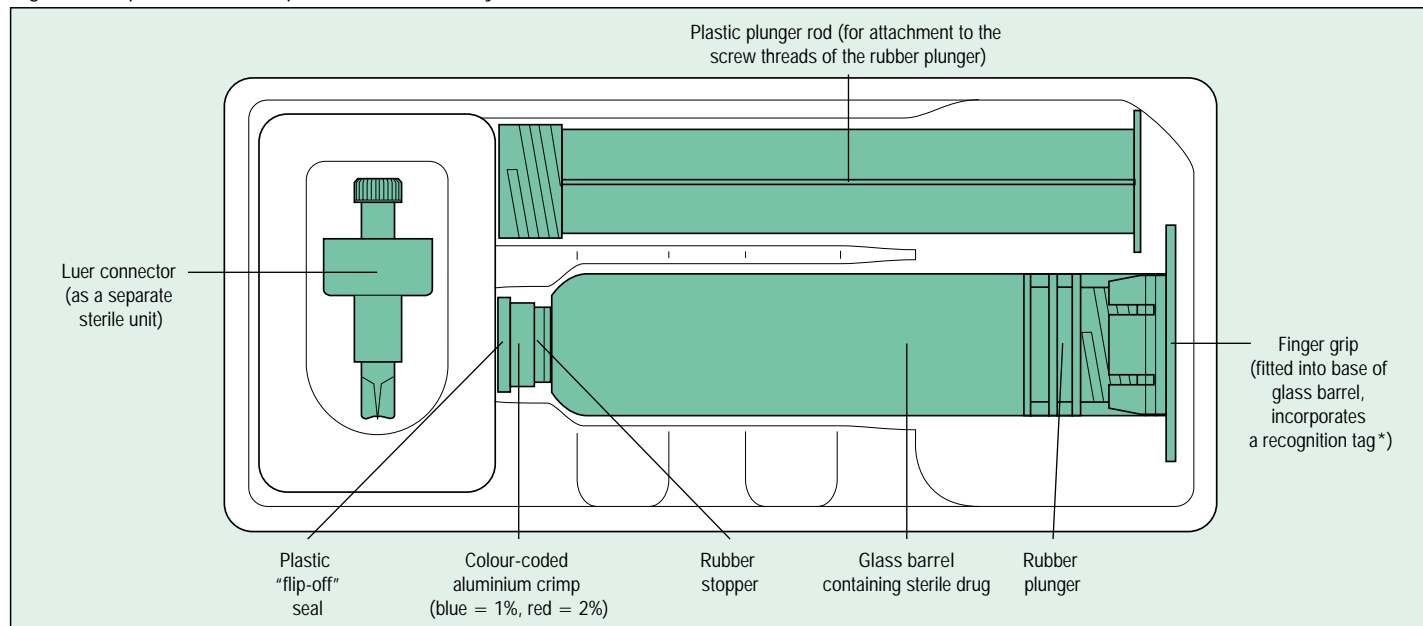
- TCI with a syringe pump that incorporates 'Diprifusor'
- "Manual" control of infusion with compatible syringe pumps i.e. appropriate setting of syringe size as for 50/60 ml B-D Plastipak
- Hand-held.

Regarding pack sizes, most markets will have 1 x 'Diprivan' PFS in a blister tray packed into an outer carton. Packaging includes statements that the 'Diprivan' PFS can be used for 'Diprifusor' TCI.

The blister tray (Figure 5) contains the following components:

- PFS (glass barrel containing sterile drug; rubber stopper and rubber plunger; colour-coded crimp and "flip-off" plastic seal)
- Finger grip (fitted into base of glass barrel, incorporates a recognition tag*)
- Plastic plunger rod (for attachment to the screw threads of the rubber plunger)
- Luer connector (as a separate sterile unit).

Figure 5. 'Diprivan' PFS components in blister tray



'Diprifusor' TCI – practical aspects

Assembly and aseptic precautions

PFS components need to be assembled before use. Detailed assembly instructions are on the back of the carton and with the blister tray. All presentations of 'Diprivan' support microbial growth and are for single use in an individual patient. The exterior of the syringe and the plunger are not sterile. Asepsis must be maintained during assembly – and subsequent use.

The standard aseptic precautions for 'Diprivan' PFS are as follows:

- Single use in an individual patient – the PFS is NOT A MULTIDOSE CONTAINER
- Maintain asepsis for both 'Diprivan' and infusion equipment
- Discard unused drug.

The maintenance of asepsis starts with alcohol swabbing or spraying of the rubber stopper after removal of the “flip-off” plastic seal.

There is a built-in safety feature with 'Diprifusor' to help prevent refilling and multiple-patient use of the 'Diprivan' PFS. A detailed description follows.

Recognition tag in finger grip

The recognition tag* (“electronic marker”) in the finger grip of a 'Diprivan' PFS provides important safety features for correct drug identification and usage.⁴³

The tag is an encoded capsule that is visible on one side of the finger grip. To load a 'Diprivan' PFS into a syringe pump that incorporates 'Diprifusor', the tagged side of the finger grip is inserted into the slot (syringe “ear groove”) and rotated. The display indicates

when the PFS has been loaded correctly. Magnetic resonance “signals” are generated by the tag. An aerial (Figure 6) in the syringe pump detects these signals and relays them to the 'Diprifusor' TCI Subsystem.

The electronics and software in the 'Diprifusor' TCI Subsystem “read” these “signals” and ensure that:

- The syringe pump will only operate in 'Diprifusor' TCI mode with a tagged 'Diprivan' PFS
- The 'Diprifusor' TCI Software recognises whether a 1% or 2% 'Diprivan' PFS has been loaded.

There are two consequences for safe operation:

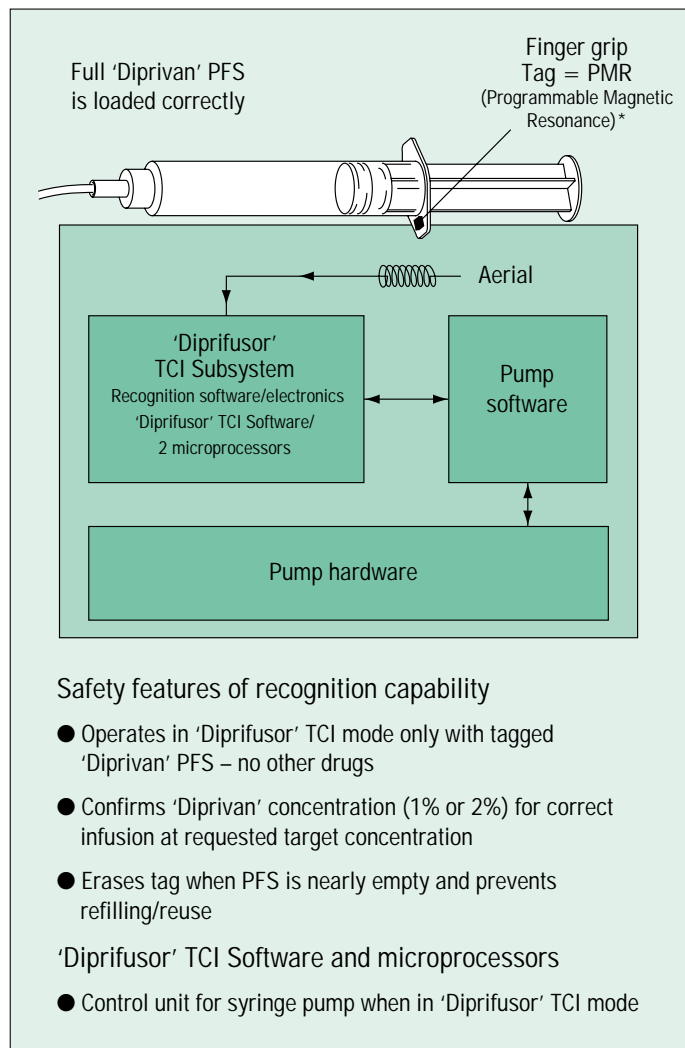
- 'Diprivan' is the only drug that is infused when the syringe pump is in 'Diprifusor' TCI mode
- The automatic confirmation of concentration means that the correct infusion pattern – and target concentration – is obtained irrespective of whether a 1% or 2% 'Diprivan' PFS is loaded.

A third feature enhances patient safety relating to aseptic precautions. When the contents of a 'Diprivan' PFS have been infused, the recognition tag is erased. This helps prevent any refilling and reuse of that syringe in TCI mode whether in the same or another patient. The user can, of course, load another tagged 'Diprivan' PFS. (The syringe pump displays instructions about loading a new 'Diprivan' PFS and 'Diprifusor' provides automatic compensation for the short interruption.)

* Programmable Magnetic Resonance (PMR) tag in the finger grip of a 'Diprivan' Pre-Filled Syringe: this technology is licensed from Scientific Generics Limited.

'Diprivan' Pre-Filled Syringe (PFS)

Figure 6. 'Diprifusor' TCI System



* Programmable Magnetic Resonance (PMR) tag in the finger grip of a 'Diprivan' Pre-Filled Syringe; this technology is licensed from Scientific Generics Limited.

'Diprifusor' TCI System

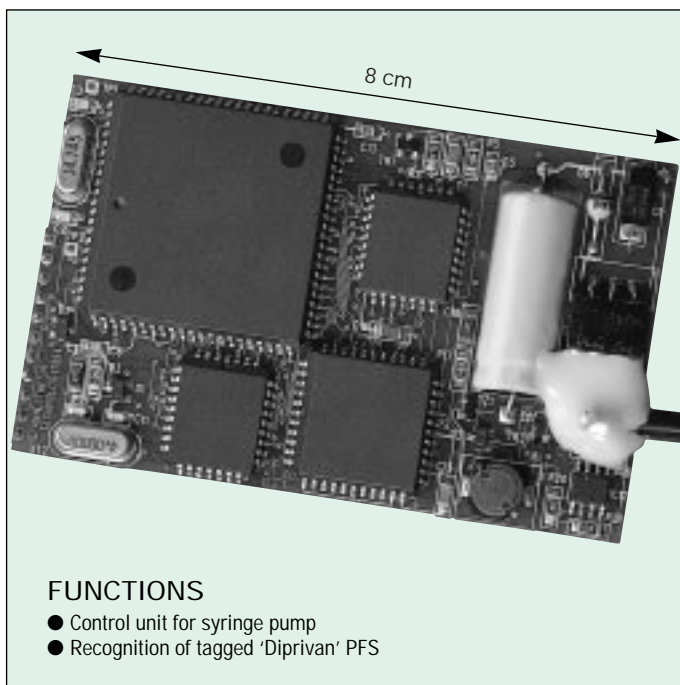
The 'Diprifusor' TCI System is the complete delivery system. Commercial systems integrate the 'Diprifusor' TCI Subsystem with a syringe pump.

'Diprifusor' TCI Subsystem

The 'Diprifusor' TCI Subsystem is the control unit ("controller") for commercially-available pumps that incorporate 'Diprifusor'.

The Subsystem contains electronic components and associated software. It can be considered as a module and measures approximately 8 x 5 x 2 cm (Figure 7). There are two functions:

Figure 7. 'Diprifusor' TCI Subsystem installed in syringe pumps that incorporate 'Diprifusor'



- Recognition of tagged 'Diprivan' PFS with software and electronic components
- Control unit for syringe pump when in TCI mode with 'Diprifusor' TCI Software and 2 microprocessors.

When in TCI mode, the syringe pump is a "slave" to these recognition and control devices. They "communicate" with the pump software to "operate" the pump hardware i.e. infuse 'Diprivan' according to the pharmacokinetic model. But the pump still retains its own special features such as alarms for EMPTY/OCCLUSION, LOW BATTERY etc.

'Diprifusor' TCI Software

'Diprifusor' TCI Software (© University of Glasgow) consists of:

- A three-compartment pharmacokinetic model with a specific set of pharmacokinetic parameters for 'Diprivan' (propofol)
- Two independent infusion control algorithms.

Pharmacokinetics has been reviewed starting on page 4 with details of the pharmacokinetic model (Figure 1) and parameters (Table 1).

Fail-safe mechanism

The two independent algorithms for infusion control run in parallel and provide a fail-safe mechanism to enhance patient safety. Both algorithms use the same pharmacokinetic model but each one operates with different mathematics. This is a more robust and secure situation than if a single algorithm were to be used.

Each control algorithm has its own microprocessor. The second microprocessor checks the output from the first microprocessor. The blood concentrations predicted by the two microprocessors are continuously calculated and compared.

'Diprifusor' TCI System

Should the discrepancy between the two be greater than 20% – for a period longer than 10 seconds – the following happens:

- An alarm is activated
- An error message is displayed
- The infusion stops.

The threshold of 20% for discrepancy between microprocessors is based on the extensive clinical experience obtained by the originators of the software (© University of Glasgow). It is also of the same order as pharmacokinetic variability between patients.

Laboratory studies led to the determination of specifications for delivery performance in terms of cumulative volume delivered (generally $\pm 5\%$ of the ideal volume) at specific time points.⁶ Thus, the tolerance level for the checking algorithm will avoid nuisance alarms during the rapid infusion phase but will detect any major discrepancy resulting from unexpected software errors.

Installation specification

Delivery performance is a measure of whether or not the syringe pump actually delivers drug at the rate that the software calculates that it should. A stringent specification of delivery performance sets the standard which pump manufacturers have achieved to demonstrate that the 'Diprifusor' Subsystem has been installed correctly in their pump.

Percentage infusion error is an index of the amount of 'Diprivan' actually delivered against the ideal amount predicted by a computer simulation. Laboratory studies have shown that there was minimal variability between 'Diprivan' Pre-Filled Syringes and between pumps used in the trial programme.⁶ The specification for commercial systems is such that the error in target concentration which can be attributed to the delivery system should generally be less than 5%. Thus, infusion error is

much less than that resulting from pharmacokinetic variability between patients.

This specification compares favourably with an international standard for anaesthesia machines (ISO 5358) which recommends that: the concentration of an inhalational agent delivered by a vaporizer should not deviate from the indicated value by more than $\pm 20\%$ of the setting, or 5% of the maximum setting, whichever is the greater.⁴⁴

Test protocols were developed for the incorporation of 'Diprifusor' by pump manufacturers. As a medical device, an infusion pump that incorporates 'Diprifusor' meets rigorous technical, delivery performance and regulatory standards to ensure:

- Correct installation
- Equivalent delivery to that of systems used for ZENECA clinical trials
- Operation in a manner consistent with revised Prescribing Information for 'Diprivan'.

Syringe pumps incorporating 'Diprifusor'

Graseby Medical (Watford, UK), Vial Médical (Fresenius Vial, Brézins, France) and ALARIS Medical Systems (Basingstoke, UK) are the manufacturers of the first commercial infusion systems to incorporate 'Diprifusor'.

Graseby has developed the Graseby 3500, a new model based on the established Graseby 3400 Anaesthesia Syringe Pump. Vial Médical has developed the Master TCI as a "sleeve" attachment to upgrade the established Pilot Anaesthesia syringe pump. ALARIS has developed the new IVAC TIVA TCI syringe pump. These pumps have a clearly visible "label" indicating that they incorporate 'Diprifusor' – with the 'Diprifusor' brand name and logotype (stylized D with arrow logo). Performance standards for drug delivery are identical.

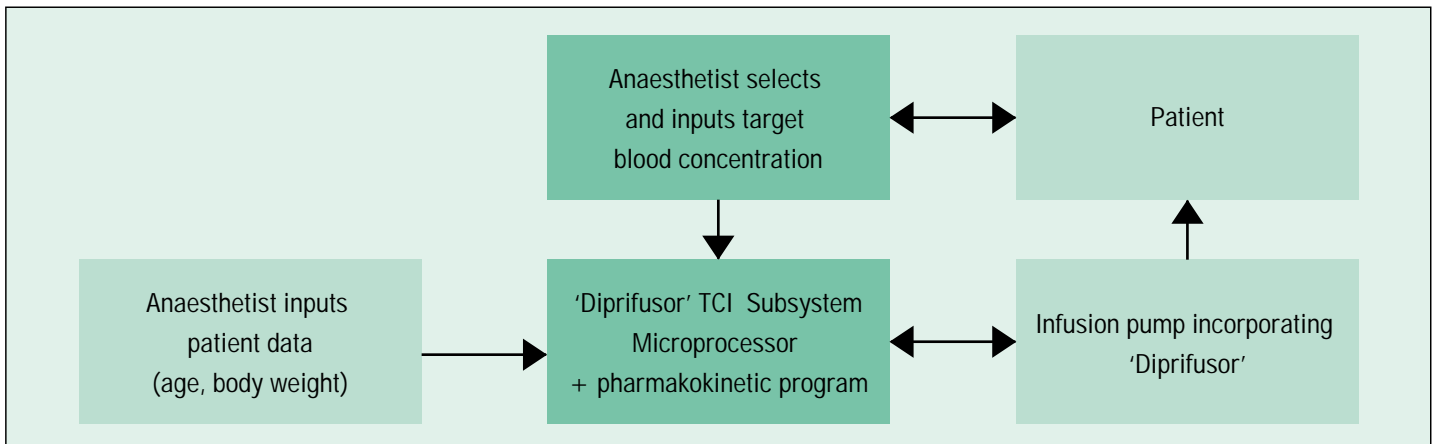
Details of the availability, features and operation of these pumps can be obtained from the local representative or office of each manufacturer. The following brief review serves to illustrate aspects of the user interface relevant to the administration of 'Diprivan' by TCI.

General principles

The following operations are required for infusion of 'Diprivan' using a pump that incorporates 'Diprifusor':

- Correct loading of tagged 'Diprivan' PFS
- Priming of the infusion line with 'Diprivan' (i.e. expelling air from the infusion line while disconnected from the patient). Priming should be done with the BOLUS or PURGE button of the pump to take up any piston "backlash"
- Selecting or ensuring that the pump is in 'Diprifusor' TCI mode
- Checking that the pump recognises 'Diprivan' 1% or 2% and prompts the necessary user inputs
- Inputting and entering
 - age of patient in years
 - body weight of patient in kilograms (kg)
 - initial target concentration in micrograms per millilitre of blood/plasma ($\mu\text{g}/\text{ml}$)
- Starting infusion.

Figure 8. Main components of a 'Diprifusor' TCI system



Syringe pumps incorporating 'Diprifusor'

In practice, the start-up procedures are much quicker and easier than implied by the above list. The actual sequences, displays, prompts and mode of input differ with the three pumps. But they are all “user friendly” and documented fully in the manual provided by the manufacturer.

Current users of the relevant anaesthesia pumps will readily understand operation in 'Diprifusor' TCI mode.

Patient data

The pumps will only accept patient data within these limits:

- Age 16–100 years
- Body weight 30–150 kg
- Target blood concentration 0.1–15 µg/ml (confirmation by user required for target greater than 10 µg/ml).

'Diprifusor' TCI is only indicated for the induction and maintenance of anaesthesia in adult patients.

Main components

The main components of a 'Diprifusor' TCI system, the data inputs and interactions between anaesthetist and patient are summarised (Figure 8).

The anaesthetist enters patient data and selects the target blood concentration.

Brief descriptions follow on the commercially available infusion systems with the emphasis on input of patient data and of target blood concentration. Each pump can also be used in manual mode. The manufacturer's manual (Instruction Manual, Operator's Guide or Directions for Use) should be consulted for details of operation.

The main features of each system are summarised in Table 6.

Table 6. Features of commercial syringe pumps that incorporate 'Diprifusor'

Feature	Graseby 3500	Vial Médical Master TCI	ALARIS IVAC TIVA TCI
Design	New model based on 3400	"Sleeve" attachment to upgrade Pilot Anaesthesia pump	New model based on ALARIS IVAC TIVA
Input/entry of patient data (age, weight)	Numeric keypad/press ENTER button	Dial value/press knob	Chevron and soft keys
Set initial target concentration	Numeric keypad/press ENTER button	Dial value/press knob	Chevron and soft keys
Small adjustment to target	Soft keys	Dial value/press knob	Single chevron keys/press START
Large adjustment to target	Input new value with numeric keypad/press START button	Dial value/press knob	Double chevron keys/press START
Screen display of target and calculated concentration	Numerical	Graphical and numerical	Graphical and numerical
Display of effect-site concentration*	Yes	Yes	Yes
Display of decrement time*	Yes	Yes	Yes
Display of infusion rate and volume	Yes	Yes	Yes
PC/printer interface to down-load data and create records	Yes	Yes	Yes
Comprehensive range of alarms	Yes	Yes	Yes

*Access, display and terminology differ between pumps and these facilities may not be available on some versions (see manufacturer's manual)
All features and specifications are subject to upgrades and other changes; the manufacturer should be consulted for details.

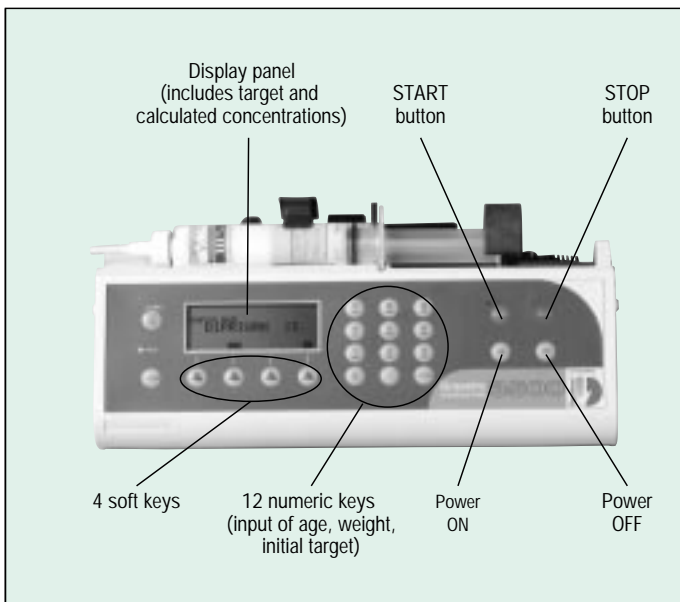
'Diprifusor' TCI – practical aspects

Graseby 3500 Anaesthesia Syringe Pump

The new 3500 model incorporating 'Diprifusor' is shown below (Figure 9). The numeric keypad is used to input the age and weight of the patient as well as the initial target concentration. (The user does not have to enter any units.) After each input, an ENTER soft key is pressed. Pressing the START button will commence the infusion.

The display (Figure 10) during infusion highlights the target concentration and the calculated concentration. The default setting of target concentration is 4 µg/ml. The current infusion rate also appears. The TOTAL soft key allows access to the current total amount of infusion.

Figure 9. Graseby 3500 pump incorporating 'Diprifusor'



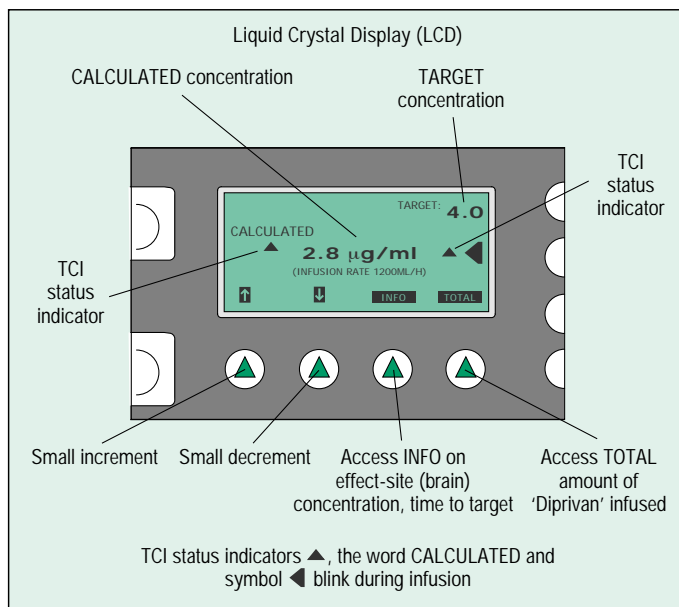
Consult Instruction Manual for details of display and operation.

Small alterations (minimum 0.1 µg/ml) to target concentration are made by pressing the up (↑) or down (↓) soft keys found below the display. For large alterations, the numeric keys/START button are used to input and confirm the new target setting and continue infusion with the new target.

When the pump is infusing, pressing the INFO soft key gives access to the following displays:

- Effect-site concentration (calculated)
- Time to target (calculated)
- Time to lower target (calculated decrement time)
- Patient details (inputted age and weight).

Figure 10. Display panel of Graseby 3500 pump during 'Diprifusor' TCI



Consult Instruction Manual for details of display and operation.

Syringe pumps incorporating 'Diprifusor'

Serial linkage of the Graseby 3500 (via an RS232 interface) to a Personal Computer (PC) enables down-loading of data and creation of a record of the anaesthetic procedure. (Please contact Graseby for the computer protocol; such facilities are features of the pump and not of 'Diprifusor'.)

Alarm messages are similar to those during manual control of infusion (see Instruction Manual).

Numerous display languages are available and can be individually selected.

Vial Médical Master TCI unit for Pilot Anaesthesia syringe pump

A Pilot Anaesthesia syringe pump can be upgraded to capability for 'Diprifusor' by adding a Master TCI unit (Figure 11).

A control knob is used to dial the following inputs:

- Age of patient
- Weight of patient
- Target concentration.

The user does not have to key in any values; the knob is turned to select the required value from a full listing on the display screen. Simply pressing the knob enters the value. The infusion begins when the START button is pressed. To set any new target,

Figure 11b

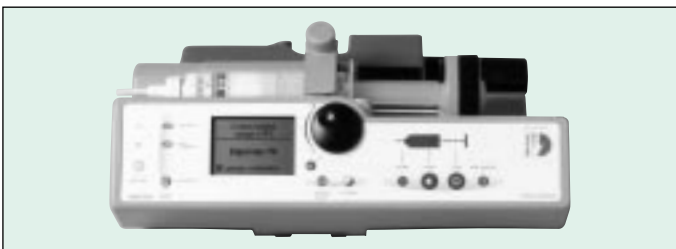
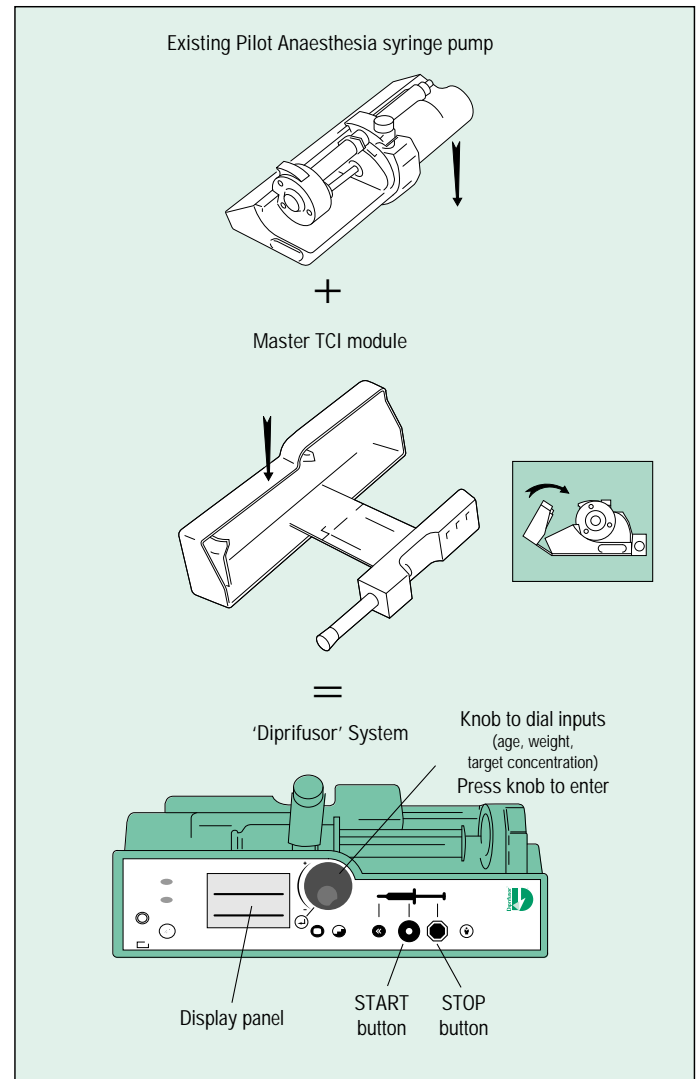


Figure 11a. Master TCI module incorporating 'Diprifusor' for Vial Médical Pilot Anaesthesia syringe pump



Consult Operator's Guide for details of display and operation.

'Diprifusor' TCI – practical aspects

the user dials up (i.e. turns the knob) to indicate the new value and then presses the knob.

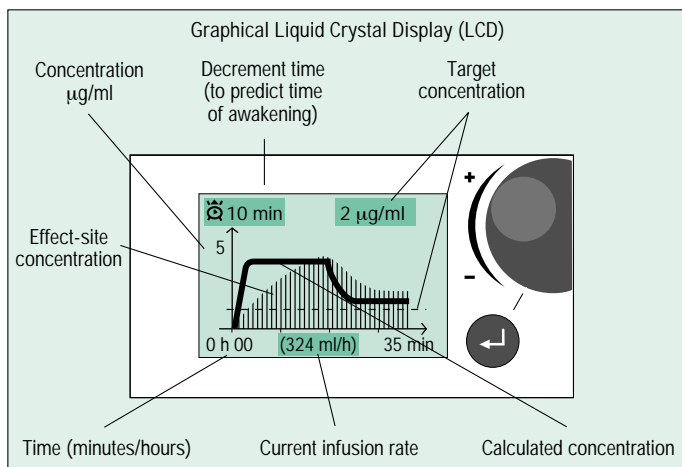
The screen becomes a graphical display (Figure 12) of calculated concentration against time with the target concentration clearly marked. The curve shows where calculated concentrations are in relation to the target. The screen can be changed to a listing of numerical values for target, calculated, infused dosage, duration and flowrate.

The main display includes calculated decrement time (based on an “awakening” concentration selected by the anaesthetist) and a graph of calculated effect-site concentration.

The Master TCI offers a choice of induction mode. The initial target concentration can be achieved as quickly as possible based on 'Diprifusor' or achieved gradually according to a selected induction time of between 30 seconds and 10 minutes.

The gradual mode of induction is not a feature of 'Diprifusor' but of the pump. This option is not included in Prescribing

Figure 12. Display panel of Vial Médical Master TCI during 'Diprifusor' TCI



Consult Operator's Guide for details of display and operation.

Information nor is it supported by clinical trials data for the administration of 'Diprivan' by 'Diprifusor' TCI.

The Master TCI has data storage (15,000 events) and retrieval capability. Patient initials or number can be assigned as an individual identifier. Data can be displayed on screen or downloaded to a PC to create documentary records including the curve of calculated concentrations against time. This facility is a feature of the pump and not of 'Diprifusor'.

Alarm messages are similar to those during manual control of infusion with a Pilot syringe pump (see Operator's Guides for Master TCI/Pilot).

ALARIS IVAC TIVA TCI Syringe Pump

The ALARIS IVAC TIVA TCI is shown opposite in Figure 13. The chevron and soft keys are used to input the age and weight of the patient as well as the initial target concentration. After confirmation, the main display is shown and pressing START will commence TCI. All the information relevant to TCI is shown on the main display.

Target concentration and the continuously changing calculated concentration are displayed numerically (Figure 14). In addition, a graphical trend is displayed of the calculated concentration which builds up as the infusion proceeds. This trend graph depicts the concentration over the last 30 minutes, 2 hours or 8 hours. The calculated effect-site concentration is shown as an icon in the top right hand corner and below this is an optional display of estimate time to a preset lower concentration (decrement time). The volume infused and infusion rate of 'Diprivan' are also displayed.

The target concentration may be titrated using the chevron keys and START is pressed to confirm the new target. The single chevron keys are used to make small changes (0.1 µg/ml), and the double chevron keys used to make larger

Syringe pumps incorporating 'Diprifusor'

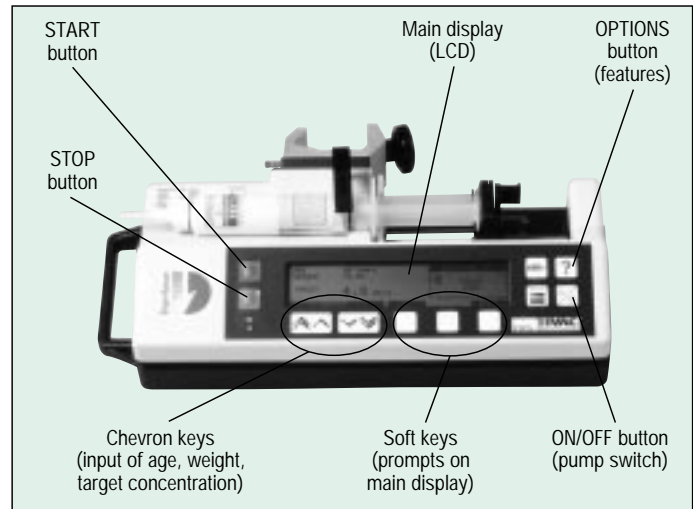
changes (1.0 µg/ml) to the target concentration.

The ALARIS IVAC TIVA TCI has an event log, including patient details, that can be reviewed on-screen and from which data can be retrieved via an RS232 interface.

Alarm messages are similar to those during manual control of infusion with an ALARIS IVAC TIVA syringe pump.

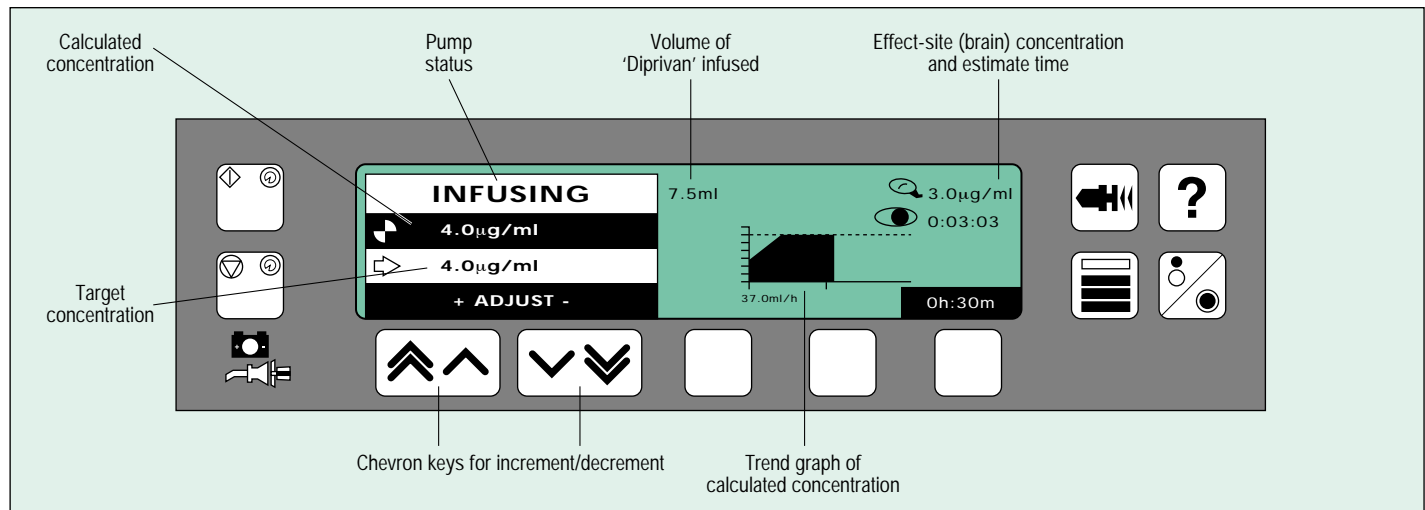
For further details of the ALARIS IVAC TIVA TCI operation, please refer to the manufacturer's Directions For Use.

Figure 13. ALARIS IVAC TIVA TCI syringe pump incorporating 'Diprifusor'



Consult Directions for Use for details of display and operation.

Figure 14. ALARIS IVAC TIVA TCI panel and main display during 'Diprifusor' TCI



Consult Directions for Use for details of display and operation.

Documentation

Key documents as set out below for the potential 'Diprifusor' user are available from the pump companies and from AstraZeneca.

Pump manufacturers

Each pump manufacturer provides a comprehensive manual on operation of their pump. The manual should be consulted for detailed information on:

- General features
- Power supply including battery
- Loading a syringe, recognition procedure
- Step-by-step guide to using 'Diprifusor' TCI
- Changing from 'Diprifusor' to manually-controlled infusion
- Alarm systems applicable to 'Diprifusor'
- Facilities available in 'Diprifusor' TCI mode
- Technical specifications
- Care and maintenance.

Pump manufacturers should be contacted for detailed information about availability, features, operation, price and technical service.

AstraZeneca

Prescribing Information (PI) for 'Diprivan' (see international version in pocket inside back cover) and package inserts cover the following aspects:

- Administration of 'Diprivan' by a 'Diprifusor' TCI system is restricted to induction and maintenance of general anaesthesia in adults
- Guidance on target concentrations
- Target concentration should be titrated against the response of the patient in order to achieve the depth of anaesthesia required
- Aseptic precautions for 'Diprivan' PFS.

Users should consult full, local prescribing information.

AstraZeneca has produced a Guide for Anaesthetists* on the administration of 'Diprivan' by 'Diprifusor' TCI that provides the following details:

- Guidance on target concentrations based on revised Prescribing Information for 'Diprivan'
- Background information, relevant to the anaesthetist, on the concept of TCI and the main features of 'Diprifusor' TCI
- Practical use of the 'Diprifusor' system.

AstraZeneca can provide a wide range of information sources (e.g. reprints of papers, reviews and symposium publications) on the medical aspects of 'Diprifusor' TCI.

* This guide is incorporated in the Instruction Manual for the Graseby 3500 pump and is included in the documentation pack provided with pumps by the other manufacturers.

Principles of setting and adjusting target concentrations

What happens when an initial target concentration has been set?

Answer

A 'Diprifusor' System can be considered as a "smart pump". 'Diprifusor' TCI Software "commands" the syringe pump to deliver a rapid infusion at a rate of 1,200 ml/h until the pharmacokinetic model calculates that the selected target concentration has been reached (Figure 15). Variable-rate infusions are then provided automatically to maintain the selected target concentration (Figure 15).

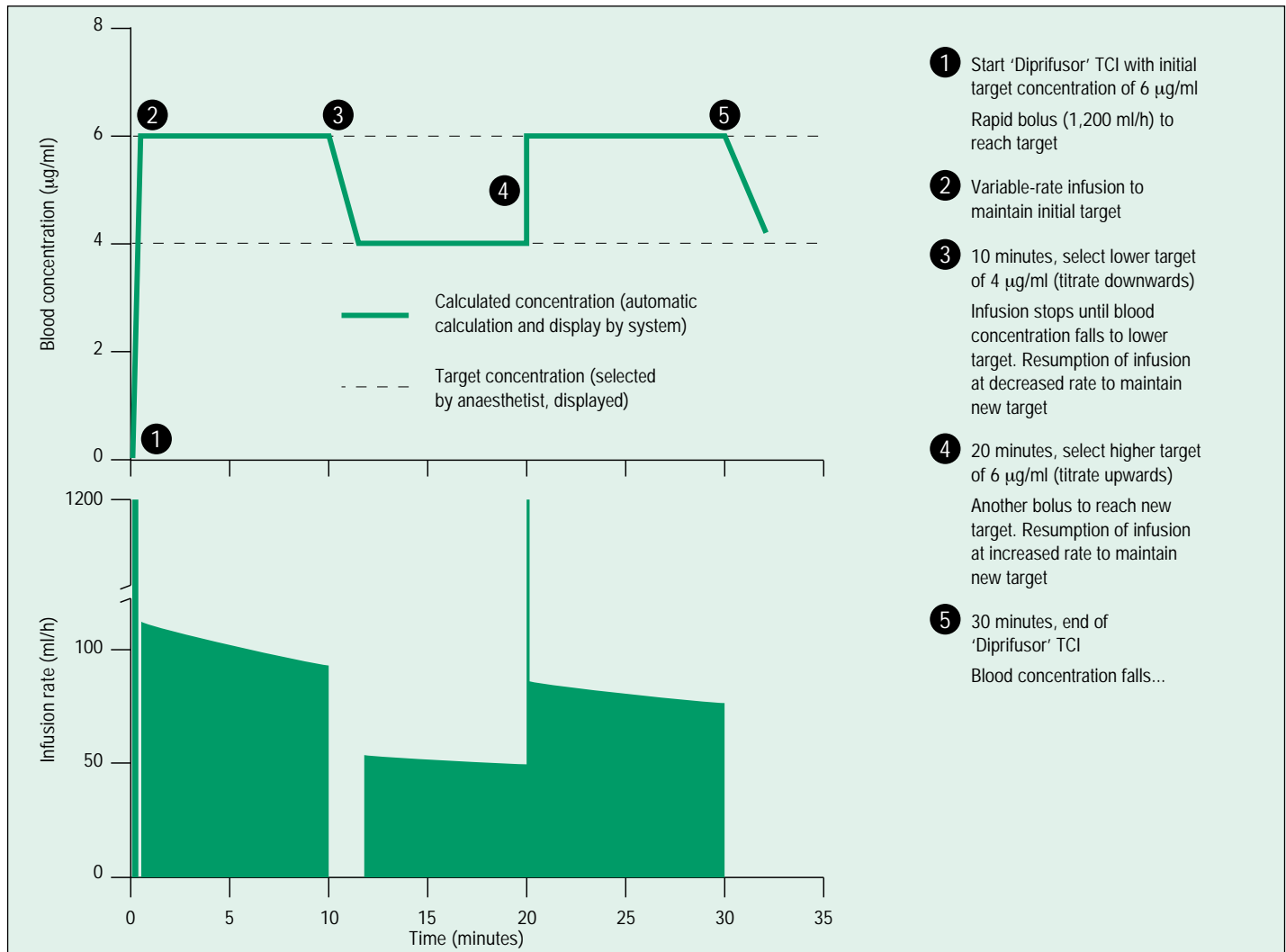
The target concentration can be changed **at any time** by the anaesthetist – and is displayed.

Selection of a higher target concentration results in administration of a bolus followed by infusion at an increased rate (Figure 15). Selection of a lower target concentration results in a temporary discontinuation of infusion followed by resumption at a lower rate (Figure 15). The calculated concentration is displayed continuously both during and after stopping drug infusion. The display of both the selected target concentration and the calculated concentration provides feedback to the anaesthetist.

These principles apply to the commercially-available pumps that incorporate 'Diprifusor' as well as to the 'Diprifusor' System used for clinical trials (see next section).

Principles of setting and adjusting target concentrations

Figure 15. Principles of setting and adjusting target concentrations with 'Diprifusor' TCI



'Diprifusor' TCI – clinical trials

This section summarises a detailed programme of clinical studies that were designed to:

- Provide guidance on target concentrations in relation to age, ASA status, premedication and supplementary analgesia
- Assess whether 'Diprifusor' TCI provides the recognised benefits of 'Diprivan':
 - smooth induction
 - good quality of maintenance
 - rapid, clear-headed recovery
- Examine whether 'Diprifusor' TCI compared with manually-controlled infusion of 'Diprivan' offers additional advantages:
 - more convenient administration (easier to use)
 - more predictable and precise control of the depth of anaesthesia (improved control).

The terms manually-controlled infusion, manual infusion and manual control are used to designate manual adjustment of infusion rates for anaesthesia syringe pumps administering 'Diprivan'.

Results from regulatory studies are supplemented by published experience with 'Diprifusor' or prototype 'Diprifusor' TCI systems.

Overview of clinical programme

There were 8 regulatory studies, 7 of which can be regarded as definitive studies⁴⁵⁻⁵¹ and 1 as a pilot study⁵² (see Table 7 for brief outline). Information about the characteristics of the study population, types of surgery and other drugs is summarised on page 47.

Consistent features of all studies included:

- Use for induction and maintenance of general anaesthesia in adults
- Assessment of efficacy and tolerability

- Definition of target blood concentrations of 'Diprivan' (propofol) for induction and maintenance
- Monitoring of haemodynamic changes
- Use of 'Diprivan' 1% (10 mg/ml)
- Use of identical 'Diprifusor' TCI Software.

All these clinical studies used 'Diprifusor' TCI Software incorporated in an external purpose-built computer linked via an RS232 serial port to a syringe infusion pump.

Table 7. Outline of clinical trials of 'Diprifusor' TCI

Centre(s)	Main objective	Design	'Diprifusor' TCI patients (n =)	Manual control of 'Diprivan' patients (n =)	Reference
Sheffield, UK*	Assessment of predictive performance	Open, non-comparative	46	–	45
Gent, Belgium	Effect of premedication	Open, comparative	45	–	46
Paris, France*	Effect of analgesic supplementation	Open, comparative	40	–	47
Durham, NC & Atlanta, GA, USA	Comparison of TCI vs manual control in cardiac patients	Double-blind, comparative	30	31	48
Oldham, UK*	Effect of ventilatory mode	Open, comparative	40	–	49
Brussels, Belgium*	Cardiac anaesthesia	Open, non-comparative	21	–	50
Birmingham & Glasgow, UK	Comparison of TCI vs manual control	Open, comparative	80	80	51
4 centres* for definitive studies	Familiarisation with TCI system	Open, non-comparative	15	–	52
TOTAL NUMBER OF PATIENTS			317	111	

Accuracy of 'Diprifusor' TCI

The accuracy of 'Diprifusor' TCI meets the standards required for clinical purposes with respect to:

1. Control of the depth of anaesthesia as shown in all clinical studies⁴⁵⁻⁵²
2. Formal measurement of predictive performance.^{45,50}

Control of the depth of anaesthesia

All 8 studies⁴⁵⁻⁵² showed consistently that 'Diprifusor' TCI delivers the required anaesthetic effect when a particular target concentration of drug is selected. The control of anaesthesia is more important than the specific blood concentration achieved. However, standardisation of device performance provides reassurance that drug delivery is reproducible at a particular target setting.

Measurement of predictive performance

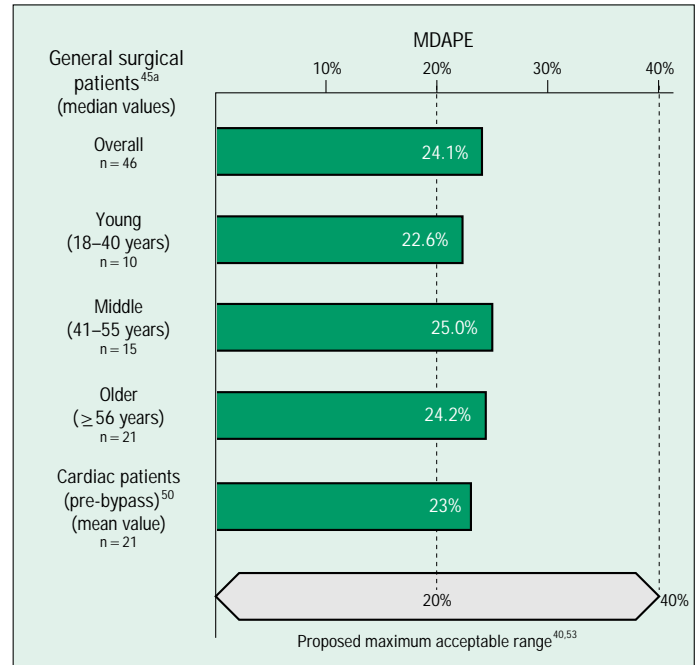
'Diprifusor' TCI meets proposed standards^{40,53} of predictive performance for the clinical acceptability of a TCI system.

Predictive performance has been quantified in clinical studies performed by groups in Sheffield, UK⁴⁵ and Brussels, Belgium.⁵⁰

Both studies measured actual drug concentration in samples of arterial blood at various times. These results were compared with the target and predicted concentrations. Median performance errors (MDPE) and median absolute performance errors (MDAPE) were calculated. MDAPE is a measure of precision and provides an indication of the size of the typical error from the predicted concentration. MDPE is a measure of bias and can represent under-prediction (positive value) or over-prediction (negative value) of the performance error. The results for MDAPE are shown in Figure 16. Also, the overall median MDPE was 16.2% in the UK study.^{45a}

It has been proposed^{40,53} that MDAPE should be no greater than 20% to 40% for the performance of a TCI system to be

Figure 16. Predictive performance of 'Diprifusor' TCI: MDAPE



clinically acceptable – and that MDPE (=bias) should be no greater than 10% to 20%.⁴⁰ 'Diprifusor' TCI meets these criteria; predictive accuracy is acceptable and the positive bias indicates that measured values are, in general, slightly higher than the predicted values.

Sources of performance error

As with any TCI system, the principal source of performance error with 'Diprifusor' TCI is pharmacokinetic variability of 20% to 30% between patients. Haemodynamic changes during anaesthesia and concomitant medication can influence pharmacokinetic variability. Some error can also be attributed to variability in the measurement of drug concentrations in blood.

'Diprifusor' TCI – clinical trials

Actual blood concentrations

Measured drug concentrations tended generally to be slightly higher than those predicted with 'Diprifusor' TCI. This was found in the UK study for three age groups^{45a} and in the Belgian study of patients before coronary artery bypass grafting.⁵⁰

The general tendency for measured drug concentrations to be higher than predicted was also shown by the Glasgow group in a study⁵⁴ of the prototype 'Diprifusor' TCI system in patients undergoing breast surgery. An additional finding in the Sheffield study^{45b} was that the predictive performance of the 'Diprifusor' TCI system did not appear to be influenced by duration of anaesthesia nor by the target concentration requested by the anaesthetist.

Predictive performance compared with available data on inhalational agents

There have not been direct comparisons.

However, the bias seen with 'Diprifusor' TCI (MDPE of 16.2%^{45a}) is comparable to the 20% difference between end-tidal and arterial partial pressure of isoflurane after 1 hour of anaesthesia i.e. the arterial concentration of isoflurane remained 20% lower than end-tidal concentration.⁵⁵ A larger discrepancy is seen when the ratio between arterial and inspired partial pressures of isoflurane is examined.⁵⁶ The vaporizer setting is only an approximate indicator of the inspired concentration of an inhalational agent and does not accurately represent actual blood concentration.

Clinical relevance of predictive performance

The anaesthetist will be more interested in the ease of making proportional changes in the depth of anaesthesia than in the absolute accuracy of a delivery system.

In an individual patient, the target concentrations required during the course of surgery may vary considerably. The target

concentration is titrated to the particular requirement of that patient at different stages of surgery. Clearly, pharmacokinetic variability of 20% to 30% is relatively unimportant compared with the larger adjustments in target concentration that are often made in response to a change in surgical stimulus. For instance, target concentration for an individual patient might be increased from 6 to 8 µg/ml following slight movement on initial surgical incision and then be gradually reduced to 2 µg/ml towards the end of surgery. Such a range of between 2 and 8 µg/ml at different stages of a procedure represents a four-fold difference (400%).

'Diprifusor' TCI offers the anaesthetist a convenient way to make proportional changes in the depth of anaesthesia with the confidence of reproducible delivery of drug at a particular target setting.

Anaesthetic effects of 'Diprivan' administered by 'Diprifusor' TCI

The anaesthetic effects of 'Diprivan' administered by 'Diprifusor' TCI have been established in the clinical trial programme with the following efficacy assessments:

- Induction time
- Quality of induction
- Quality of maintenance
- Haemodynamic effects
- Recovery time.

In all studies⁴⁵⁻⁵² information was recorded on target concentrations set during induction and maintenance of anaesthesia.

'Diprifusor' TCI was used for the unified anaesthetic management of the patient i.e. throughout the induction and maintenance phases. No studies involved induction with 'Diprifusor' TCI followed by maintenance with an inhalational agent. Statistical analyses are included as available (e.g. for induction time). In general, formal statistical analysis was not carried out on assessments of the quality of induction and maintenance.

Induction time

Induction time (usually defined as the interval from the start of administration until loss of verbal contact) was recorded in all clinical studies.⁴⁵⁻⁵²

Overall findings in clinical trial programme

'Diprifusor' TCI allows the anaesthetist to achieve a desired speed of induction by setting and adjusting the target blood concentration. Induction time is faster:

- With a high target concentration

- When the patient has received premedication with a benzodiazepine or receives a concomitant opioid analgesic.

A high initial target concentration equates to a large induction dose.

Guidance on target concentration and induction time, based on study results,⁴⁵⁻⁵² is given in revised Prescribing Information for 'Diprivan' (see pocket inside back cover). Full, local prescribing information should be consulted. The following summary is intended as a guide only:

- *Target blood concentrations of propofol should be titrated against the response of the patient in order to achieve the depth of anaesthesia required*
- *In adults (under 55 years of age), anaesthesia can usually be induced with target concentrations of 4 to 8 µg/ml*
- *In premedicated patients, an **initial** target concentration of 4 µg/ml is advised*
- *In unpremedicated patients an **initial** target concentration of 6 µg/ml is advised*
- *Induction time with these targets is generally within the range of 60 to 120 seconds*
- *A lower initial target concentration should be used in patients over the age of about 55 years and in patients of ASA grades III or IV.*

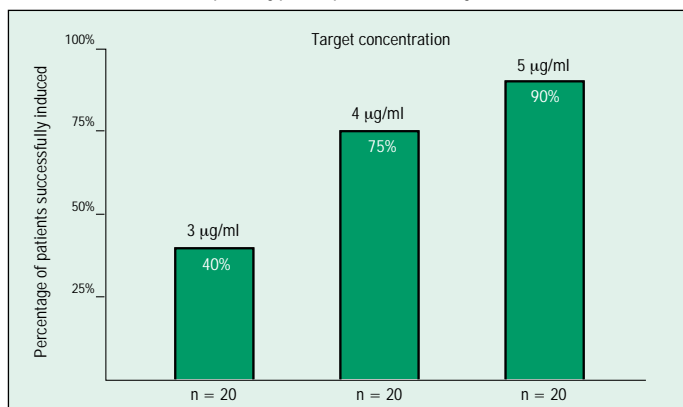
'Diprifusor' TCI – clinical trials

Note that induction time with the above target concentrations for healthy adults aged under 55 years is generally within the range of 60-120 seconds. Higher targets will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression. Also, the age and fitness of the patient influence the selection of an initial target concentration – and induction time.

Target concentrations should be titrated against the response of the patient. The anaesthetist can quickly and easily set a new target concentration during induction with 'Diprifusor' TCI. The principle of titration to effect is similar to manual infusion of 'Diprivan' – and to altering the inspired concentration of an inhalational agent with a vaporizer. It is easier to set a new target concentration with 'Diprifusor' TCI than to change a manual infusion rate.

The constantly changing display of predicted (calculated) concentrations, together with the information from monitoring the patient, enables the anaesthetist to assess whether further changes are required.

Figure 17. Effect of initial target concentration on successful induction of anaesthesia with a prototype 'Diprifusor' TCI system⁵⁷



Failure of induction (patients not induced within 3 minutes of achieving the target concentration): target increased to 6 µg/ml.

Prototype 'Diprifusor' TCI systems

Published experience⁵⁷⁻⁶⁰ with prototype 'Diprifusor' TCI systems in adult patients provides additional support for successful induction of anaesthesia in most patients with the target concentrations given for guidance.

A study⁵⁷ in patients premedicated with temazepam showed that a target concentration of 5 µg/ml successfully induced anaesthesia in 90% of patients with a mean induction time of 103 seconds (range 45–136 seconds); lower target concentrations (3 or 4 µg/ml) were less effective (Figure 17). Broadly similar results have been obtained in other studies.⁵⁸⁻⁶⁰

Effect of midazolam

Small IV doses of midazolam enhance the anaesthetic effects of 'Diprivan', including during induction with 'Diprifusor' TCI.

A study⁶¹ of 80 patients premedicated with temazepam compared the effects of varying doses of midazolam administered as an IV bolus 4 minutes before the start of 'Diprifusor' TCI (fixed target concentration of 3 µg/ml). Anaesthesia was successfully induced within 3 minutes of starting 'Diprifusor' TCI in 45% of patients receiving no midazolam, in 70% receiving 1 mg, in 85% receiving 2 mg and in 95% receiving 4 mg; between-group differences did not reach statistical significance.⁶¹

'Diprifusor' TCI compared with manual infusion

'Diprifusor' TCI may allow improved control of the induction rate compared with manually-controlled infusion of 'Diprivan'.

Induction of anaesthesia with 'Diprifusor' TCI has been compared with various manual pump methods for the administration of 'Diprivan' in studies performed in the UK,^{51a} USA⁴⁸ and Belgium.⁶² Findings are summarised opposite and must be interpreted in the context of the rapid initial infusion rate (1,200 ml/h) provided by 'Diprifusor' TCI, the initial target setting and the total administered dose of 'Diprivan'.

Anaesthetic effects of 'Diprivan' administered by 'Diprifusor' TCI

UK study

The UK two-centre, open, randomised study^{51a} was in 160 patients mainly of ASA grade I or II requiring a variety of different surgical procedures involving skin incision and lasting between 20 and 60 minutes. All patients were premedicated with temazepam (20 mg orally) and received a single dose of fentanyl (1.5 µg/kg IV) approximately 2 minutes before induction of anaesthesia. Anaesthesia was induced with a rapid infusion of 600 ml/h of 'Diprivan' in the manual control group. In the 'Diprifusor' TCI group, the mean target concentration was 7.5 µg/ml (range 4 to 12 µg/ml) during the first minute of induction with titration thereafter according to response.

The mean induction time was significantly shorter ($p < 0.01$) with 'Diprifusor' TCI compared with manual infusion (Figure 18)^{51a} and the mean difference was 20 seconds. This difference is probably due to the difference in peak infusion rates (600 ml/h for manual control and 1,200 ml/h for TCI). Also, the mean time to successful insertion of the laryngeal mask airway (LMA) was significantly shorter ($p < 0.05$) with 'Diprifusor' TCI (114 seconds) compared with manual control (132 seconds); the mean dose of 'Diprivan'

administered at this time was significantly higher ($p < 0.05$) with 'Diprifusor' TCI (201 mg) than with manual control (160 mg).^{51a}

USA study

The USA two-centre, double-blind randomised study⁴⁸ was in patients of ASA grades III or IV requiring cardiopulmonary bypass surgery. All patients were premedicated with lorazepam (2 to 4 mg orally). Anaesthesia was induced with an infusion of 1.0 to 1.5 mg/kg of 'Diprivan' titrated to individual clinical response in the manual control group. In the 'Diprifusor' TCI group, the guideline for target concentration was 3.0 to 4.0 µg/ml, titrated to clinical response.

The mean induction time was significantly shorter with 'Diprifusor' TCI (81.7 seconds) compared with manual infusion (101.2 seconds).⁴⁸ The mean dose of 'Diprivan' required to achieve induction was similar in the 'Diprifusor' TCI group (0.98 mg/kg) and manual control group (1.0 mg/kg).

Belgium study

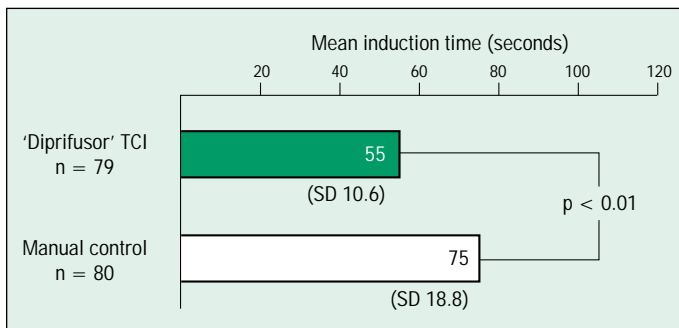
In the Belgium single-centre study, 90 women of ASA grades I or II requiring gynaecological surgery as day cases were randomised to the following groups:

- 'Diprifusor' TCI (initial target concentration of 4 µg/ml increased by 2 µg/ml after 3 minutes if consciousness was not lost)
- Manual control with induction bolus of 1,200 ml/h
- Manual control with induction bolus of 600 ml/h.⁶²

All patients received a single bolus dose of a benzodiazepine (midazolam 0.03 mg/kg IV, 7 minutes before induction) and an opioid (alfentanil 10 µg/kg IV, 2 minutes before induction).

Mean induction times were 78 seconds with 'Diprifusor', 51 seconds with the manual induction bolus of 1,200 ml/h and 62 seconds with the manual induction bolus of 600 ml/h; the difference between the two manual induction groups was statistically

Figure 18. Induction time with 'Diprifusor' TCI in healthy patients^{51a}



The initial infusion rate was higher with 'Diprifusor' TCI (1,200 ml/h) than with manual control (600 ml/h). The mean dose of 'Diprivan' administered at the time of insertion of the laryngeal mask airway was significantly higher ($p < 0.05$) with 'Diprifusor' TCI (201 mg) than with manual control (160 mg).

'Diprifusor' TCI – clinical trials

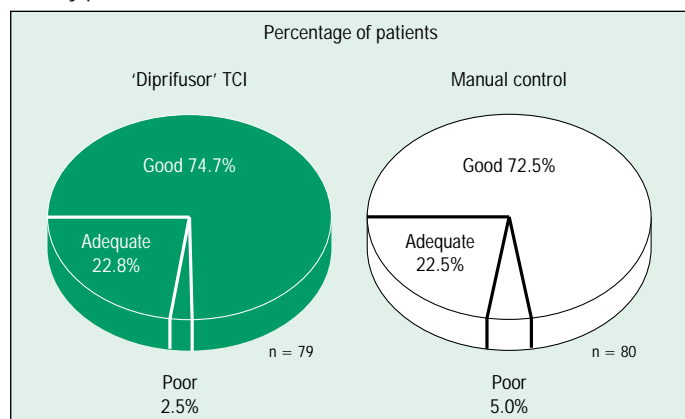
significant ($p < 0.05$). The corresponding mean induction doses were 1.31 mg/kg ('Diprifusor' TCI), 2.74 mg/kg (manual 1,200 ml/h) and 1.71 mg/kg (manual 600 ml/h); all between-group differences were statistically significant ($p < 0.05$). Therefore, less 'Diprivan' was used for induction in the 'Diprifusor' TCI group without producing a significantly longer induction time.⁶²

Computer simulation of predicted blood and effect-site concentrations showed that there was "overshoot" with the fast manually-controlled infusion rate (high dose) but not with the slower infusion rate or when using 'Diprifusor' TCI.⁶²

Quality of induction

In the study population⁴⁵⁻⁵² of 317 adult patients, the quality of induction with 'Diprifusor' TCI was assessed as good or adequate in the vast majority of patients.

Figure 19. Quality of induction of anaesthesia with 'Diprifusor' TCI in healthy patients^{51b}



The initial infusion rate was higher with 'Diprifusor' TCI (1,200 ml/h) than with manual control (600 ml/h). The mean dose of 'Diprivan' administered at the time of insertion of the laryngeal mask airway was significantly higher ($p < 0.05$) with 'Diprifusor' TCI (201 mg) than with manual control (160 mg).

This finding highlights the fact that 'Diprifusor' TCI is a convenient way of delivering a major clinical benefit of 'Diprivan' – smooth induction of anaesthesia.

The quality of induction of anaesthesia in the UK study^{51b} was assessed by an observer at each centre as *good*, *adequate* or *poor*. Prior to the study, the anaesthetists who administered study drugs had little or no previous experience of the use of 'Diprivan' by infusion. They quickly became familiar with the techniques and obtained a similar quality of induction with 'Diprifusor' TCI and manual control (Figure 19).

Prior to the study,⁵¹ the anaesthetists were unfamiliar with infusion techniques for 'Diprivan'.

Quality of maintenance

The quality of maintenance, especially the ease of control of the depth of anaesthesia, achieved with 'Diprifusor' TCI has been assessed in all clinical studies.⁴⁵⁻⁵²

Assessments included:

- Overall quality
- Ease of control
- Quality of anaesthesia score
- Depth of anaesthesia score.

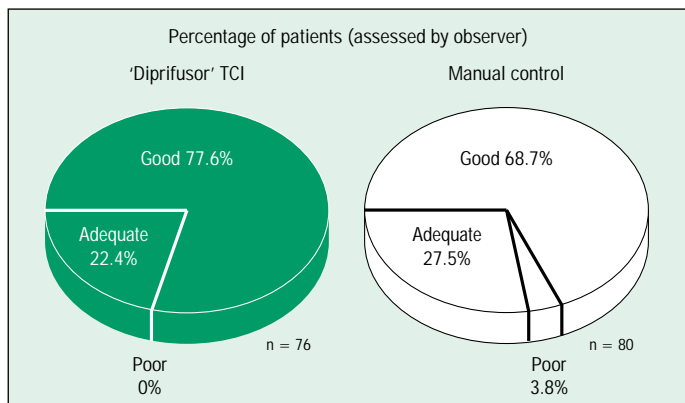
The trial programme also provided detailed information about maintenance target concentrations.

Overall quality

Overall quality of anaesthesia was rated as *good* (uncomplicated maintenance), *adequate* (minor problems but easily managed) or *poor* (significant problems) in 7 studies.^{45-47,49-52} For the great majority of patients, overall quality was rated as either good or adequate during maintenance of anaesthesia with 'Diprifusor' TCI.

Anaesthetic effects of 'Diprivan' administered by 'Diprifusor' TCI

Figure 20. Overall quality of maintenance of anaesthesia with 'Diprifusor' TCI in healthy patients^{51b}



Results from the UK comparative study^{51b} showed that the overall quality of anaesthesia (anaesthetic conditions as assessed by observers) was similar with 'Diprifusor' TCI and manual control (Figure 20).

Ease of control

Ease of control of the depth of anaesthesia was rated as *good*, *adequate* or *poor* (without further definition of these ratings in protocols) in all studies.^{45–52} For all but a few patients, the ease of control of anaesthesia was rated as either good or adequate during maintenance of anaesthesia with 'Diprifusor' TCI. Ease of control of anaesthesia was similar with 'Diprifusor' TCI and manual control by anaesthetists who had just learned the techniques.^{51b}

Quality of anaesthesia score

A *quality of anaesthesia score*⁶³ was used in several studies.^{46,47,49–52} The scoring system included evaluations of response to surgical stimulation, respiratory depression, haemodynamic instability and recovery times. The range of total possible scores is from 0 (ideal) to 29.

In general, the trial programme supports the good quality of anaesthesia achieved with 'Diprifusor' TCI. Published experience with the prototype 'Diprifusor' TCI system in a large population of adult patients provides additional support for successful maintenance of anaesthesia in most patients.

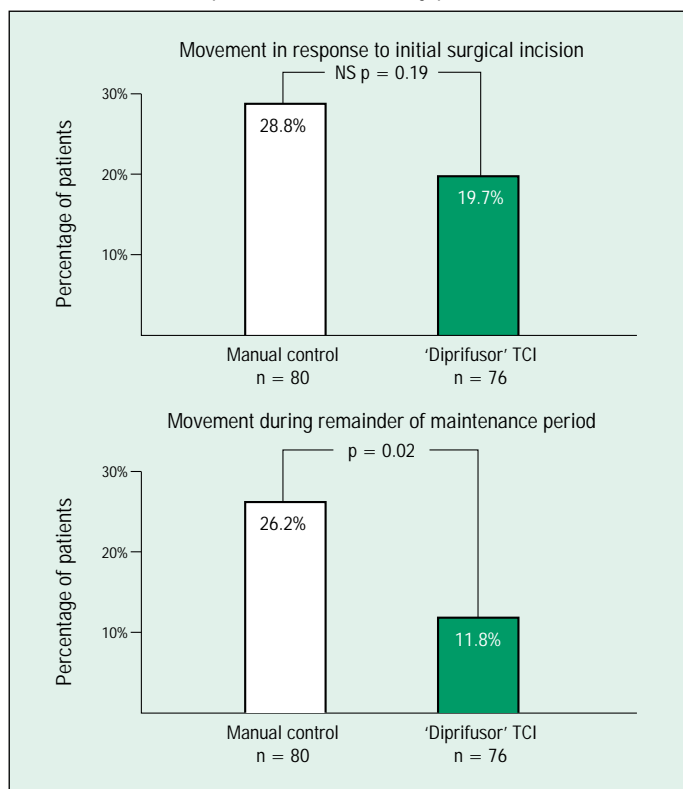
Quality of maintenance may be slightly better with 'Diprifusor' TCI than with manual control. In the UK comparative study,^{51b} the mean value of the total quality of anaesthesia score was 3.63 with 'Diprifusor' TCI and 4.11 with manual control, suggesting a marginally better quality of maintenance with 'Diprifusor' TCI although a statistical analysis was not performed. Also, the mean overall infusion rate during maintenance was significantly greater ($p=0.001$) in the 'Diprifusor' TCI group (13.2 mg/kg/h) than in the manual control group (8.2 mg/kg/h). The range of mean values for the total quality of anaesthesia score in other studies (1.80⁴⁹ to 7.85⁴⁷) was broadly similar to that seen with 'Diprifusor' TCI in the UK comparative study.^{51b}

Movement by the patient in response to the initial surgical incision – and during the remaining period of maintenance of anaesthesia – was observed in numerically fewer patients in the 'Diprifusor' TCI group than in the manual control group (Figure 21).^{51a} The difference in movement during maintenance was statistically significant ($p=0.02$) but failed to reach statistical significance ($p=0.19$) for initial incision. Once again, such findings must be interpreted in the context of the higher infusion rate with 'Diprifusor' TCI than with manual control.

Patient movement that interrupted surgery was less likely during maintenance with 'Diprifusor' TCI than with manual control.^{51a} During the maintenance period, there were 4/80 patients (5%) with movement assessed as "marked" that led to a temporary interruption to surgery in the manual control group and 1/76 such patients (1.3%) in the 'Diprifusor' TCI group.^{51a} Clearly, the higher infusion rate with 'Diprifusor' TCI than with manual control should be considered.

'Diprifusor' TCI – clinical trials

Figure 21. Movement in response to surgical stimuli during maintenance with 'Diprifusor' TCI in healthy patients^{51a}

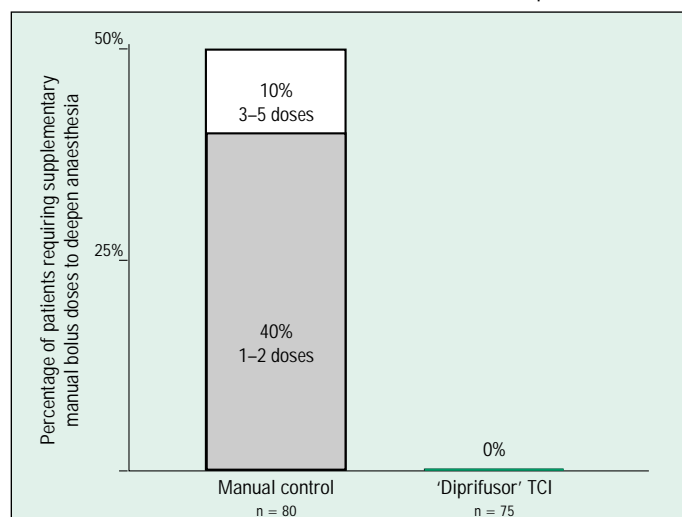


The mean overall infusion rate during maintenance was significantly greater ($p = 0.001$) in the 'Diprifusor' TCI group (13.2 mg/kg/h) than in the manual control group (8.2 mg/kg/h).

In the manual control group supplementary bolus doses were required in 50% of patients so as to deepen anaesthesia at times of increased surgical stimulation.^{51b} Manually-administered bolus doses were not required for any patient in the 'Diprifusor' TCI group^{51b} (Figure 22); the setting of a higher target with 'Diprifusor' TCI resulted in the automatic delivery of a bolus dose followed by infusion at an increased rate.

The practical implication is that 'Diprifusor' TCI avoids the inconvenience of manual administration of supplementary bolus doses to increase the depth of anaesthesia. The potential benefits include user convenience, improved control and more time to monitor the patient.

Figure 22. Need for supplementary manual bolus doses during maintenance of anaesthesia with manual control or 'Diprifusor' TCI^{51b}



The mean overall infusion rate during maintenance was significantly greater ($p = 0.001$) in the 'Diprifusor' TCI group (13.2 mg/kg/h) than in the manual control group (8.2 mg/kg/h). Setting a higher target concentration with 'Diprifusor' TCI results in automatic administration of a bolus.

Depth of anaesthesia score

A *depth of anaesthesia score*⁶³ was used in several studies.^{45,47,49-52} The range of total possible scores is from -9 (deepest level of anaesthesia) to +19 (lightest level of anaesthesia).

In general, the trial programme supports the good control of the depth of anaesthesia achieved with 'Diprifusor' TCI. In the UK comparative study,^{51b} the mean value of the depth of anaesthesia score was -1.79 in the 'Diprifusor' TCI group and -0.46 in the

Anaesthetic effects of 'Diprivan' administered by 'Diprifusor' TCI

manual control group, suggesting that a deeper level of anaesthesia was obtained with 'Diprifusor' TCI.

Maintenance target concentrations

Maintenance target concentrations were recorded in all studies.^{45–52} Supplementary analgesia was used routinely. In general, the trial programme showed that target concentrations in the region of 3 to 6 µg/ml usually maintain satisfactory anaesthesia. Additional support comes from several published studies with prototype 'Diprifusor' TCI systems.

Consult local prescribing information for dosage recommendations.

Mean target concentrations (or approximate range of means) used for maintenance in specific patient types as studied in the trial programme are summarised (Table 8). Lower maintenance target concentrations should be used for the following patient types:

- ASA grades III or IV
- Age over 55 years
- Those receiving large amounts of supplementary analgesia.

The mode of ventilation had no effect on maintenance target concentrations required for acceptable anaesthesia in a direct comparison of controlled ventilation and spontaneous respiration.⁴⁹

Table 8. Maintenance target concentrations in 'Diprifusor' TCI trial programme

Patient type	Mean maintenance target concentration
Healthy adult patients (ASA I or II) ^{45–47,49,51b,52}	3.5 to 5.3 µg/ml
Cardiac patients (ASA II, III or IV) ^{48,50}	2.8 to 3.4 µg/ml
Age over 55 years ^{45a}	3.5 µg/ml

The concurrent administration of 67% nitrous oxide with 'Diprifusor' TCI reduced the EC₅₀ (Effective Concentration 50, the concentration at which 50% of patients do not respond to a painful stimulus) of 'Diprivan' by approximately 30% in ASA I or II female patients breathing oxygen.⁵⁴

Changes in target concentration

There is a delay of 2 to 3 minutes between the achievement of a target concentration in blood and equilibration (maximum concentration) in the effect site (brain). Thus, particularly in elderly or ASA grade III or IV patients, adequate time should be allowed to assess the effect obtained at a particular target concentration before making any further alterations to the target setting (see page 13).

The number of times the target is changed depends on the type of patient and surgery – and the duration of the procedure. In the UK comparative study,^{51b} adjustments to the manual infusion rate or the target concentration occurred with similar frequencies and ranged between 1 and 10 times for most patients. A large study⁶⁴ with a prototype 'Diprifusor' TCI system used by 31 anaesthetists for 746 adult patients illustrates the variability. The median number of target alterations was 6 per procedure (range 0–28) whilst the mean time of maintenance was 26.1 minutes (range 1.1–268 minutes).⁶⁴

A practical advantage is that it is easier to change target concentration with 'Diprifusor' TCI than to calculate and adjust infusion rates and/or administer supplementary bolus doses with manual control.

Haemodynamic effects

Haemodynamic effects during induction and maintenance of anaesthesia with 'Diprifusor' TCI have been documented in all studies.^{45–52}

Overall results from clinical trial programme

During induction with 'Diprifusor' TCI in healthy adults,^{45,47,49,51,52}

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falls in mean systolic blood pressure (SBP) in the range of 12 to 26% and in mean diastolic pressure (DBP) in the range of 16 to 28% were comparable in magnitude to those known to occur with manual administration of 'Diprivan'. A similar pattern was seen with 'Diprifusor' TCI in patients aged over 55 years.⁴⁵ In cardiac patients, the hypotensive effect was exacerbated when opioid infusion was started before 'Diprifusor' TCI.⁵⁰ Premedication with benzodiazepines had no significant effect on haemodynamic response.⁴⁶

In healthy adults^{45,47,49,51,52} and in cardiac patients,^{48,50} there was usually little further change from induction to the maintenance phases. In patients aged over 55 years, the changes in SBP during maintenance were greater than those seen in younger age groups.^{45b}

Results of comparative studies^{48,51b} did not support the hypothesis that 'Diprifusor' TCI might attenuate the hypotensive effect compared with manual control by avoiding an "overshoot" in blood concentration at induction. Mean changes in SBP and DBP were very similar with 'Diprifusor' TCI and with manually controlled infusions during both induction and maintenance of anaesthesia. A possible explanation is the use of an infusion induction technique in the manual groups.

Recovery times

Mean recovery times (usually from end of infusion to eyes opening) after 'Diprifusor' TCI in the clinical trial programme were consistent with the rapid early-phase recovery established after 'Diprivan' administration.

After short procedures (30 to 40 minutes), mean recovery times were in the range of 5.0 to 10.3 minutes.^{46,49,51a} After longer procedures (lasting up to 6 hours), mean recovery times were in the range of 9.6 to 21.3 minutes.^{45,47,52}

The UK comparative study^{51a} showed marginal extensions (not statistically significant) in mean times to recovery (eyes opening spontaneously or to speech) and to orientation (recall of date of birth) in the 'Diprifusor' TCI group compared with manual control. Most

patients in both groups made a prompt, clear-headed recovery.^{51a}

As mentioned, a deeper level of anaesthesia was achieved with 'Diprifusor' TCI than with manual control in this study – and the mean overall maintenance infusion rate was higher ($p=0.001$) in the 'Diprifusor' TCI group (13.2 mg/kg/h) than in the manual control group (8.2 mg/kg/h).^{51b} There was no evidence that the study investigators gradually reduced target concentrations towards the end of surgery. In practice, 'Diprifusor' TCI may facilitate "tail off" of dose before the end of a surgical procedure in two ways:

- Ease of reduction of target concentrations
- Display of predictive information about awakening time.

Thus, commercial infusion pumps incorporating 'Diprifusor' enable the anaesthetist to optimise the speed of recovery.

Confirmation of the quality of recovery comes from studies with prototype 'Diprifusor' TCI systems in day-case patients.^{59,60} Emergence was rapid when measured by time to awakening^{59,60} and by time to orientation.⁶⁰ Patients soon left the postanaesthesia recovery room.⁵⁹ Patients were fit for discharge home at 2 hours after surgery when assessment showed no nausea and vomiting, ability to converse normally, walk unaided, retain oral fluids and full recovery of cognitive mental function.⁶⁰

Calculated concentrations on recovery

From clinical studies with 'Diprifusor' TCI^{45b,47,49,65} and prototype systems,⁶⁶ it can be concluded that, in the majority of patients, waking (eyes open) will occur at calculated concentrations in the region of 1 to 2 µg/ml. The mean calculated concentration was at the lower end of this range (1.1 to 1.3 µg/ml) in the study^{45b} where the greatest amount of analgesic supplementation was used.

A detailed investigation⁶⁵ of electrophysiological variables during emergence from anaesthesia after 'Diprifusor' TCI showed that bispectral index values before eye opening were linearly related to calculated blood concentrations.

Wide range of adult patients

The clinical trial programme included a wide range of adult patients requiring general anaesthesia for a variety of surgical procedures performed as inpatients or outpatients (day cases).

Characteristics of study population, types of surgery and other drugs

'Diprifusor' TCI was used in a total of 317 patients.⁴⁵⁻⁵² Duration of treatment ranged from 10 minutes to over 8 hours. Table 9 summarises the characteristics of the study population and lists the types of frequently performed surgery plus the wide range of premedicants and supplementary analgesics used in studies.

Additional experience

Published experience with 'Diprifusor' or prototype 'Diprifusor' TCI systems extends to over 1,500 anaesthetised adults. Types of surgery included the following: urological,⁶⁷ gynaecological,^{62,66,67} orthopaedic,⁶⁸ vascular⁶⁹ and ophthalmic,^{60,70,71} neurosurgical,⁷² general and day case.⁷³

Case reports endorsed the value of the technique in patients with particular anaesthetic problems such as:

- Bronchopleural fistula⁷⁴
- Undrained⁷⁵ or drained⁷⁶ pneumothorax
- Difficult airway due to fixed-flexion deformity of cervical spine⁷⁷
- Myotonic dystrophy.⁷⁸

The anaesthetist was able to maintain precise control over the depth of anaesthesia by making small incremental changes in target concentrations. In most cases, the patient could be anaesthetised without episodes of apnoea or exposure to nitrous oxide.

Published experience with other TCI systems that administered 'Diprivan' – but differ from 'Diprifusor' TCI in pharmacokinetic models and/or control software - extends to over 1,000 anaesthetised patients.

Table 9. Patient characteristics, surgical procedures and other drug therapy in 'Diprifusor' TCI clinical programme⁴⁵⁻⁵²

<p>Adult patients</p> <ul style="list-style-type: none"> ● Age range 16 to 83 years (mean 45.4 years) ● Male (n = 186) or female (n = 131) ● ASA Class I, II, III and IV ● Inpatients and outpatients/day cases ● Spontaneous breathing and controlled ventilation
<p>Type of surgery</p> <ul style="list-style-type: none"> ● General ● Cardiac ● Neurosurgery ● Gynaecological ● Orthopaedic ● Arthroscopic
<p>Other drug therapy</p> <ul style="list-style-type: none"> ● Premedication <ul style="list-style-type: none"> – benzodiazepines (temazepam, diazepam, midazolam) – ranitidine ● Pre-induction analgesia <ul style="list-style-type: none"> – opioids (alfentanil, fentanyl, sufentanil) – ketorolac ● Supplementary analgesia <ul style="list-style-type: none"> – nitrous oxide – alfentanil – sufentanil – alfentanil + nitrous oxide/oxygen – fentanyl + nitrous oxide ● Neuromuscular blocking drugs <p>n = 317</p>

Tolerability profile of 'Diprifusor' TCI

The tolerability profile of 'Diprivan' is unchanged when administered by TCI.

Adverse events

In the clinical trial programme,⁴⁵⁻⁵² the total number of patients with an adverse event was similar for 'Diprifusor' TCI (7.3%, 23/317 patients) and for manually-controlled infusions of 'Diprivan' (6.3%, 7/111 patients).

Published studies with prototype 'Diprifusor' TCI systems and other TCI systems for 'Diprivan' did not reveal any unexpected adverse events.

As expected, there have been occasional reports of the following well-recognised types (and examples) of side effect with 'Diprivan' when administered by TCI:

- Cardiovascular (e.g. sinus bradycardia, hypotension)
- Respiratory (e.g. apnoea, hypoxia)
- CNS (e.g. mild excitatory phenomena, dreaming)
- Local reactions (e.g. pain or discomfort on injection).

Of the events reported in the clinical trial programme for 'Diprifusor' TCI, only sinus bradycardia (1.26%, 4/317 patients) and hypotension (1.58%, 5/317 patients) occurred at a frequency greater than 1%. There were no reports of awareness in the 'Diprifusor' TCI trial programme.

Equipment reliability

There were infrequent reports of technical problems related to the equipment used in the trial programme; an infusion pump was interfaced with an external control unit.

Examples related to operator error (13 incidents) included problems with:

- The printer or syringe pump
- Occlusion or disconnection of the IV infusion line
- Low battery condition in the external computer.

Communication errors (6 incidents) between the external computer and syringe pump were resolved by restarting TCI or reverting to a manual or alternative technique. Communication problems should not occur in the validated, commercial syringe pumps that incorporate 'Diprifusor' in an integrated TCI system.

In all cases, the action taken prevented any adverse patient outcome.

User surveys with 'Diprifusor' TCI

Anaesthetists quickly became familiar with the technique^{51b,52} and confident in its use^{51a} – and expressed a preference for 'Diprifusor' TCI over manually-controlled infusion.^{51a}

Familiarisation of anaesthetists

The UK comparative study^{51a} involved 8 consultant anaesthetists who were unfamiliar with the use of 'Diprivan' by infusion prior to the study. They attended a workshop where they received instruction and practical demonstration of 'Diprifusor' TCI and manual control. Comprehensive written instructions in the rationale of each technique and practical aspects were provided.

Each consultant anaesthetised 10 patients in sequential fashion with each technique.^{51a} All quickly became familiar and confident^{51a} with the use of 'Diprifusor' TCI or manual control usually after anaesthetising 2 or 3 patients.^{51b}

In an initial familiarisation trial,⁵² investigators who were experienced in the use of 'Diprivan' by infusion, became confident

with the 'Diprifusor' TCI technique after anaesthetising only 1 or 2 patients. These anaesthetists then proceeded to definitive studies with 'Diprifusor' TCI at centres in Belgium,⁵⁰ France⁴⁷ and the UK.^{45,49}

Preference of anaesthetists

At the end of the UK comparative study,^{51a} the preferences of the 8 investigators on ease of use of each technique were assessed with a questionnaire. Most of these anaesthetists expressed "an overall preference" for 'Diprifusor' TCI over manual control (Table 10); 6/8 considered 'Diprifusor' TCI to be easier to use and 7/8 would choose to use the system.^{51a}

Subsequently, an extensive European multicentre study⁷⁹ (see page 51) confirmed that the use of 'Diprifusor' TCI does not require extensive training and, when compared with manual control, is preferred by anaesthetists because of its simplicity.

Table 10. User preferences on ease of use (convenience) of 'Diprifusor' TCI or manual control as assessed by questionnaire^{51a}

Feature or variable	Number of anaesthetists (n = 8) expressing preference		
	'Diprifusor' TCI	Manual control	No preference
Ease of set-up	●	○○○	○○○○
Ease of setting target or infusion rate	●●●●●●		○○
Ease of adjusting depth of anaesthesia	●●●●	○	○○○
Portability		○○○○	○○○○
Reliability	●	○○	○○○○○
Easier to use	●●●●●●	○	○
Preferred choice of infusion technique	●●●●●●		○

Statistical analysis was not performed.

'Diprivan' TCI – clinical trials

Factors relating to the overall preference^{51a} for 'Diprifusor' TCI may include:

- Increased confidence regarding predictability of anaesthetic effects
- The fact that, when making the transition to IV anaesthesia, traditional anaesthetic skills are used with 'Diprifusor' TCI
- Target concentrations can be increased or decreased according to response in the same way that anaesthetists are familiar with varying the inspired concentration of inhalational agents.^{51a}

The equipment used in the UK study^{51a} and European multicentre study⁷⁹ linked a syringe pump to an external computer containing 'Diprifusor' Software (© University of Glasgow). Commercially-available syringe pumps incorporate 'Diprifusor' in a single unit and have various "user friendly" features (see page 24). Therefore, the portability and reliability of 'Diprifusor' should be improved in the integrated systems that are marketed.

In a questionnaire survey⁶⁴ of anaesthetists who used prototype 'Diprifusor' TCI systems to anaesthetise over 700 patients, 27 of 30 respondents indicated that the technique facilitated the administration of 'Diprivan' for maintenance. The main reasons cited were "**greater ease of use and more confidence in the predictability of anaesthetic effects**" compared with manually-controlled infusions.⁶⁴

The convenience or ease of use of 'Diprifusor' reflects the simplicity of changing target concentrations with 'Diprifusor' TCI without the need to calculate infusion rates, administer supplementary bolus doses etc in response to changing anaesthetic conditions and surgical stimuli.

Although not documented in clinical trials, there are potential benefits that stem from user convenience, including:

- 'Diprifusor' TCI should allow the anaesthetist more time to monitor the patient
- 'Diprifusor' TCI compensates rapidly and automatically for any interruption to drug administration (e.g. replacement of a syringe)
- 'Diprifusor' TCI might avoid errors in dosage sometimes associated with the calculation and administration by manual control of complex infusion regimens.

Advantages that relate to the features of syringe pumps that incorporate 'Diprifusor' are summarised on pages 24 to 29.

European multicentre study

A European multicentre study confirmed that anaesthetists preferred ‘Diprifusor’ TCI to manual control in a wide variety of clinical settings.⁷⁹ The study also provided confirmatory data on target concentrations as well as the efficacy and tolerability of ‘Diprifusor’ TCI for induction and maintenance of anaesthesia.

A total of 29 centres in 6 European countries (see Table 11) collected data on the primary endpoint (preference for ‘Diprifusor’

Table 11. European multicentre study of ‘Diprifusor’ TCI versus manual control in general surgery^{79a}

Countries	
<ul style="list-style-type: none"> ● France (Paris, Villejuif, Rennes, Nancy, Bordeaux, Créteil, Marseille, Clichy, Vandoeuvre-lès-Nancy) ● Germany (Mainz, Solingen, Erlangen, Münster, Ulm) ● Holland (Utrecht, Enschede) ● Ireland (Dublin, Cork, Ballinasloe) ● Portugal (Vila Franca De Xira, Coimbra) ● UK (Nottingham) 	
Patient population	
<ul style="list-style-type: none"> ● Male or female subjects requiring general anaesthesia for elective surgery ● ASA Class I, II or III ● Aged 18 years or older 	
Randomised patients	
<ul style="list-style-type: none"> ● ‘Diprifusor’ TCI <ul style="list-style-type: none"> – mean age 46 years – ASA Class I 65%, II 31%, III 4% – duration of anaesthesia (mean 99, range 7–519 minutes) 	n = 283
<ul style="list-style-type: none"> ● Manual control <ul style="list-style-type: none"> – mean age 45 years – ASA Class I 63%, II 34%, III 4% – duration of anaesthesia (mean 98, range 6–560 minutes) 	n = 279

or manual control) and efficacy endpoints (e.g. dose for induction, target concentrations). The anaesthetists had previous experience of manual infusion techniques for the administration of ‘Diprivan’ but most had never used TCI before. ‘Diprifusor’ Software was incorporated in an external control unit interfaced with a conventional syringe pump.

Characteristics of randomised patients are summarised in Table 11. Surgical procedures ranged from day cases to intra-abdominal or neurosurgical procedures of longer duration. Most patients received premedication (with a benzo-diazepine or hydroxyzine) and an opioid prior to induction.

Preference of anaesthetists

More than 90% of anaesthetists had an overall preference for ‘Diprifusor’ TCI over manual control (Figure 23) based on completion of a questionnaire.⁷⁹ Factors that contributed to the overall preference for ‘Diprifusor’ TCI included ease of use and aspects of control of the depth of anaesthesia (Figure 23).

Induction and maintenance

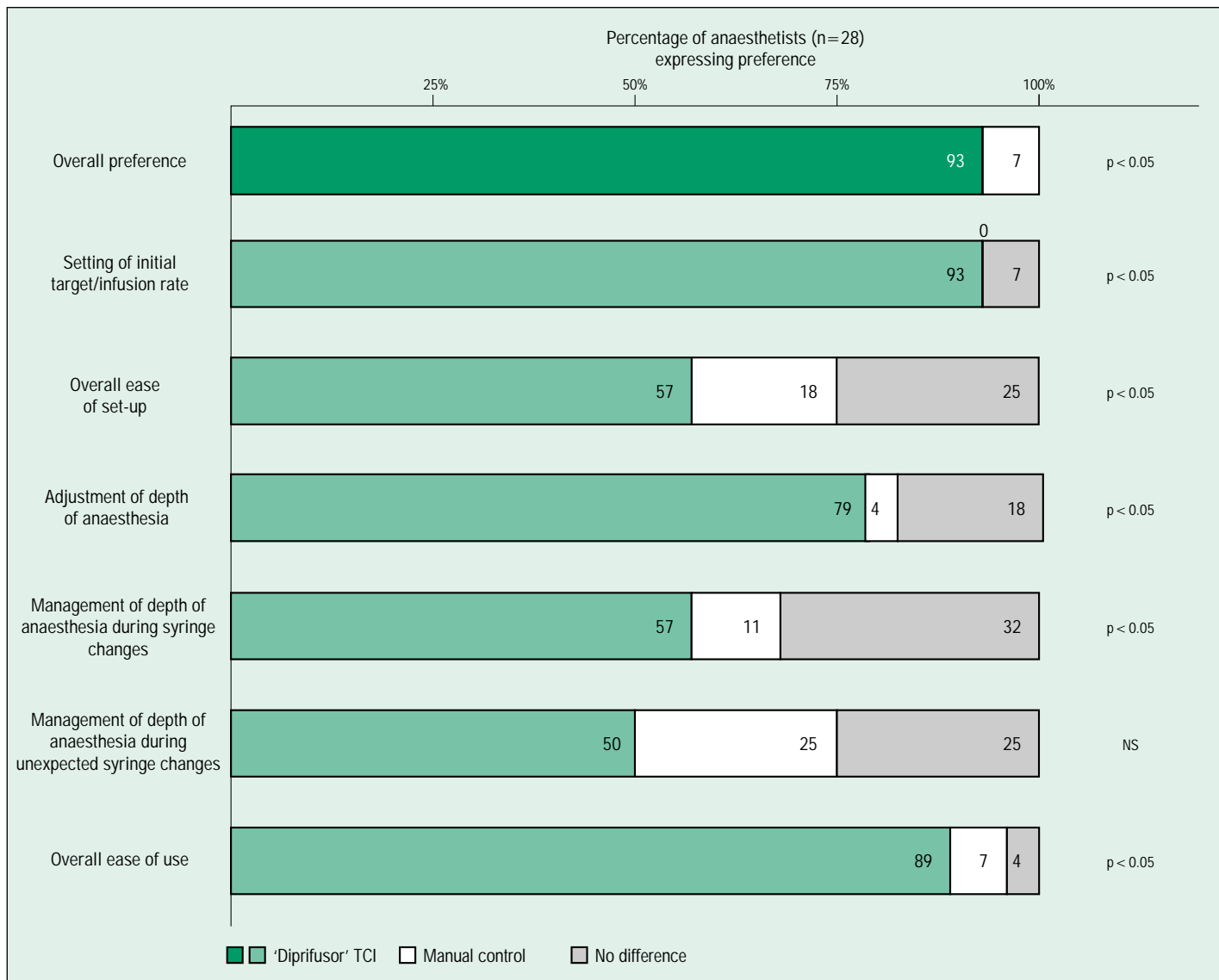
The study^{79b} confirmed the general guidelines (see page 39) for target concentrations during induction, including:

- A suitable range for adult patients aged less than 55 years is 4 to 8 µg/ml
- Initial target should be reduced in premedicated patients and those who receive pre-induction opioids
- A lower initial target and titration to effect are appropriate in patients who are debilitated or of advancing age.

The dose of ‘Diprivan’ for induction was lower with ‘Diprifusor’ TCI (mean 1.69 mg/kg) than with manual control (mean 2.31 mg/kg, $p < 0.001$).^{79a}

'Diprivan' TCI – clinical trials

Figure 23. User preference for 'Diprifusor' TCI or manual control as assessed by questionnaire^{79b}



European multicentre study

Target concentrations and infusion rates were titrated downwards as anaesthesia progressed. The overall infusion rate for 'Diprivan' was slightly greater ($p < 0.05$) in the 'Diprifusor' TCI group (mean 12.1 mg/kg/h) than in the manual control group (mean 11.0 mg/kg/h) and recovery time (time to opening eyes) was slightly prolonged ($p < 0.05$) after 'Diprifusor' TCI (mean 15 minutes) compared with manual control (mean 14 minutes). The control of anaesthesia in the 'Diprifusor' TCI group was easier and more precise, as shown by a reduced incidence of movement on surgical incision (Figure 24).^{79a}

Anaesthetists made more adjustments to the manual infusion rate than to target concentrations illustrating the user convenience of 'Diprifusor' TCI (Figure 25).^{79a}

Tolerability

This European multicentre study^{79b} confirmed the finding from regulatory studies⁴⁵⁻⁵² (see page 48) that the tolerability profile of 'Diprivan' is unchanged when administered by TCI. The overall pattern and incidence of side effects (e.g. hypotension and sinus bradycardia) was similar for 'Diprifusor' TCI and manually-controlled infusion of 'Diprivan'.^{79b}

Conclusions

- *'Diprifusor' TCI was easily learnt and well accepted by anaesthetists*
- *For anaesthesia with 'Diprivan', the clinical profiles of 'Diprifusor' TCI and manual control are very similar*
- *Overall user preference: of the two techniques, 'Diprifusor' TCI was preferred by most anaesthetists (93%) and they found it easier to use (89%).*

Figure 24. Movement in response to surgical stimuli during maintenance with 'Diprifusor' TCI or manual control^{79a}

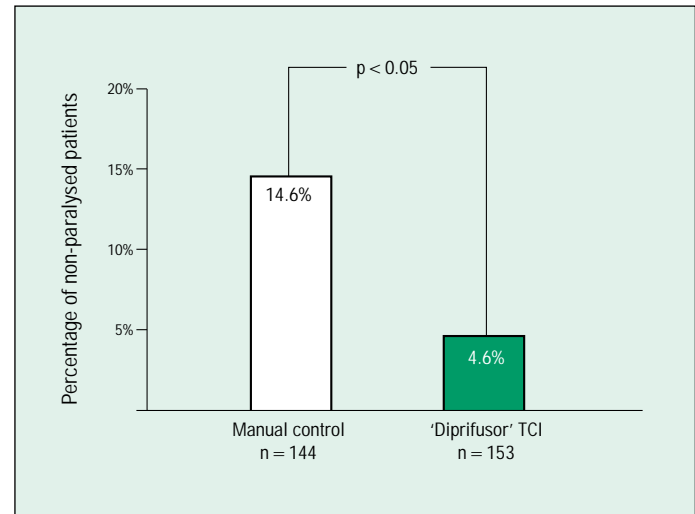
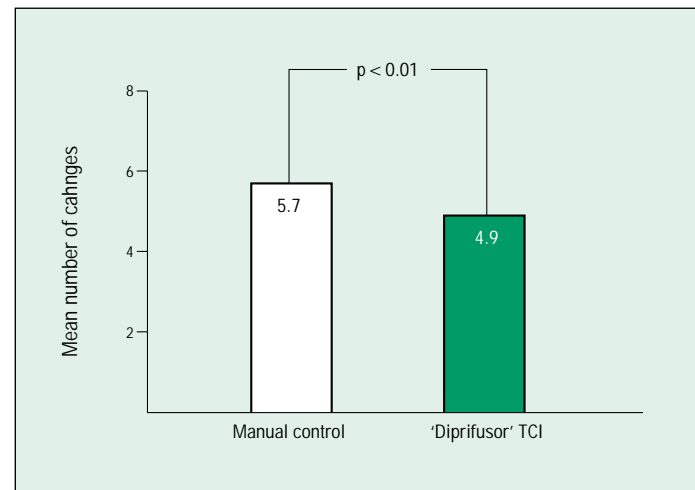


Figure 25. Need for changes to dosage rate with 'Diprifusor' TCI (target concentration) or manual control (infusion rate)^{79a}



'Diprifusor' TCI – main points

Use: induction and maintenance of anaesthesia in adult patients

General principles

- The anaesthetist adjusts the target blood concentration of propofol – and depth of anaesthesia – as required on clinical grounds
- Infusion rates are altered automatically according to a validated pharmacokinetic model

User requirements

- Documentation – from pump manufacturer (e.g. Instruction Manual) and from AstraZeneca (e.g. Guide for Anaesthetists, revised Prescribing Information)
- Drug – tagged 'Diprivan' Pre-Filled Syringe (PFS)
- Delivery system – commercially-available syringe pump incorporating 'Diprifusor'

Marketed 'Diprifusor' Systems

- Graseby 3500 Anaesthesia Syringe Pump (new model based on 3400)
- Vial Médical TCI ("sleeve" attachment to upgrade Pilot Anaesthesia syringe pump)
- ALARIS IVAC TIVA TCI syringe pump (new model based on ALARIS IVAC TIVA)

Clinical trial programme

- Provides guidance on target concentrations in relation to age, ASA status, premedication and supplementary analgesia
- Confirms that 'Diprifusor' TCI provides the major benefits of 'Diprivan':
 - smooth induction
 - good quality of maintenance
 - rapid, clear-headed recovery with low frequency of PONV
- Shows that 'Diprifusor' TCI compared with manually-controlled infusion of 'Diprivan' offers additional advantages:
 - more convenient administration (easier to use)
 - improved control (more predictable and precise control of the depth of anaesthesia)

Benefits to anaesthetist

- More convenient than manually-controlled infusion
- Avoids the need for time-consuming calculation of infusion rates
- Continuous process for induction and maintenance
 - more convenient than intravenous induction/vaporizer for maintenance
- Allows wider appreciation and experience of the clinical benefits of 'Diprivan'

Induction and maintenance of anaesthesia

Diprivan

Control and Recovery



Target Controlled Infusion (TCI)

Convenience and Control



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TCI Glossary

‘Diprifusor’

‘DIPRIFUSOR’ is a trade mark, the property of ZENECA Limited. This trade mark can be applied to software and hardware for the administration of ‘Diprivan’ by Target Controlled Infusion (TCI).

Target Controlled Infusion (TCI)

A technique of drug administration using an infusion system which allows the anaesthetist to select, on the infusion pump, a target blood concentration of a drug required for a particular pharmacodynamic effect.

‘Diprifusor’ TCI

A computer assisted technique for the target controlled infusion of ‘Diprivan’ using a ‘Diprifusor’ TCI system.

‘Diprifusor’ TCI Software

Software for the administration of ‘Diprivan’ by Target Controlled Infusion (TCI). This software, which has been licensed by the manufacturers of ‘Diprivan’ from the University of Glasgow, incorporates infusion control algorithms linked to a pharmacokinetic simulation programme. The simulation is based upon a three-compartment model, programmed with pharmacokinetic parameters (constants) specific for propofol.

‘Diprifusor’ TCI pump

An infusion pump incorporating ‘Diprifusor’ TCI software.

‘Diprifusor’ TCI module

The module, approximately 8 x 5 x 2cm, contains electronic components and associated software. It has been developed by the manufacturers of ‘Diprivan’ and is intended for inclusion in conventional infusion pumps to provide an additional function for the administration of ‘Diprivan’ by ‘Diprifusor’ TCI. The module incorporates ‘Diprifusor’ TCI software and additional software to provide a syringe recognition system.

‘Diprifusor’ TCI Subsystem

Comprises the ‘Diprifusor’ TCI module connected to an aerial in the pump and an identification tag in the pre-filled syringe finger grip.

‘Diprifusor’ TCI System

A complete delivery system (including an infusion pump) which utilises ‘Diprifusor’ TCI software for the administration of ‘Diprivan’ by ‘Diprifusor’ TCI.

Infusion Control Algorithms

Mathematical equations written as a computer program, which derive appropriate infusion rates required to achieve and maintain a desired (target) concentration.

Pharmacokinetic Model/PK Model

Mathematical representation of the distribution and elimination of a drug within an individual.

Pharmacokinetic Parameters

Values for the volume of the central compartment of the pharmacokinetic model, the elimination rate constant, and intercompartmental distribution rate constants.

Calculated Blood Propofol Concentration

The blood concentration calculated by 'Diprifusor' TCI software. At most times this will equal the target concentration. However, the calculated propofol concentration will differ from the target concentration for a time following a decrease in target concentration.

Calculated Effect-Site Concentration

The propofol concentration calculated to exist at the effect-site in the brain. This concentration tends to lag behind the blood concentration when the target concentration is increased, and provides an indication of the degree of equilibration which exists at a given time between blood and brain concentrations of propofol.

'Diprifusor' TCI Recognition System

The 'Diprifusor' TCI module is connected to an aerial in the pump and comprises electronics and software which will allow it to detect the presence of a recognition tag (also referred to as a PMR tag, programmable magnetic resonance tag) in the finger grip of a 1% 'Diprivan' pre-filled syringe. Data encoded in the recognition tag will identify the presence of a syringe containing 1% 'Diprivan'.

Target Blood Propofol Concentration

The desired target blood concentration set by an anaesthetist on a 'Diprifusor' TCI system. Recommended target propofol concentrations for Induction and Maintenance of General Anaesthesia in adult patients will be provided in 'Diprivan' prescribing information.

'Diprivan' Prescribing Information

Please retain International Prescribing Information in this pocket

Consult full, local prescribing information

'Diprivan' International Prescribing Information

NAME OF MEDICINAL PRODUCT

'DIPRIVAN' Injection (1% & 2%).

QUALITATIVE AND QUANTITATIVE COMPOSITION

Propofol 10 mg/ml ('Diprivan' 1%) or 20 mg/ml ('Diprivan' 2%).

PHARMACEUTICAL FORM

White aqueous isotonic oil-in-water emulsion for iv injection.

CLINICAL PARTICULARS

Therapeutic Indications

'Diprivan' is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia.

'Diprivan' may also be used for sedation of ventilated adult patients receiving intensive care.

'Diprivan' may also be used for conscious sedation for surgical and diagnostic procedures.

Dosage and Method of Administration

Supplementary analgesic agents are generally required in addition to 'Diprivan'.

'Diprivan' has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalation agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of 'Diprivan' may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

For specific guidance relating to the administration of 'Diprivan' using the 'Diprifusor' target controlled infusion (TCI) system, which incorporates 'Diprifusor' TCI software, see section **Target Controlled Infusion - Administration of 'Diprivan' by 'Diprifusor' TCI System**. Such use is restricted to induction and maintenance of anaesthesia in adults. The 'Diprifusor' TCI system is not recommended for use in ICU sedation or conscious sedation, or in children.

Adults

INDUCTION OF GENERAL ANAESTHESIA

'Diprivan' 1% may be used to induce anaesthesia by slow bolus injection or infusion.

'Diprivan' 2% should be used to induce anaesthesia by infusion and only in those patients who will receive 'Diprivan' 2% for maintenance of anaesthesia.

In unpremedicated and premedicated patients, it is recommended that 'Diprivan' should be titrated (approximately 40 mg every 10 seconds in an average healthy adult by bolus injection or infusion) against the response of the patient until the

clinical signs show the onset of anaesthesia. Most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg/kg of 'Diprivan'. The total dose required can be reduced by lower rates of administration (20-50 mg/min.). Over this age, the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 20 mg every 10 seconds).

MAINTENANCE OF GENERAL ANAESTHESIA

Anaesthesia can be maintained by administering 'Diprivan' either by continuous infusion or by repeat bolus injections to maintain the depth of anaesthesia required.

Continuous Infusion: 'Diprivan' 1% or 'Diprivan' 2% may be used. The required rate of administration varies considerably between patients but rates in the region of 4 to 12 mg/kg/h usually maintain satisfactory anaesthesia.

Repeat Bolus Injections: It is recommended that only 'Diprivan' 1% is used. If a technique involving repeat bolus injections is used, increments of 25 mg to 50 mg may be given according to clinical need.

SEDATION DURING INTENSIVE CARE

When used to provide sedation for ventilated adult patients undergoing intensive care, it is recommended that 'Diprivan' be given by continuous infusion. The infusion rate should be adjusted according to the depth of sedation required but rates in the region of 0.3 to 4.0 mg/kg/h should achieve satisfactory sedation.

Administration of 'Diprivan' by a 'Diprifusor' TCI system is not recommended for sedation during intensive care.

CONSCIOUS SEDATION FOR SURGICAL AND DIAGNOSTIC PROCEDURES

To provide sedation for surgical and diagnostic procedures rates of administration should be individualised and titrated to clinical response.

Most patients will require 0.5 to 1 mg/kg over 1 to 5 minutes to initiate sedation.

Maintenance of sedation may be accomplished by titrating 'Diprivan' infusion to the desired level of sedation - most patients will require 1.5 to 4.5 mg/kg/h. In addition to the infusion, bolus administration of 10 to 20 mg may be used if a rapid increase in the depth of sedation is required. In patients in ASA grades 3 and 4 the rate of administration and dosage may need to be reduced.

Administration of 'Diprivan' by a 'Diprifusor' TCI system is not recommended for conscious sedation.

Elderly Patients

'Diprivan' should be titrated against the response of the patient. Patients over the age of about 55 years may require lower doses of 'Diprivan' for induction of anaesthesia and for conscious sedation for surgical and diagnostic procedures.

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Children

INDUCTION OF GENERAL ANAESTHESIA

'Diprivan' is not recommended for use in infants less than 1 month old.

When used to induce anaesthesia in children, it is recommended that 'Diprivan' be given slowly until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or weight. Most patients over 8 years of age are likely to require approximately 2.5 mg/kg of 'Diprivan' for induction of anaesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades 3 and 4.

MAINTENANCE OF GENERAL ANAESTHESIA

'Diprivan' is not recommended for use in infants less than 1 month old.

Anaesthesia can be maintained by administering 'Diprivan' by infusion or repeat bolus injection to maintain the depth of anaesthesia required. It is recommended that only 'Diprivan' 1% is used if repeat bolus injections are used. The required rate of administration varies considerably between patients but rates in the region of 9 to 15 mg/kg/h usually achieve satisfactory anaesthesia.

CONSCIOUS SEDATION FOR SURGICAL AND DIAGNOSTIC PROCEDURES

'Diprivan' is not recommended for sedation in children as safety and efficacy have not been demonstrated.

SEDATION DURING INTENSIVE CARE

'Diprivan' is not recommended for sedation in children as safety and efficacy have not been demonstrated. Although no causal relationship has been established, serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections given doses in excess of those recommended for adults.

Administration of 'Diprivan' by a 'Diprifusor' TCI system is not recommended for any indication in children.

Administration

Administration of 'Diprivan' 2% by bolus injection is not recommended.

'Diprivan' can be used for infusion undiluted from plastic syringes or glass infusion bottles or 'Diprivan' pre-filled syringes. When 'Diprivan' is used undiluted to maintain anaesthesia, it is recommended that equipment such as syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

'Diprivan' 1% may also be used diluted with 5% Dextrose Intravenous Infusion only, in PVC infusion bags or glass infusion bottles. Dilutions, which must not

exceed 1 in 5 (2 mg propofol/ml) should be prepared aseptically immediately before administration. The mixture is stable for up to 6 hours.

The dilution may be used with a variety of infusion control techniques but a giving set used alone will not avoid the risk of accidental, uncontrolled infusion of large volumes of diluted 'Diprivan'. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be taken into account when deciding the maximum amount of dilution in the burette.

'Diprivan' may be administered via a Y-piece close to the injection site, into infusions of Dextrose 5% Intravenous Infusion, Sodium Chloride 0.9% Intravenous Infusion or Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion.

The glass pre-filled syringe (PFS) has a lower frictional resistance than plastic disposable syringes and operates more easily. Therefore, if 'Diprivan' is administered using a hand held pre-filled syringe, the line between the syringe and the patient must not be left open if unattended.

When the pre-filled syringe presentation is used in a syringe pump appropriate compatibility should be ensured. In particular, the pump should be designed to prevent siphoning and should have an occlusion alarm set no greater than 1000 mm Hg. If using a programmable or equivalent pump that offers options for use of different syringes then choose only the 'B-D' 50/60 ml 'PLASTIPAK' setting when using the 'Diprivan' pre-filled syringe.

'Diprivan' 1% may be premixed with alfentanil injection containing 500 µg/ml alfentanil ('Rapifen'; Janssen Pharmaceuticals Ltd.) in the ratio of 20:1 to 50:1 v/v. Mixtures should be prepared using sterile technique and used within 6 hours of preparation.

To reduce pain on initial injection, 'Diprivan' 1% used for induction may be mixed with Lignocaine Injection in a plastic syringe in the ratio of 20 parts 'Diprivan' 1% with up to one part of 0.5 or 1% Lignocaine Injection immediately prior to administration.

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DILUTION AND CO-ADMINISTRATION OF 'DIPRIVAN' WITH OTHER DRUGS OR INFUSION FLUIDS

(see section **Warnings and Precautions for Use**)

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing	Dextrose 5% Intravenous Infusion	Mix 1 part of 'Diprivan' 1% with up to 4 parts of Dextrose 5% Intravenous Infusion in either PVC infusion bags or glass infusion bottles. When diluted in PVC bags it is recommended that the bag should be full and that the dilution be prepared by withdrawing a volume of infusion fluid and replacing it with an equal volume of 'Diprivan' 1%.	Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours.
	Lignocaine Hydrochloride Injection. (0.5% or 1% without preservatives)	Mix 20 parts of 'Diprivan' 1% with up to 1 part of either 0.5% or 1% Lignocaine Hydrochloride Injection.	Prepare mixture aseptically immediately prior to administration. Use for Induction only.
	Alfentanil injection (500 µg/ml)	Mix Diprivan 1% with alfentanil injection in a ratio of 20:1 to 50:1 v/v.	Prepare mixture aseptically; use within 6 hours of preparation.

Co-administration via a Y-piece connector	Dextrose 5% Intravenous Infusion	Co-administer via a Y-piece connector.	Place the Y-piece connector close to the injection site.
	Sodium Chloride 0.9% Intravenous Infusion	As above	As above
	Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion	As above	As above

Target Controlled Infusion - Administration of 'Diprivan' by 'Diprifusor' TCI System.

Administration of 'Diprivan' by a 'Diprifusor' TCI system is restricted to induction and maintenance of general anaesthesia in adults. It is not recommended for use in ICU sedation or conscious sedation, or in children.

To achieve induction and maintenance of anaesthesia in adults, 'Diprivan' may be administered with the assistance of a Target Controlled Infusion (TCI) system. Such systems allow the anaesthetist to achieve and control a desired speed of induction and depth of anaesthesia by setting and adjusting target (predicted) blood concentrations of propofol. 'Diprivan' may be administered by TCI only with a 'Diprifusor' TCI system incorporating 'Diprifusor' TCI software. Such systems will operate only on recognition of electronically tagged pre-filled syringes containing 'Diprivan' 1% or 2% injection. The 'Diprifusor' TCI system will automatically adjust the infusion rate for the concentration of 'Diprivan' recognised. Users must be familiar with the infusion pump users manual and with the administration of 'Diprivan' by TCI and with the correct use of the syringe identification system, all of which are set out in the 'Diprifusor' training manual available from AstraZeneca at the address below.

Guidance on propofol target concentrations is given below. In view of interpatient variability in propofol pharmacokinetics and pharmacodynamics, in both premedicated and unpremedicated patients the target propofol concentration should be titrated against the response of the patient in order to achieve the depth of anaesthesia required.

In adult patients under 55 years of age anaesthesia can usually be induced with target propofol concentrations in the region of 4 to 8 µg/ml. An initial target of 4 µg/ml is recommended in premedicated patients and in unpremedicated patients

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an initial target of 6 µg/ml is advised. Induction time with these targets is generally within the range of 60-120 seconds. Higher targets will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression.

A lower initial target concentration should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4. The target concentrations can then be increased in steps of 0.5 to 1.0 µg/ml at intervals of 1 minute to achieve a gradual induction of anaesthesia.

Supplementary analgesia will generally be required and the extent to which target concentrations for maintenance of anaesthesia can be reduced will be influenced by the amount of concomitant analgesia administered. Target propofol concentrations in the region of 3 to 6 µg/ml usually maintain satisfactory anaesthesia.

The predicted propofol concentration on waking is generally in the region of 1.0 to 2.0 µg/ml and will be influenced by the amount of analgesia given during maintenance.

Contraindications

'Diprivan' is contraindicated in patients with a known allergy to 'Diprivan'.

Warnings and Precautions for Use

'Diprivan' should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in Intensive Care). Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. 'Diprivan' should not be administered by the person conducting the diagnostic or surgical procedure.

When 'Diprivan' is administered for conscious sedation for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.

An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia. Very rarely the use of 'Diprivan' may be associated with the development of a period of post-operative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.

As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients.

'Diprivan' lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an

anticholinergic agent before induction or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when 'Diprivan' is used in conjunction with other agents likely to cause a bradycardia.

When 'Diprivan' is administered to an epileptic patient, there may be a risk of convulsion.

Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

It is recommended that blood lipid levels should be monitored if 'Diprivan' is administered to patients thought to be at particular risk of fat overload. Administration of 'Diprivan' should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the 'Diprivan' formulation; 1.0 ml of 'Diprivan' contains approximately 0.1 g of fat.

EDTA-containing formulation only:

EDTA is a chelator of metal ions, including zinc. The need for supplemental zinc should be considered during prolonged administration of 'Diprivan', particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

Additional Precautions

'Diprivan' contains no antimicrobial preservatives and supports growth of micro-organisms. When 'Diprivan' is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both 'Diprivan' and infusion equipment throughout the infusion period. Any infusion fluids added to the 'Diprivan' line must be administered close to the cannula site. 'Diprivan' must not be administered via a microbiological filter.

'Diprivan' and any syringe containing 'Diprivan' are for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion of 'Diprivan' must not exceed 12 hours. At the end of the procedure or at 12 hours, whichever is the sooner, both the reservoir of 'Diprivan' and the infusion line must be discarded and replaced as appropriate.

Interactions with other Medicaments and Other Forms of Interactions

'Diprivan' has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of 'Diprivan' may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

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Pregnancy and Lactation

Pregnancy

'Diprivan' should not be used in pregnancy. 'Diprivan' has been used, however, during termination of pregnancy in the first trimester.

Obstetrics

'Diprivan' crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia.

Lactation

Safety to the neonate following the use of 'Diprivan' in mothers who are breast feeding has not been established.

Effects on Ability to Drive and Use Machines

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anaesthesia.

Possible Adverse Reactions

General

Induction of anaesthesia is generally smooth with minimal evidence of excitation. During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedicants and other agents.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of 'Diprivan' during the period of anaesthetic maintenance.

During the recovery phase, nausea, vomiting and headache occur in only a small proportion of patients.

There have been very rare reports of rhabdomyolysis when 'Diprivan' has been administered at doses greater than 4 mg/kg/hr for ICU sedation.

Epileptiform movements, including convulsions and opisthotonus, have been reported rarely during induction, maintenance and recovery.

Rarely, clinical features of anaphylaxis, which may include angioedema bronchospasm, erythema and hypotension, occur following 'Diprivan' administration.

Pulmonary oedema has been observed. There have been reports of post-operative fever.

As with other anaesthetics sexual disinhibition may occur.

Rarely, discolouration of urine has been reported following prolonged administration of 'Diprivan'.

Local

The local pain which may occur during the induction phase can be minimised by the use of the larger veins of the forearm and antecubital fossa. With 'Diprivan' 1% local pain can also be minimised by the co-administration of Lignocaine (see

section **Dosage and Method of Administration**). Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies showed minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

Overdosage

Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require lowering of the patient's head and, if severe, use of plasma expanders and pressor agents.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Propofol (2, 6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood.

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when 'Diprivan' is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low.

Although ventilatory depression can occur following administration of 'Diprivan', any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

'Diprivan' reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and post-operative nausea and vomiting.

In general, there is less post-operative nausea and vomiting following anaesthesia with 'Diprivan' than following anaesthesia with inhalational agents. There is evidence that this may be related to an antiemetic effect of propofol.

'Diprivan', at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

Pharmacokinetic Properties

The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a three compartment open model. The first phase is characterised by a very rapid distribution (half-life 2-4 minutes) followed by rapid elimination (half-life 30-60 minutes) and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

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Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5-2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

When 'Diprivan' is used to maintain anaesthesia, blood concentrations of propofol asymptotically approach the steady-state value for the given administration rate. The pharmacokinetics are linear over the recommended range of infusion rates of 'Diprivan'.

Pre-clinical Safety Data Relevant to the Prescriber

Propofol is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Core Prescribing Information.

PHARMACEUTICAL PARTICULARS

Incompatibilities

'Diprivan' should not be mixed prior to administration with injections or infusion fluids with the exception of 'Diprivan' 1% which can be mixed with 5% Dextrose in PVC bags or glass infusion bottles or Lignocaine Injection or alfentanil injection in plastic syringes (see section **Dosage and Method of Administration**).

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same iv line as 'Diprivan' without prior flushing.

Shelf life

As packaged for sale:

3 years for 'Diprivan' and 'Diprivan' (EDTA-containing formulation)

1% ampoules and vials.

2 years for 'Diprivan' and 'Diprivan' (EDTA-containing formulation)

2% vials.

2 years for 'Diprivan' and 'Diprivan' (EDTA-containing formulation) 1% and

2% pre-filled syringes.

After dilution use within 6 hours of dilution.

Special Precautions for Storage

Store between 2°C and 25°C. Do not freeze.

Nature and Content of Containers*

'Diprivan' 1% (and EDTA-containing formulation):

glass ampoules (20 ml) (boxes of 5)

glass vials (50 ml) (100 ml)

glass pre-filled syringe (20 ml) (50 ml)

'Diprivan' 2% (and EDTA-containing formulation):

glass pre-filled syringe (10 ml) (50 ml)

glass vial (50 ml)

Instructions for Use/Handling

Containers should be shaken before use. Any portion of the contents remaining after use should be discarded.

Asepsis for 'Diprivan' and infusion equipment must be maintained (see warnings and precautions for use.)

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* Your local AstraZeneca representative or office can advise on available presentations.

Consult full, local prescribing information

Further information is available on request

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