Anthony R. Absalom
Keira P. Mason
Editors

Total Intravenous Anesthesia and Target Controlled Infusions

A Comprehensive Global Anthology

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Dedication by Keira P. Mason

My dedication is foremost to my mother and father, whose sacrifice, love, and encouragement enabled me to pursue my goals and dreams. Leading by example, they showed me to persevere, remain positive, optimistic, and always strive to achieve my personal best. My deepest gratitude and appreciation to my family, Ed, and my two sons, Colin and Tyler. Tyler, you are a tender soul, inventive, hardworking, and brave when faced with challenges beyond your years, and special beyond words. Colin, your tenacity, creativity, and drive make you a unique gem. I am so proud of you both. I hope that I may guide, nurture, and provide for you both as my parents did for me. Never forget your middle name, Jigme. . .... the name given to monarchs—a reminder for you both to be proud and brave, and to persevere and pursue your dreams, even in the face of adversity and challenges.

Dedication by Anthony R. Absalom

I dedicate this book to the authors, whose expertise and time made this book possible, and to my family, who have supported me "through thick and thin."

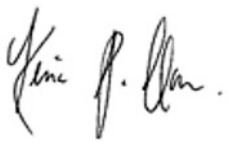
Anthony (Tony) Absalom

Preface

We are honored to present *Total Intravenous Anesthesia and Target Controlled Infusion*. This book is a testament to the passion and expertise of the contributing authors who are all committed to the field of intravenous anesthesia and target controlled infusion. The author list reads like a "Who's who" of anesthetic pharmacology, and includes experts from diverse disciplines and specialties, from 20 countries around the world. We are very appreciative of and honored by their efforts and extend a sincere "thank you" to each author.

This book is a unique contribution to the field. It is the first to address these topics in a comprehensive manner. Each chapter was written by a specialist in that particular area and is intended to be of value to all providers of intravenous sedation and anesthesia. It may be read cover to cover, or read ad hoc, one chapter at a time, out of succession. There is intentional, albeit minimal, repetition of topics. The repetition is intended not only to consolidate important information for the reader but also to convey relevant information for those who may not be reading the book cover to cover. Even when there is "repetition," it is presented in a different style by each of the individual authors, which in most cases masks the repeated elements.

We wish our readers much reading pleasure. Our primary goal is to help improve the care of patients worldwide, and we trust that this book, which represents a true international collaboration among multiple specialists, will be a timeless resource for clinicians and researchers working in the field of intravenous delivery of sedation and anesthesia.



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Part I

Introduction/Background

When and How Did It All Begin? A Brief History of Intravenous Anesthesia

1

John William Sear

Among the first reports of the intravenous injection of drugs are those describing the studies of Wren and Major [1, 2]. They injected opium dissolved in water into the venous system of a dog, which caused it to be stupefied but did not kill it! Despite this observation made more than 350 years ago, the history of clinical intravenous anesthesia does not really become significant before the late nineteenth century.

The delivery of drugs by the intravenous route requires specific equipment; and for this, we must be grateful for the development of the hollow needle by Francis Rynd in 1845, and the syringe in 1853 by Charles Gabriel Pravaz. The latter was not initially designed for intravenous drug administration but rather for the delivery of perineural and intra-arterial injections. More recently the development of target-controlled infusion delivery regimens aimed at achieving given plasma or effect-site target drug concentrations has usually required dedicated infusion apparatus linked to computer systems that control the rate of drug dosing.

Among the earliest pioneers studying the delivery of intravenous anesthesia to patients was Pierre-Cyprian Ore (Professor of Physiology, University of Bordeaux), who, in 1872, reported 36 cases of anesthesia using chloral hydrate as an intravenous anesthetic in the treatment of patients with tetanus, to the Societe Chirugicale de Paris [3]. Despite his enthusiasm, these early attempts at intravenous anesthesia (IVA) were associated with a high incidence of mortality. As a result, this delayed the further development of IVA until the beginning of the twentieth century.

1909 saw the development of hedonal (a urethane derivative) which was used for the treatment of insomnia. Krawkow and Fedoroff described its role to provide general anesthesia [4, 5]. They described this as the "first intravenous agent that produced fairly adequate surgical anesthesia with a moderate degree of safety." However, the agent was not sufficiently water soluble, and resulting "weak" solutions acted very slowly to produce anesthesia, and had a long duration of effect. Hence the search for other agents continued with Noel and Souttar examining the possible role of paraldehyde [6]; while Peck and Meltzer described the use of intravenous magnesium sulfate [7]; and ethanol infusions were studied by Naragawa, and Cardot and Laugier [8, 9].

The anesthetic properties of the barbiturates were first observed with diethylbarbituric acid, which was synthesized by Fischer and von Mering [10]. But, again, its low water solubility and prolonged duration of action lead to a delayed further development of the drug. Use of the first barbiturate for intravenous anesthesia was reported in 1921, when Bardet and Bardet studied a mixture of the diethylamines of di-ethyl and di-allyl barbituric acid (Somnifen) [11]. The sodium salt of sec-butyl-(2-bromoallyl)-barbiturate (Pernocton) had greater water solubility, and was introduced into clinical practice in 1927. Further developments lead to the synthesis by Kropp and Taub, and initial clinical studies by Weese and Scharpff of the short-acting, rapid onset hexobarbital (Evipan) [12], although the drug had a high incidence of excitatory side effects. Nevertheless, use of Evipan was recommended as the agent of choice in those individuals with a tendency to bronchospasm.

Barbiturates

The first major development and advance from a clinical viewpoint was the introduction of thiopental, which was administered in separate studies by Lundy, and Waters [13, 14]. At the same time, Tabern and Volwiler had initiated a research program to prepare a series of thiobarbiturates where there was substitution of the oxygen at the C(2) position with a sulfur atom [15]. This led to agents having a

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shorter period of hypnosis. One of these molecules was thiopental. It was devoid of the excitatory side effects seen with hexobarbital. The barbiturate was completely metabolized with only <0.3 % excreted unchanged in the urine. In man, there was a comparatively high rate of metabolism (16–24 % per hour). Thiopental had no analgesic properties, but had the tendency to increase the sensitivity of an individual to pain and touch.

Although it was originally studied in the USA, it was subsequently introduced into the United Kingdom by Jarman and Abel [16]. At this time, maintenance of anesthesia was normally provided by di-ethyl-ether or one of the other volatile agents (all of which had undesirable side effects). As a result, researchers started using infusions of thiopental to maintain anesthesia. However, they found that if the barbiturate was given without opioids or muscle relaxants, large doses of barbiturates were needed to suppress movement, and these doses caused side effects of cardio-respiratory depression and delayed awakening (the pharmacokinetics and metabolism of the barbiturate were not fully defined until much later by Price [17]).

Use of thiopental by infusion has also been cited as the cause of many deaths among the casualties at Pearl Harbor in 1941—with the often quoted, but misconceived and incorrect statement from a surgical colleague "that intravenous anesthesia was an ideal method of euthanasia!!" [18, 19].

Pentobarbital (a metabolite of thiopental) had previously been used as an anesthetic by Lundy in 1932. It caused less laryngospasm than was seen after thiopental, but there was a suggestion that it was associated with an improved recovery profile.

Since the Second World War, further developments have taken place with other drugs being used to provide intravenous anesthesia. Beside thiopental, several other intravenous thio-barbiturates were assessed including thiamylal and thialbarbitone; drugs having the same duration of action and spectrum of activity as thiopental, but lower potency.

Introduction of a methyl thio-ethyl group into the side chain of methitural was aimed at accelerating the breakdown of the drug. Its development led to a drug that was popular in Germany as Thiogenal, and as Neraval in the USA, although the quality of anesthesia was inferior to that of thiopental. Similar comments were made about buthalitone (marketed as Transithal in the UK; as Ulbreval in the USA; and Baytinal in Germany) which was synthesized in the USA in 1936, but not studied until 1954 by Weese and Koss. The potency of buthalitone was about half that of thiopental.

However, a greater advance was seen with the introduction of hexobarbital which causes rapid onset of anesthesia. This property was attributed to the addition of a methyl group at the C1 position. Further development of this molecule led to the introduction in 1957 of methohexital, which was of shorter duration of action and had a shorter half-life than thiopental [20]. It was irritating to the subcutaneous tissues if accidentally given extravascularly, but more irritant and dangerous if given intra-arterially. Methohexital has two asymmetrical carbon atoms, so existing as four separate isomers. The proprietary drug is a mixture of two of these: α-dl pair (a mixture of all four isomers was shown by Taylor and Stoelting to produce excessive skeletal muscle activity and possible convulsions [21]).

There have been a number of studies described that used the drug by continuous infusion to maintain anesthesia without prolonged recovery times [22, 23]. However, its use was associated with the side effect of pain on injection and a high incidence of involuntary muscle movements. Several other methyl-thiobarbiturates have been studied, but again all had very high incidences of excitatory side effects.

Benzodiazepines

Although a number of benzodiazepines have been studied as sedative drugs since the synthesis of chlordiazepoxide in 1955 (e.g., diazepam, lorazepam), only diazepam has enjoyed any use as an anesthetic induction agent. Titration of the drug to the exact induction dose is difficult, as the drug's profile includes a slow onset of action and prolonged duration. The benzodiazepine is water insoluble, which requires the use of a lipid solvent, but early solvents caused venous irritation. The introduction of an emulsion formulation reduced the incidences of pain on injection and thrombophlebitis, but had no effect on the recovery profile after large doses of diazepam.

More recent advances with the benzodiazepines as agents for the maintenance of anesthesia have revolved around the introduction of firstly midazolam, and more recently remimazolam. The former has been used for the induction and maintenance of intravenous anesthesia [24, 25]. One advantage of these agents is the parallel development of a specific antagonist, flumazenil, which can be given at the termination of anesthesia to facilitate recovery. However, this has not been totally straightforward, as the mismatch between the pharmacokinetics and pharmacodynamics of the agonist and antagonist has resulted in reports of cases showing "rebound hypnotization" after initial recovery [26].

Propanidid

Propanidid (a phenoxyacetic acid derivative of eugenol, the chief constituent of oil of cloves) was a short-acting sedative-hypnotic containing an ester moiety which was broken down by body (pseudochline-esterase) and tissue esterases. It was the first clinically acceptable non-barbiturate intravenous anesthetic when introduced in 1965 but was withdrawn

in 1984 because of a high incidence of anaphylactic reactions—again, believed to be due to the polyoxyethylated castor oil solvent, Cremophor EL (BASF, Ludwigshafen, Germany).

When attempts were made to find an alternative solvent, it was shown that a liposomal formulation had a similar potency in rats to the Cremophor one; it also appeared superior as far as tolerance with a reduced incidence of clonic seizures [27]. A further study was therefore conducted in swine, but this failed to confirm any potential advantage of the liposomal formation over other existing hypnotics [28].

More recently another metabolically active ester with a structure similar to propanidid (AZD 3043) has been evaluated in man—this time, formulated in the lipid emulsion used for propofol [29]. Although the drug had a short context-sensitive half-time, there were some undesirable side effects—water insolubility; low potency; a dose-related increase in heart rate during drug infusion; sporadic episodes of involuntary movements and increased muscle tone (especially during the recovery phase); and in three patients there were episodes of erythema, chest discomfort, and dyspnea after drug dosing. Overall, one or more adverse side effects occurred in 29 % of the patients studied.

Etomidate

This imidazole derivative was discovered in 1964 at Janssen Pharmaceutica in Belgium and introduced into clinical practice in 1974. Unlike many other intravenous agents, etomidate caused little hemodynamic depression, and its use was not associated with histamine release. The agent had the profile of rapid onset and offset, but its use was accompanied by significant adverse side effects: pain on injection—due primarily to the propylene glycol solvent; myoclonic activity; and a high incidence of postoperative nausea and vomiting.

In 1983 it was reported that when the drug was given by continuous infusion to provide ICU sedation to multiply traumatized patients, there was an increase in patient mortality when compared with other sedation regimens [30]. In vitro and in vivo studies have shown that infusions (and single doses) of etomidate result in an inhibition of adrenal steroidogenesis.

As a result, the present role of etomidate in anesthesia practice is confined mainly to use as an induction drug for patients at risk of hemodynamic instability; for those who have shown previous allergic reactions to other induction agents; and electro-convulsive therapy (since etomidate decreases seizure thresholds).

A reformulation of etomidate in a lipid emulsion reduces the incidence of pain on injection, but does not address the issue of reduced cortisol synthesis. More recent attempts at addressing the effects of the imidazole compound on cortisol biosynthesis are further discussed in Chaps. 12 and 16.

Steroids

In 1927, Cashin and Moravek reported the ability of a colloidal suspension of cholesterol to induce anesthesia in cats [31]. Subsequent studies showed no apparent relationship between the hypnotic (anesthetic) and hormonal properties of the steroids, with the most potent anesthetic steroid being pregnan-3,20-dione (pregnanedione) which is virtually devoid of endocrine activity.

Over the next 80 or more years, the anesthetic properties of a large number of steroids were assessed both in vitro, and in vivo in laboratory animals and man. One of the main problems with steroid agents has been their lack of water solubility. Most steroids show high therapeutic indices in animals, but a variable effect in man in terms of the onset of hypnosis, and the rapidity and completeness of recovery.

In 1941, Selye reported that injections of progesterone produced sleep in rodents [32]; however, it was not until the studies by P'An et al., and Murphy and colleagues that the first clinical report of the anesthetic effects of the water soluble steroid hydroxydione was published [33, 34]. However, this drug did not have an ideal profile—as the onset of hypnosis was delayed (not occurring until 3–5 min after drug administration). Was this because the hypnotic effect of hydroxydione was due to a metabolite? It also had a long duration of action; and a high incidence of thrombophlebitis—so requiring the drug to be administered as a high volume, dilute solution. Other side effects included a fall in blood pressure and respiratory depression which also did not occur until sometime after initial drug administration. However, compared with thiopental, hydroxydione had a far greater therapeutic index; other features were an association with a low incidence of postoperative nausea and vomiting.

In the early 1970s, studies were undertaken of a new compound that was a mixture of two steroids (alfaxalone and alfadolone acetate) solvented in polyoxyethylated castor oil (Cremophor EL solution). This resulted in the hypnotic agent Althesin [35]. The main component of the combination was alfaxalone; the alfadolone acetate being added to increase the solubility of the alfaxalone. Althesin was a rapid onset, short-acting drug, which was used to both induce anesthesia, and provide anesthesia when given by repeat intravenous bolus doses or as a continuous infusion. The features of rapid onset and high potency have been associated with the presence of a free-OH group at the C (3) position of the A ring of the pregnane nucleus.

In lower doses, the drug was used to provide sedation during regional anesthetic blocks or to allow controlled

ventilation of patients in the intensive care unit. The drug also had advantageous effects on cerebral metabolism with a reduction in cerebral oxygen consumption, and a decrease in cerebral blood flow and CSF pressure leading to a reduction in intracerebral pressure (so making the drug very useful for neuroanesthesia); a low incidence of venous sequelae including thrombophlebitis.

One important facet of its pharmacology was that repeat bolus dosing of Althesin was not associated with a progressive increased duration of effect, as had been seen with barbiturate drugs. This finding led several authors to explore the concept of maintaining anesthesia by a continuous infusion of the steroids [36–40]. These pivotal studies underpin the development of continuous intravenous anesthesia.

However, it was soon found that the use of Althesin was associated with a high incidence of hypersensitivity reactions [41–43]. Research studies aimed at establishing the cause of these reactions were never completely conclusive, and attempts at reformulation were similarly unsuccessful. Hence the drug was withdrawn from clinical practice in 1984, although its use continued in some veterinary species. Recent interest in the use of steroids to provide anesthesia has led to further attempts at reformulation (see Chap. 16).

Other steroid anesthetic agents have been evaluated in animals and man—including minaxolone citrate, eltanolone (5β-pregnanolone), ORG 21465 and ORG 25435—but all have failed to display improved pharmacokinetic or pharmacodynamics profile when compared with other anesthetic agents available at that time.

Phencyclidines

These cyclohexylamine compounds act to produce a different type of anesthesia than that seen with other anesthetic agents—namely, a state of unconsciousness in which the patient appears to be in a cataleptic (or dissociative) state, but able to undergo surgery without any recall of events. Several drugs of this type have been studied, but the first significant compound was phencyclidine (Sernil; or PCP). This is still used today in some veterinary practices; but has been superseded in man because of its high associated incidence of post-anesthetic psychotomimetic side effects and delirium.

The main drug today is ketamine, which was synthesized in 1962 by Stevens at Parke-Davies laboratories, with the first clinical studies undertaken in 1965. Widespread clinical use originates in 1970, and it is still the drug of choice for many clinical scenarios in both human and veterinary practices (this being the case despite evidence of psychotomimetic activity and cardiovascular stimulation in many patients [44, 45]).

There are some data to suggest that the drug (which is a racemic mixture of two optical isomers) may show an improved profile when given as the S (+) isomer alone. Both animal and human studies confirm this to be the more effective isomer, with shorter emergence and faster return of cognitive function. However, its use does not totally abolish the occurrence of the postoperative sequelae.

Propofol

The history underlying the development of the present lead compound (propofol—di-isopropyl phenol) has not been straightforward. Propofol, a substituted derivative of phenol was synthesized by Glen and colleagues at ICI, UK in the early 1970s [46]. Because of the drug's water insolubility, initial studies were conducted with it formulated in three different solvents. The main study programme was conducted with a formulation solvented in Cremophor EL. This resulted in a number of cases of anaphylactoid reactions, and the temporary withdrawal of the drug.

In 1983, a lipid emulsion formulation of the drug was available, with the first dose delivered by my erstwhile colleague, Nigel Kay, in Oxford, UK [47]. The subsequent clinical trials programme showed it to be a drug of great potential, with the drug being licensed for general release in the UK and Europe in 1986 followed by FDA approval in the USA in 1989.

Since that time, the drug has been used worldwide; and the full pharmacokinetic and pharmacodynamics profile of the agent have been defined when used for induction and maintenance of anesthesia; for sedation for minor procedures (with or without regional blockade); and for sedation in the intensive care unit.

The Concept of 'Balanced Anesthesia'

The concept of balanced anesthesia was first introduced by George Crile during the period 1900–1910, with the aim of providing a light general anesthetic with obtunding of the responses to noxious stimuli associated with surgery being achieved by the administration of local anesthetic blocks. In 1926, Lundy used the same term to indicate the balance between a mixture of premedication (often heavy and often excessive), regional anesthesia and general anesthesia [48]. The first use of an intravenous balanced anesthetic technique was thiopental in combination with nitrous oxide and oxygen as reported by Organe and Broad [49]. This concept of using several different components of a total anesthetic was further expanded by Neff et al. with nitrous oxide-oxygen anesthesia being supplemented

by intravenous pethidine (meperidine), a neuromuscular relaxant (d-tubocurarine) and sodium thiopental [50].

It is from these roots that present day intravenous anesthesia or total intravenous anesthesia is derived.

Intravenous anesthesia for practice outside the operating theater.

Although anesthesia is usually conducted within the confines of the hospital, office practice, or surgery, there is increasing need for the delivery of anesthesia at various sites of trauma—such as at traffic accidents, other disasters or in the theater of war. The need to develop intravenous anesthesia for these scenarios originates partly from the anesthetic techniques used during the Chaco War (1932–1935) between Bolivia and Paraguay, and the Spanish Civil War (1936–1939).

Apart from hexobarbital, which was introduced in 1932, the medical staff had few other options available, and had to revert to the use of intravenous ethanol and tri-bromomethanol (Avertin). The main advantage of hexobarbital compared to previous barbiturates was its induction of anaesthesia in one arm-brain circulation time.

Again the introduction of thiopental in 1934 by Lundy and Tovell changed practices in these cases. Despite the adverse comments levelled at the use of thiopental at Pearl Harbor by civilian surgical personnel, intravenous agents must remain a key component of anesthesia in these circumstances. The editorial comments of Halford have often overshadowed the truth as presented in the accompanying paper by Adams and Gray. Thankfully suggestion that the use of thiopental was associated with increased adverse outcomes including mortality has not resulted in the abandonment of intravenous anesthesia in the shocked patient.

However, present anesthetic practices outside of the hospital environment have been influenced through the introduction of two key intravenous agents—ketamine in 1970 and Althesin in 1971, together with the availability of a number of short-acting analgesics (initially pentazocine, and later fentanyl, alfentanil, sufentanil, and more recently remifentanil). Examples of successful techniques used by the British army are typified by the studies of Restall and Jago [51, 52]; while American practice was largely based around the use of ketamine, and remains that way to this day. The more recent introduction of propofol into "field anesthesia" represents another new development, which remains to be fully evaluated.

The research and development of new intravenous anesthetic agents continues; but progress is likely to be slower than the rate and pattern of growth seen over the last hundred or so years. Will we see new innovative agents? Only time will tell!

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The Development and Regulation of Commercial Devices for Target-Controlled Drug Infusion

2

John B. Glen

Introduction

The mathematical background to the concept of target-controlled infusion (TCI) and its application to the administration of intravenous anaesthetic and analgesic drugs will be discussed elsewhere in this book (see Chap. 25—"Pharmacokinetics and Pharmacodynamics in the Pediatric Patient" by Anderson and Chap. 6—"Basic Pharmacology: Kinetics and Dynamics for Dummies" by Rader). As I was closely involved in the development of propofol, and the clinical trial programme and related studies required to support the introduction of the 'Diprifusor'™ TCI system, this chapter sets out to provide a personal account of the development and regulatory approval of commercial TCI systems.

The Development of Infusion Devices Suitable for Use in Anaesthesia

Propofol, first marketed as an anaesthetic agent for induction and short term maintenance of anaesthesia in 1986, was developed by the Pharmaceuticals Division of Imperial Chemical Industries (ICI, becoming Zeneca in 1993, and in 1999 merging with Astra to form AstraZeneca—these are referred to as ICI or by the generic term "the Company" hereafter). From an early stage in the pharmacological evaluation of the drug, it was apparent that propofol had a pharmacokinetic profile which would allow its use by continuous infusion to maintain anaesthesia, an observation critical to its selection as a candidate drug. Further regulatory approvals were obtained to extend the use of propofol to long term maintenance of anaesthesia and as a sedative, used in association with regional anaesthesia, or to facilitate ventilation in patients requiring intensive care.

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A limiting factor in the clinical development of infusion techniques was the lack of suitable equipment in operating theatres. While anaesthesiologists were familiar with the use of volumetric infusion pumps in the intensive care environment, these devices with their high capital cost and a requirement for expensive disposable cartridges were not suitable for routine theatre use. While some syringe drivers were available, most of these had a maximum delivery rate of 99 ml h^{-1}. In 1986 I wrote to a large number of the infusion device manufacturers to elicit their interest in a collaborative approach to the development of equipment more suitable for routine operating theatre use. Among a small number of positive responses, that from the Ohmeda Company, a subsidiary of BOC Healthcare was the most encouraging. They built a prototype which incorporated a bolus facility for the rapid delivery of loading infusions and could be interfaced with a controller for computer-controlled infusions. Clinical evaluation of this prototype confirmed that it fulfilled all the requirements of an infusion device for anaesthesia, such that the Ohmeda 9000 became the first of a new generation of syringe drivers [1]. This device could provide 'bolus' infusion rates up to 1200 ml h^{-1} suitable for induction of anaesthesia and a continuous infusion rate up to 200 ml h^{-1}. Syringe pumps with similar features were subsequently developed by a range of manufactures around the world.

First Steps Towards Commercial TCI Systems

In the late 1980s I recall a discussion with Walter Nimmo, who was at that time Professor of Anaesthesia at Sheffield University. He had recently returned from a visit to Duke University, North Carolina, where he had been impressed by the work Jerry Reeves and Peter Glass were doing with pharmacokinetic model-driven infusion and suggested that we should consider this approach for the administration of propofol. Studies on the maintenance of anaesthesia in Europe had been done principally with conventional syringe pumps,

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with depth of anaesthesia adjusted simply by altering the infusion rate in ml per hour to deliver drug within the range of 4–12 mg kg^{-1} h^{-1}. This appeared to be quite satisfactory and was consistent with my experience in laboratory animals, where the response to a change to infusion rate was a prompt change in depth of anaesthesia. As such, I was not convinced at that time that a more sophisticated, 'computer-controlled' system would offer significant benefits to justify the likely cost and added complexity. However, as the various international research groups continued to work with a range of independently developed computer-controlled infusion systems, and began to apply them to the administration of propofol, in early 1990 I persuaded ICI to allow me to organise a workshop on computer simulation and control of i.v. infusions in anaesthesia, with the following objectives:

1. To allow common interest groups to exchange ideas and discuss future developments
2. To promote a degree of standardisation in systems developed for the infusion of propofol
3. To facilitate the development of more convenient systems for the administration of i.v. anaesthetics.

The attendees were mainly academic anaesthesiologists with interests in pharmacokinetics and pharmacodynamics, a number of whom had developed their own prototype computer-controlled systems for the administration of hypnotic or analgesic agents. These included Chris Hull, Cedric Prys-Roberts, Peter Hutton, Gavin Kenny, Martin White and Bill Mapleson from the UK, Luc Barvais, Alain d'Hollander, Frederic Camu and F Cantraine from Belgium, Pierre Maitre and Don Stanski from Switzerland, Jürgen Schüttler and Siggi Kloos from Germany, Xavier Viviand and Bruno Lacarelle from France, Anders Nilsson from Sweden and Peter Glass, Jim Jacobs and Steven Shafer from the USA. Martyn Gray (Ohmeda, UK) and Jim Skakoon (Bard, USA) provided input from infusion device manufacturers, and from the Company, I was accompanied by Ian Cockshott (pharmacokinetics), Philip Arundel (mathematics and electronics) and Katie Hopkins (medical research).

This meeting achieved its objectives in that the participants welcomed the opportunity to share their experience and to seek a route towards wider availability of computer-controlled infusion systems. It was clear that there would need to be a degree of standardisation and discussion of product liability issues highlighted the need for pharmaceutical companies to provide regulatory authorities with more information, before guidance on computer-controlled infusion could be included in drug prescribing information. By the end of this meeting I was convinced that computer-controlled systems could facilitate the administration of propofol for maintenance of anaesthesia but commercial support for a complex and potentially expensive development was yet to be obtained. Together with Jos Heykants of Janssen Pharmaceutica, I organised a second international workshop on 'Target Control Titration in intravenous anesthesia' in the Netherlands just prior to a World Congress of Anaesthesiology congress being held there in June 1992. This meeting was chaired by Carl Hug from the USA and attended by almost 40 academic anaesthesiologists (Fig. 2.1), a number of industry participants and representatives from a regulatory agency (FDA, USA) and a Notified Body (TUV, Germany). I had first suggested the term 'Target Control Titration' as an alternative to the various acronyms that had been used to describe prototype systems developed by different groups when speaking at a Swedish Postgraduate Meeting at Leondahl Castle in October 1991. Gavin Kenny was another speaker at this meeting who agreed that it was desirable to avoid the implication that a computer rather than an anaesthesiologist controls the depth of anaesthesia and thereafter began to refer to Target Controlled Infusion in subsequent papers. In time this terminology, and the acronym TCI, was endorsed by other leaders in the field [2]. The interest of anaesthesiologists and medical device manufacturers in this approach was clearly increasing and possible approaches to commercial development were emerging. The group at Glasgow University had modified their original system [3] to produce a portable system which used a Psion Organiser (POS 200) interfaced with the Ohmeda 9000 syringe pump [4]. Reports of local use of this system, which were later published [5] indicated that 27 of 30 anaesthesiologists who had used the system found that it had changed their use of propofol for maintenance of anaesthesia, the main reasons being greater ease of use and more confidence in the predictability of effects, in comparison with manually controlled infusion. This began to elicit commercial interest within ICI and a project team was constituted in August 1992 to determine the feasibility of developing a TCI system linked to a prefilled syringe presentation of propofol which was already under development.

The 'Diprifusor' TCI Development

The development of the Diprifusor TCI system and associated technology has been described elsewhere [6, 7], but a brief summary is included here to illustrate the strategy adopted. Despite extensive academic experience with TCI, there was no precedent within regulatory agencies for dealing with this kind of drug—device combination, and extensive discussions with drug and device regulatory authorities were held to seek a way forward. A proposal by the Company to link the development to electronically tagged prefilled syringes (Fig. 2.2), to confirm the drug and drug concentration present, was welcomed by these authorities.

Fig. 2.1 Delegates invited to attend a workshop on 'Target Controlled Titration in Intravenous Anaesthesia', co-sponsored by ICI Pharmaceuticals and Janssen Pharmaceutica in Holland in 1992. Academic delegates from the USA included Julie Barr, Peter Glass, Carl Hug, Jerry Reeves, David Watkins, Steve Shafer and Don Stanski, from the UK Michael Halsey, Cedric Prys-Roberts, Gavin Kenny and Martin White, from Germany Jürgen Schüttler, from Belgium Elisabeth Gepts, Alain D'Hollander and Luc Barvais, from France Frederique Servin, from Australia David Crankshaw and Laurie Mather, from South Africa Johan Coetzee, and a representative of the FDA in the USA, Dan Spyker. (Reproduced with kind permission from Springer Science + Business Media: The Wondrous Story of Anesthesia, EI Eger, II et al. (eds) 2014, Chapter 66, Some examples of industry contributions to the history of anesthesia. Leazer R, Needham D, Glen J, Thomas P, Fig. 66.6, p. 919)

Fig. 2.2 Plastic finger grip with electronic tag utilising Programmed Magnetic Resonance to confirm presence of propofol and identify concentration in glass prefilled syringe (Reproduced with kind permission from AstraZeneca)

This added a significant level of technical complexity to the development but had the commercial benefit to the Company that the new technique would be restricted to use with 'Diprivan'™ the Company's brand of propofol. It is unlikely that commercial support for the development would have been achieved without this approach. It was considered important to separate clearly the responsibilities of the drug company in selecting the pharmacokinetic model and providing guidance on usage, with the addition of target concentration settings to the drug prescribing information, from those of the pump manufacturer. The plan to achieve this involved the development by the Company of the Diprifusor TCI module (Fig. 2.3) containing the TCI control software, with a preferred pharmacokinetic model and software to communicate with the electronic identification tag, the pump display and the pump motor, which could be incorporated by the device manufacturer into a conventional syringe infusion pump. Results of clinical trials with devices containing the preferred model, and proposed guidance on target concentration settings for inclusion in Diprivan labelling, would be submitted to drug regulatory authorities. Within Europe both the Diprifusor TCI module (as an 'Accessory') and integrated devices incorporating the module would be submitted for conformity assessment by a Notified Body (G-MED, France) as designated by EEC Directive 93/42 which came into effect in Jan 1995. The Company spent a considerable time developing a delivery performance specification with a series of test input profiles. Demonstration of conformity with this specification by a device manufacturer, using a final integrated device,

Fig. 2.3 Diprifusor™ TCI module (8 × 5 × 1 cm) developed by ICI Pharmaceuticals (now AstraZeneca) and containing the Marsh pharmacokinetic model and two microprocessors running independent versions of TCI control software as developed by the University of Glasgow (Reproduced with kind permission from AstraZeneca)

provided a link between the medicines authority assessing the clinical trials submission and the Notified Body evaluating the device. Discussions with the FDA in 1995 concluded that the submission of both clinical and device data should be in the form of a Pre Market Approval (PMA) application, to the group primarily responsible for the assessment of new devices in the USA.

In late 1991, the Ohmeda Company, possibly as a consequence of marketing priority being given to desflurane, decided to stop manufacture of the Ohmeda 9000 pump. As a result, Martyn Gray, an electronics expert who had been collaborating with the Glasgow University group, became available to work as a consultant for the Company. A decision was made to licence the Glasgow University TCI technology as the Company was satisfied that the two processor design incorporated in this system was likely to offer the most robust approach to TCI and Martyn was already familiar with this software. Martyn Gray (Anaesthesia Technology Ltd, Wetherby, UK) played a key role in the design and validation of the Diprifusor TCI module, thus transforming the Glasgow University software into a format that could communicate with and be installed in infusion pumps from a range of manufacturers. The development of the drug concentration identification system also required close collaboration between Martyn Gray and another external consultancy (Scientific Generics Ltd, now Sagentia, Cambridge, UK). An indication of the complexity of this aspect of the development can be seen in the equipment required to manufacture the electronic tag in the syringe finger grip (Fig. 2.4).

To ensure standardisation of drug delivery at a particular target setting, it was important to select a single pharmacokinetic model. Philip Arundel at ICI had developed the pharmacokinetic simulation program EXPLICIT [8] and I selected models described by Dyke and Shafer [9], Tackley et al. [10], and Marsh [11] for comparison. Detailed information on drug infusion rates and measured blood propofol concentrations were available from healthy control patients in a pharmacokinetic study of propofol [12]. Simulation of the infusion rates used in this study with EXPLICIT showed a degree of positive bias (measured concentrations greater than predicted) with all three models. The degree of positive bias was small and similar with the Tackley and Marsh models and was somewhat greater with the Dyck and Shafer set. Similar results were later obtained in a prospective comparative study with the same three models [13], and in view of the greater clinical experience already obtained with the Marsh model, this was selected for further clinical studies. Meetings continued with academics working in this field and it was agreed that results obtained up to that time would be pooled to obtain a set of population pharmacokinetic parameters. Preliminary results were reviewed in 1993 but the figures obtained at that time using NON-MEM software showed no significant improvement in predictive performance. The Marsh model used in Diprifusor systems incorporates a minor reduction in central volume of distribution but in other respects uses the rate constants described by Gepts and colleagues [14]. A minor typographical error occurred in the description of the adult model given in a study related to the development of a model for children [11] in that Diprifusor systems use a value for k_{12} of 0.114 min^{-1} as described by Gepts rather than the value of 0.112 min^{-1} given in the Marsh publication. This disparity has a very minor effect on propofol delivery.

For the programme of Company sponsored clinical studies, the Glasgow University software was incorporated in a customised 'Backbar' computer developed by Martyn Gray at Anaesthesia Technology Ltd and linked via a serial port to an Ohmeda 9000 or Graseby 3400 computer compatible syringe pump. Delivery performance tests confirmed that,

Fig. 2.4 Equipment required to manufacture and insert the electronic tag into the plastic fingergrip for glass prefilled syringes of 'Diprivan'™ (Reproduced with kind permission from AstraZeneca)

Table 2.1 Example of Diprifusor drug delivery specification in 50 kg subject with an initial target blood propofol concentration of 6 μg ml^{-1}, reduced to 4 μg ml^{-1} at 10 min and increased to 6 μg ml^{-1} at 20 min

Time (min)	1	5	10	20	21	30
Ideal vol (ml)	8.44	15.51	23.59	30.48	34.21	46.41
Min balance vol (ml)	7.60	14.73	22.41	28.96	32.50	44.09
Max balance vol (ml)	8.86	16.29	24.77	32.00	35.92	48.73

at a series of target settings, the delivery of propofol with these two systems was equivalent. Further tests examined inter-syringe and inter-pump variability, linearity of output over a target concentration range of 1–8 μg ml^{-1}, delivery performance over a 6 h period and performance at extremes of body weight accepted by Diprifusor systems (30 and 150 kg). Cumulative volume of drug delivered was measured with an electronic balance and compared with an ideal volume obtained by computer simulation of the same target input using Diprifusor software. At selected time points, infusion error was calculated as follows:

$$\text{Infusion error}\,\% = \frac{(\text{Balance volume} - \text{Ideal volume})}{\text{Ideal volume}} \times 100$$

Initial response time was also calculated as the time required for the predicted target to reach 90 % of the target set when the balance output was fed into Diprifusor software. This work led to a delivery performance specification, with a series of five test protocols, which was supplied to the manufacturers of commercial 'Diprifusor' systems. Initial response times for these test protocols ranged from 0.4 to 1.0 min and infusion error allowed was generally ±5 %. By demonstrating conformity with this specification, manufacturers were able to demonstrate that the Diprifusor module had been correctly installed in their pump and would operate in a manner consistent with the systems used in clinical trials. An example of the specification for one test profile is shown in Table 2.1

Eight prospective clinical studies with the selected TCI control program and using the Marsh pharmacokinetic model for induction and maintenance of anaesthesia in adults were completed and submitted to drug regulatory authorities in Europe and the USA in 1995. The principal objectives of the trial programme were as follows:

1. To determine the target concentration settings required to induce and maintain anaesthesia
2. To examine the influence of premedication [15], analgesic supplementation [16] and mode of ventilation [17] on the target concentrations required.
3. Two studies assessed the predictive performance of the Marsh model using the methods proposed by Varvel and colleagues [18]. Both studies showed an acceptable degree of positive bias (i.e. measured blood propofol concentrations greater than predicted) with median values of 16 % in one study in general surgery patients [19] and 25 % in patients undergoing cardiac surgery [20].
4. To determine the target concentrations required in elderly patients and in patients undergoing cardiac surgery [20]. One unpublished study in cardiac surgery patients was conducted with a double blind study design as requested by FDA and demonstrated no clinically relevant differences between the groups in haemodynamic or safety assessments.
5. To compare the characteristics of anaesthesia and ease of use of the Diprifusor TCI system with manually controlled infusion [21].

Efficacy and safety assessments made in these studies were consistent with previous experience with propofol and the following guidance on target blood propofol concentrations when using Diprifusor TCI systems for induction and maintenance of anaesthesia was proposed as an amendment to 'Diprivan' prescribing information:

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 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 should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4. The target concentration 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.

Drug labelling also highlights the requirement for the target concentration to be titrated to the response of the patient, in view of interpatient variability in propofol pharmacokinetics and pharmacodynamics, and for users to be familiar with the instructions for use in the "'Diprifusor' Guide for Anaesthetists" which provided further information on the concept of TCI and advice on the practical use of the system.

Approvals for amendments to the drug prescribing information and EC certificates of conformance with the requirements of directive 93/42/EEC, allowing CE marks of conformance to be attached to the Diprifusor TCI module and integrated devices containing the module, began to be achieved in the UK and most European countries from 1996 onwards. The first integrated Diprifusor TCI system to gain approval in Europe was the Becton Dickinson Master TCI pump (Vial, later Fresenius, Bresins, France) followed by the Graseby 3500 (Smiths Medical, UK), Alaris IVAC TIVA TCI pump (Alaris Medical, later Carefusion, UK) and later in Japan, the Terumo TE-372 syringe pump.

Further submissions were made to drug authorities to extend the use of Diprifusor TCI systems to conscious sedation for surgical and diagnostic procedures and for intensive care sedation [22], but these submissions have not been made in every country in which approval for induction and maintenance of anaesthesia has been granted. No submission to allow the use of Diprifusor TCI systems in children has been made in any country. Currently used Diprifusor systems display predicted effect-site propofol concentration using a blood–brain equilibration rate constant (k_{e0}) of 0.26 min^{-1}. This value was obtained from a preliminary analysis of a study in which pharmacodynamic data was obtained by monitoring EEG auditory evoked potentials [23]. A final non-parametric analysis of the study data provided a mean k_{e0} value of 0.2/min [24]. Subsequently, a modified k_{e0} of 1.21 /min was proposed for use with the Marsh model [25] but was not endorsed by AstraZeneca. The opportunity to control effect-site concentration was not incorporated in the original Diprifusor TCI module because of the complexity of the regulatory process, the impossibility of measuring effect-site concentrations and uncertainty about the most appropriate k_{e0} value for use with the Marsh model. More recently the latest version of the Diprifusor TCI module has been modified to allow the control of effect-site concentrations with an intermediate k_{e0} of 0.6 min^{-1}, a value found to be most likely to achieve a stable effect when the target is fixed at a time when a desired effect has been achieved [26]. In a further comparative study the Marsh model and a k_{e0} of 0.6 min^{-1} achieved induction of anaesthesia more rapidly than the Marsh model in blood concentration control or the Schnider model [27, 28] with a k_{e0} of 0.46 min^{-1} in effect-site control with no differences between groups in the magnitude of blood pressure changes or the frequency of apnoea [29].

The clinical trial documentation submitted in Europe was sufficient to gain approval for amendments to Diprivan labelling to allow administration by TCI in most countries in which TCI devices have been approved. Notable exceptions were Japan and the USA. In Japan the 1 % Diprivan Prefilled Syringe with electronic tag drug identification was evaluated and approved as a 1 % Diprivan Injection-Kit following four studies which examined usefulness, benefits, microbiology and use by conventional methods of administration. This was followed by a TCI user study in Japanese patients in which the Graseby 3500 infusion pump with the Diprifusor TCI module was used to assess efficacy, safety and controllability. Predictive performance was also assessed and median bias of 18.8 % was similar to that seen in European studies [30]. Guidance on administration of Diprivan by TCI in Japan recommends the use of slightly lower target settings:

Diprivan should be administered using Diprifusor TCI function of a Diprifusor TCI pump.

(1) Induction

Usually in adults, infusion should be started intravenously with a target blood propofol concentration of 3 μg/ml, which should be increased in steps of 1.0 to 2.0 μg/ml at intervals of one minute if clinical

signs do not show onset of anaesthesia in 3 minutes after start of infusion.

In adult patients, anaesthesia can usually be induced with target concentration in the range of 3.0 to 6.0 μg/ml within the range of 1 to 3 minutes.

In elderly patients and in patients of ASA grade 3 and 4, a lower initial target should be used.

(2) Maintenance

The required depth of anaesthesia can usually be maintained by continuous infusion of the drug in combination with oxygen or a mixture of oxygen and nitrous oxide, while the target concentration is titrated against the response of the patient. Target concentrations in the region of 2.5 to 5.0 μg/ml usually maintain satisfactory anaesthesia in adults.

Analgesics (narcotic analgesics, local anaesthetics, etc.) should be used concomitantly.

Despite a lengthy evaluation process during which FDA reviewers and regulatory strategy changed, approval for the Diprifusor TCI system in the USA was not obtained and the agency issued a non-approvable letter in 2001, stating that lack of precision in dosing posed an unacceptable risk. The Company responded that no pharmacokinetic model could be expected to eliminate variability in the concentrations achieved at a particular target setting and that such variability had not been associated with any safety concerns, but approval was not achieved and the Company withdrew the US submission in 2004. A theoretical treatise has since then proved that TCI devices can neither create nor eliminate biological variability, the overall spread of observations being an intrinsic property of the drug [31]. More detailed information on the failure to obtain approval for TCI in the USA is discussed in a recent publication on the history of TCI [32].

'Open' TCI Systems

Around 2002, as 'Diprivan' patents began to expire, a number of medical device manufactures began their independent development of TCI devices without a drug recognition facility which therefore allowed their use with generic preparations of propofol. Among the first of these were the 'Orchestra'® Base Primea introduced by Fresenius Vial in 2003 and the 'Asena'® PK syringe pump (Alaris Medical, now Cardinal Health Care). By this time continuing academic research had led to the publication of an alternative pharmacokinetic model for propofol, developed in volunteers, with covariates for age, weight, height and lean body mass [27]. This study also included characterisation of the relationship between plasma concentration and the time course of drug effect, and proposed a value for the blood–brain equilibration rate constant (k_{e0}) of propofol of 0.456 min^{-1} and a predicted time of peak effect of 1.7 or 1.6 min when assessed by visual inspection of the EEG [28]. Algorithms to achieve and maintain stable drug concentrations at the site of drug effect had been published earlier [33, 34] and medical device companies came under pressure from academic groups to provide TCI systems which would not only allow the administration of generic propofol with the Marsh model, but would also allow the choice of the alternative pharmacokinetic model, the choice to control plasma or effect-site drug concentrations and the ability to deliver remifentanil or sufentanil by TCI. While these devices refer to plasma rather than blood concentrations, this chapter continues to describe blood concentrations as in the regulatory studies with propofol and remifentanil whole blood concentrations were measured and guidance on target settings in drug labelling is provided in terms of blood concentrations.

In Europe these systems were submitted to a Notified Body to assess conformity with the standards set out in the European Medical Device Directive 93/42 in the same way that the Diprifusor module and integrated Diprifusor TCI pumps were evaluated. As devices intended to deliver anaesthetic (i.e. 'potentially hazardous' substances), these come within Class IIb of the Directive classification and require inspection by a Notified Body with regard to their design, manufacture and quality assurance. A key feature of the Directive is that devices bearing a CE mark, indicating that they have demonstrated a satisfactory assessment of conformity with the requirements of the Directive, can then be marketed throughout Europe and CE marking has also been recognised as a sign of approval by other countries outside Europe. Directive 93/42 provides a series of 'Essential Requirements' which have to be met in relation to safety and performance. In terms of performance, it is sufficient to demonstrate that a device incorporating a particular model at particular target settings will deliver an infusion profile and predict plasma or effect-site drug concentrations in line with mathematical predictions for the same model obtained by computer simulation. Literature publications describing clinical experience with particular models can be used to justify the choice of target settings used in these studies. There is no requirement for the Notified Body to have any contact with the relevant Medicines Authority responsible for the marketing authorisation of the drugs to be infused or the manufacturer of these drugs. A similar approach to device approval has been used by newer entrants in the field. The Perfusor® Space and Infusomat® Space pumps (B Braun, Germany), the Volumed® μVP 7000 and Syramed® μSP600 devices (Arcomed AG, Switzerland) and the Pion® TCI pump (Bionet, Korea) have incorporated the Marsh and Schnider models for propofol, the Minto

model for remifentanil and in some cases models for administration of sufentanil, alfentanil, fentanyl, midazolam, ketamine and dexmedetomidine by TCI.

In the case of propofol, the introduction of open TCI systems giving users a choice of pharmacokinetic models and modes of administration has led to a degree of confusion [35] which will be discussed in the section on propofol TCI with open systems. In the following sections the author has used the pharmacokinetic simulation programs TIVAtrainer© (Version 9.1 GuttaBV, Aerdenhout, The Netherlands) and PK-SIM (Specialized Data Systems, Jenkintown, PA, USA) to illustrate, in example subjects, the performance of different pharmacokinetic models or their implementation.

Remifentanil TCI

By the time open TCI systems became available there were already a large number of literature publications on the administration of remifentanil by TCI based on the use of non-approved TCI software and prototypes in research studies. A number of different pharmacokinetic models for remifentanil had been described and I was commissioned by GlaxoSmithKline to assist Professor Jürgen Schüttler with the preparation of a Clinical Overview to support the administration of remifentanil by TCI and to provide guidance on appropriate target remifentanil concentrations for inclusion in drug labelling. This involved a detailed review of 41 published clinical studies involving a total of 2650 subjects, comparison of the performance of the different pharmacokinetic models and the selection of a preferred model, overviews of efficacy and safety and conclusions on risks and benefits. The pharmacokinetic model described by Minto and colleagues [36] was advocated for the following reasons:

1. This model was derived from a composite analysis of data from 65 healthy adults with an age range of 20–85 years
2. A population pharmacokinetic model was developed to account for an observed effect of age and lean body mass on the pharmacokinetics of remifentanil
3. This study also provided a k_{e0} value for remifentanil related to patient age, predicting slower equilibration in patients older than 40 years and faster equilibration in younger patients.
4. Widely used in prototype TCI systems with good clinical results
5. A prospective evaluation of the predictive performance of this model provided acceptable values for bias (−15 %) and inaccuracy (20 %) [37].

Once approved, guidance on the administration of remifentanil by TCI was added to the Statement of Product Characteristics (SPC) for remifentanil ('Ultiva', GlaxoSmithKline) in territories where approved TCI devices were available. Extracts from the SPC include the following:

'Ultiva' may also be given by target controlled infusion (TCI) with an approved infusion device incorporating the Minto pharmacokinetic model with covariates for age and lean body mass. For TCI the recommended dilution of Ultiva is 20–50 micrograms/ml.

Ultiva TCI should be used in association with an intravenous or inhalational hypnotic agent during induction and maintenance of anaesthesia in ventilated adult patients. In association with these agents, adequate analgesia for induction of anaesthesia and surgery can generally be achieved with target blood remifentanil concentrations ranging from 3 to 8 nanograms/ml. Ultiva should be titrated to individual patient response. For particularly stimulating surgical procedures target blood concentrations up to 15 nanograms/ml may be required. At the end of surgery when the TCI infusion is stopped or the target concentration reduced, spontaneous respiration is likely to return at calculated remifentanil concentrations in the region of 1 to 2 nanograms/ml. As with manually-controlled infusion, post-operative analgesia should be established before the end of surgery with longer acting analgesics. There are insufficient data to make recommendations on the use of TCI for spontaneous ventilation anaesthesia and use of TCI for the management of post-operative analgesia is not recommended.

In association with an intravenous or inhalational agent, adequate analgesia for cardiac surgery is generally achieved at the higher end of the range of target blood remifentanil concentrations used for general surgical procedures. Following titration of remifentanil to individual patient response, blood concentrations as high as 20 nanograms/ml have been used in clinical studies

Because of the increased sensitivity of elderly patients to Ultiva, when administered by TCI in this population the initial target concentration should be 1.5 to 4 nanograms/ml with subsequent titration to response.

In obese patients, with the calculation of lean body mass (LBM) used in the Minto model, LBM is likely to be underestimated in female patients with a body mass index (BMI) greater than 35 kg/m2 and in male patients with BMI greater than 40 kg/m2. To avoid underdosing in these patients, remifentanil TCI should be titrated carefully to individual response.