

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.

J.B. Glen, BVMS, PhD, FRCA (✉)
Glen Pharma, 35 A Bexton Road, Knutsford, Cheshire WA16 0DZ, UK
e-mail: iglen2@compuserve.com

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,

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 Siggie Kloos from Germany, Xavier Viviani 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 anaesthesia’ 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*, El 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 ($8 \times 5 \times 1$ 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 $6 \mu\text{g ml}^{-1}$, reduced to $4 \mu\text{g ml}^{-1}$ at 10 min and increased to $6 \mu\text{g ml}^{-1}$ 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 $1\text{--}8 \mu\text{g ml}^{-1}$, 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 $\pm 5\%$. 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 $0.2/\text{min}$ [24]. Subsequently, a modified k_{e0} of $1.21/\text{min}$ 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 manufacturers 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 remifentanyl or sufentanyl 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 remifentanyl 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 TIVAtainer© (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.

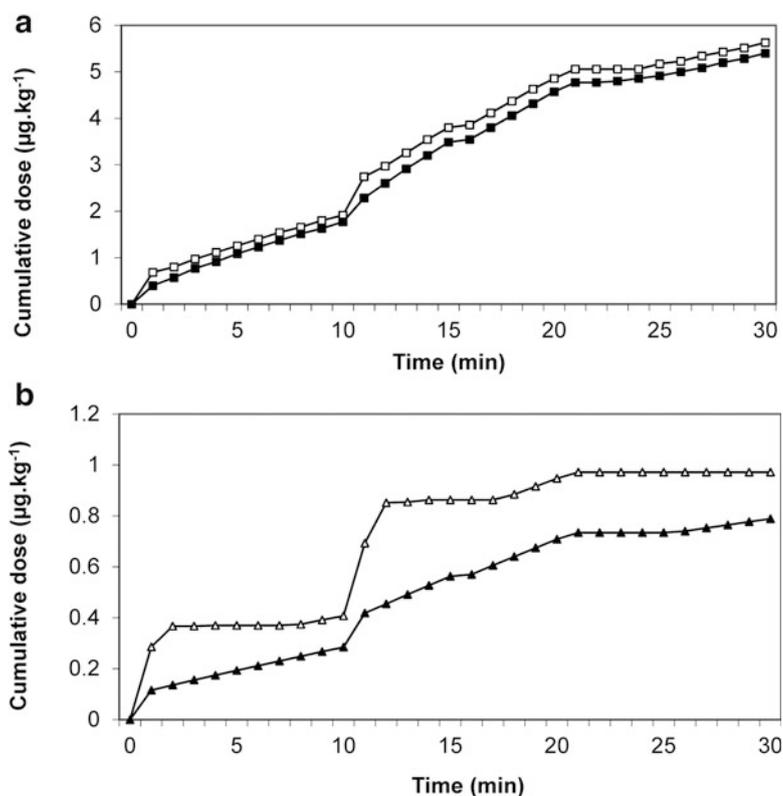
In obese patients, with the calculation of lean body mass (LBM) used in the Minto model, LBM is likely to be underestimated in female patients with a body mass index (BMI) greater than 35 kg/m² and in male patients with BMI greater than 40 kg/m². To avoid underdosing in these patients, remifentanil TCI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

In ASA III/IV patients a lower initial target of 1.5 to 4 nanograms/ml should be used and subsequently titrated to response.

In many respects, the approach adopted for remifentanyl TCI was ideal in that a single pharmacokinetic model is recommended and advice on suitable target concentration settings is provided in the drug labelling. Although some studies had used the pharmacodynamic parameters provided by Minto and colleagues to deliver remifentanyl by effect-site TCI, GlaxoSmithKline did not wish to recommend this approach. While some of the open TCI systems now available do provide the option to control effect-site concentrations of remifentanyl, this mode of administration leads to very minor differences in drug delivery in comparison with plasma concentration control (Fig. 2.5). With a drug with such rapid onset and offset characteristics as remifentanyl, it is unlikely that a study comparing the two modes of administration would detect any clinical differences.

One defect in the Minto model is the use of the James equation [38] which underestimates lean body mass in obese patients. However, this was recognised at the time of the regulatory submission and notification of this effect was added to the drug labelling. Estimation of lean body mass will be discussed in more detail in a later section.

Fig. 2.5 Cumulative dose ($\mu\text{g kg}^{-1}$) of remifentanyl (a) and sufentanil (b) delivered by blood concentration (C_{b_T}) or effect site TCI (C_{e_T}). Remifentanyl C_{b_T} filled square, C_{e_T} open square targets 3 ng ml^{-1} , increased to 6 ng ml^{-1} at 10 min, and decreased to 3 ng ml^{-1} at 20 min. Sufentanil C_{b_T} filled triangle, C_{e_T} open triangle, targets 0.5 ng ml^{-1} increased to 1 ng ml^{-1} at 10 min, and decreased to 0.5 ng ml^{-1} at 20 min



Sufentanil TCI

Sufentanil is not marketed in the UK but is used in the USA and a number of European countries and the ability to administer sufentanil by TCI with the pharmacokinetic model described by Gepts and colleagues [39] has been incorporated in some of the open TCI systems now available. In France a brief addendum concerning drug concentrations has been included in the French prescribing information for 'Sufenta'TM. Guidance on suggested plasma concentrations includes the following:

Efficient concentration

- *Anaesthesia.* After iv administration, the following plasma concentration of 0.15 to 0.6 ng/ml is usually used to maintain general anaesthesia when combined with hypnotics. Concentrations of 0.4 to 2 ng/ml are requested in cardiac surgery. Plasma and effect site (brain) concentrations equilibrate after 6 min. Spontaneous ventilation is observed at a mean concentration of 0.2 ng/ml.
- *Sedation.* Combined with a benzodiazepine for long term sedation, the concentration is usually between 0.3 to 2 ng/ml.

Although a specific pharmacokinetic model is not mentioned, the pharmacokinetics of the drug as described indicates values for V_c (the central volume of distribution) and clearance which are identical to those described by Gepts [39]. Some open TCI systems also provide the

opportunity to control effect-site concentrations of sufentanil using the Gepts model combined with a blood–brain equilibration constant (k_{e0}) of 0.112 min^{-1} derived from the mean equilibration half life of 6.2 min described by Scott and colleagues [40]. With a drug such as sufentanil with a relatively slow onset, control of effect-site concentration will lead to the administration of a significantly larger initial dose (Fig. 2.5) and a more rapid onset of effect. One concern with some implementations of the Gepts model is that the model is not weight proportional and without age and weight limits could deliver excessive doses if used in small children.

Propofol TCI with Open TCI Devices

The ability to deliver generic preparations of propofol is possible with open systems which do not require the added security of the electronic identification of the drug and its concentration. Isolated cases have been reported where the wrong concentration of propofol emulsion has been selected [41] or where propofol and remifentanil syringes were mistakenly reversed [42] and in one case led to accidental awareness [43]. Anecdotal reports suggest that such mistakes may occur more frequently than reported. Failure to use the correct syringe brand selection can also lead to errors in drug delivery, in some cases up to almost 20 % of the nominal delivery [44].

Providing users with a choice of two pharmacokinetic models for the administration of propofol by TCI has led to a significant degree of confusion which has probably hindered the wider adoption of the technique [35]. Possible sources of confusion are discussed as follows:

Simple Versus Complex Model

With the Marsh model, as the central volume of distribution (V_1) is related to body weight, both volumes of distribution and clearance are related to body weight and a single set of rate constants can be used for all patients. The consequence is that, at any given target setting, drug delivery in terms of mg kg^{-1} or $\text{mg kg}^{-1} \text{ h}^{-1}$ or $\mu\text{g kg}^{-1} \text{ min}^{-1}$ is the same for all

patients, independent of body weight, gender or patient age. Although age is requested as an input, this is only to ensure that this adult model is not used in patients younger than 16 years. It is expected that target settings will be titrated to achieve the depth of anaesthesia or sedation desired, and lower targets are recommended in older or debilitated patients. Guidance on recommended target settings is provided in ‘Diprivan’ labelling and changes in target settings provide proportional changes in the rate of drug delivery. The introduction of this system was accompanied by the provision by the pharmaceutical company of more detailed information on the technique in training materials such as the ‘Diprifusor’ Guide for Anaesthetists and an extensive programme of training courses provided by local marketing companies with the assistance of local and international experts, often accompanied by demonstrations of the technique achieved with live video links to an operating theatre. The Marsh model has been used extensively and safely for many years since its first introduction in Diprifusor TCI systems in 1996 and it can be estimated that about 25,000 such systems have been introduced to clinical use.

In contrast to the simplicity of the Marsh model the Schnider model is more complex. It is difficult without further calculation to gain much information on the likely performance of a particular pharmacokinetic model from the series of rate constants used as inputs in a TCI program. However, if the volumes and clearances of the three-compartment model are presented in the terms of ml kg^{-1} for volumes and $\text{ml kg}^{-1} \text{ min}^{-1}$ for clearances as in Tables 2.2 and 2.3, some prediction of the differences between models in delivery performance is facilitated. In the Schnider model, V_1 is constant at 4.27 l, age is a covariate for the volume of the second compartment (V_2) and rapid peripheral clearance (Cl_2); and weight, height and lean body mass are all covariates for metabolic clearance (Cl_1). Although gender is not a covariate, it has an influence on Cl_1 as the James equation used to calculate lean body mass is gender specific in such a way that metabolic clearance is about 15–30 % greater in female subjects, the higher figure being seen in heavier patients (Table 2.3). The best way to compare the performance of different pharmacokinetic

Table 2.2 Influence of age and gender on volumes of distribution and clearance with the Marsh and Schnider pharmacokinetic models for propofol

	Marsh	Schnider 30 year, M	Schnider 50 year, M	Schnider 80 year, M	Schnider 30 year, F	Schnider 50 year, F	Schnider 80 year, F
V_1 (ml kg^{-1})	228	61	61	61	61	61	61
V_2 (ml kg^{-1})	473	398	287	119	398	287	119
V_3 (ml kg^{-1})	2895	3400	3400	3400	3400	3400	3400
Cl_1 ($\text{ml kg}^{-1} \text{ min}^{-1}$)	27.1	23.4	23.4	23.4	28.7	28.7	28.7
Cl_2 ($\text{ml kg}^{-1} \text{ min}^{-1}$)	26	26.3	19.5	9.2	26.3	19.5	9.2
Cl_3 ($\text{ml kg}^{-1} \text{ min}^{-1}$)	9.6	11.9	11.9	11.9	11.9	11.9	11.9

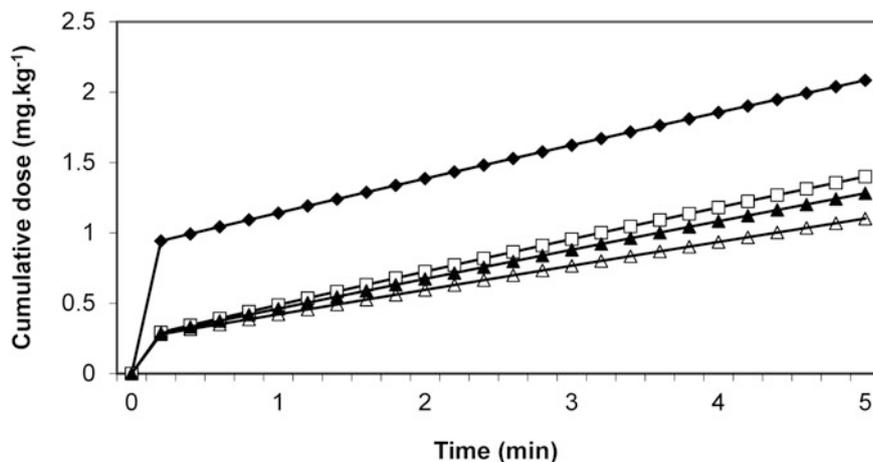
All subjects 70 kg, 170 cm

Table 2.3 Influence of body weight and gender on volumes of distribution and clearance with the Marsh and Schnider pharmacokinetic models for propofol

	Marsh	Schnider 50 kg, M	Schnider 70 kg, M	Schnider 110 kg, M	Schnider 50 kg, F	Schnider 70 kg, F	Schnider 110 kg, F
V_1 (ml kg ⁻¹)	228	85	61	39	85	61	39
V_2 (ml kg ⁻¹)	473	401	287	182	401	287	182
V_3 (ml kg ⁻¹)	2895	4760	3400	2164	4760	3400	2164
Cl_1 (ml kg ⁻¹ min ⁻¹)	27.1	30	23.4	24	34.4	28.7	31.2
Cl_2 (ml kg ⁻¹ min ⁻¹)	26	27.2	19.5	12.4	27.2	19.5	12.4
Cl_3 (ml kg ⁻¹ min ⁻¹)	9.6	16.7	11.9	7.6	16.7	11.9	7.6

All subjects 50 year, 170 cm

Fig. 2.6 The influence of patient age on the cumulative dose (mg kg⁻¹) of propofol delivered with the Marsh and Schnider models at a target blood concentration (C_{bT}) of 4 μ g ml⁻¹ in 70 kg, 170 cm male subjects. Filled diamond Marsh C_{bT} all ages, open square Schnider C_{bT} 30 year, filled triangle Schnider C_{bT} 50 year, open triangle Schnider C_{bT} 80 year



models is to examine delivery performance in terms of the cumulative amount of drug given over the first few minutes (i.e. the induction dose) and thereafter the infusion rate profile delivered in the maintenance phase. The cumulative dose delivered over an extended period can also be useful to give an overall picture of the induction and maintenance phases.

Figure 2.6 shows a comparison of the influence of patient age on the cumulative amount of propofol delivered over 5 min with the Marsh and Schnider models in a 70 kg, 170 cm male subject at a target blood propofol concentration of 4 μ g ml⁻¹. It can be seen that the Schnider model, with a much smaller central compartment volume than the Marsh model, delivers a much smaller initial dose by rapid infusion than the Marsh model. By 2 min the Schnider model has delivered only 0.7 mg/kg in the 50-year-old patient whereas the Marsh model has provided 1.4 mg kg⁻¹, independent of patient age. The initial dose delivered by the Schnider model is also independent of patient age but thereafter the slopes of the delivery profiles reflect age related changes in rapid peripheral clearance (Cl_2) (Table 2.2). Figure 2.7 shows a comparison of the two models with respect to patient weight in 50 year, 170 cm male subjects. Again, the cumulative dose delivered is much smaller with the Schnider model and as V_1 is constant in this model, the weight related reduction

in V_1 in terms of ml kg⁻¹ (Table 2.3) leads to weight related changes in initial dose delivered in terms of mg kg⁻¹ with a larger initial dose in lighter patients. Weight related changes in clearance in terms of ml kg⁻¹ min⁻¹ (Table 2.3) also explain the age related divergence in the cumulative dose lines in the figure.

Because the Schnider model delivers such a small initial dose it has become routine practice in centres which use this model to select an option to control effect-site propofol concentrations. Figure 2.8 shows the cumulative dose of propofol delivered with the Marsh model in blood concentration control mode and the Schnider model in effect control mode (k_{e0} 0.46 min⁻¹) in 50 year, 170 cm male patients of 50, 70 and 110 kg at targets of 4 μ g ml⁻¹. In the 70 kg subject, the initial dose delivered with the Schnider model is now similar to that provided by the Marsh model in blood control mode, while that in lighter patients is greater and that in heavier patients is smaller. Once a requested target is reached there is very little difference between blood and effect site modes of control in the infusion rate required to maintain this target. Figure 2.9 shows the infusion rates delivered by the Marsh model in blood concentration control (C_{bT}) and the Schnider model in blood and effect-site control (C_{eT}) in 50 year, 170 cm male patients of 50 and 100 kg when propofol target concentrations of 3 μ g ml⁻¹ have been

Fig. 2.7 The influence of patient weight on the cumulative dose (mg kg^{-1}) of propofol delivered with the Marsh and Schnider models at a target blood concentration (C_{bT}) of $4 \mu\text{g ml}^{-1}$ in 50 year, 170 cm male subjects. *Filled diamond* Marsh C_{bT} all weights, *filled square* Schnider C_{bT} 50 kg, *open square* Schnider C_{bT} 70 kg, *filled triangle* Schnider C_{bT} 110 kg

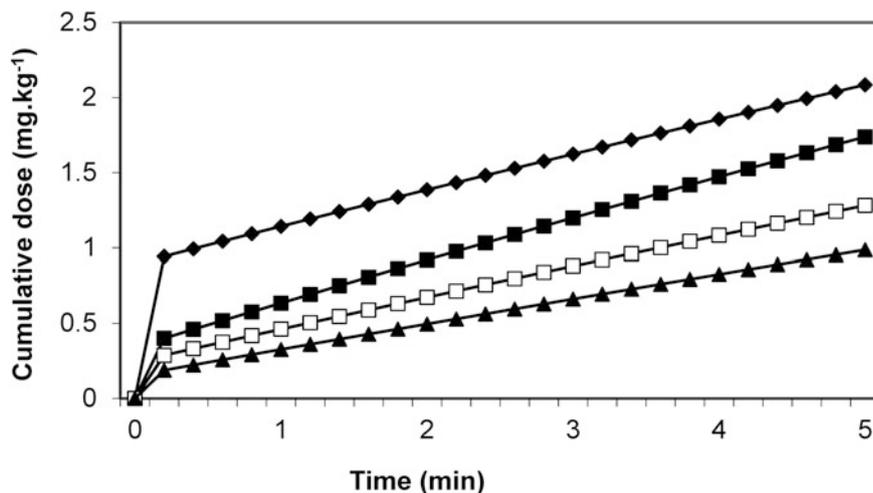


Fig. 2.8 The influence of patient weight on the cumulative dose (mg kg^{-1}) of propofol delivered with Marsh model in blood concentration control (C_{bT} $4 \mu\text{g ml}^{-1}$) and the Schnider model in effect control (C_{eT} $4 \mu\text{g ml}^{-1}$) in 50 year, 170 cm male subjects. *Filled square* Schnider C_{eT} 50 kg, *filled diamond* Marsh C_{bT} all weights, *open square* Schnider C_{eT} 70 kg, *filled triangle* Schnider C_{eT} 110 kg

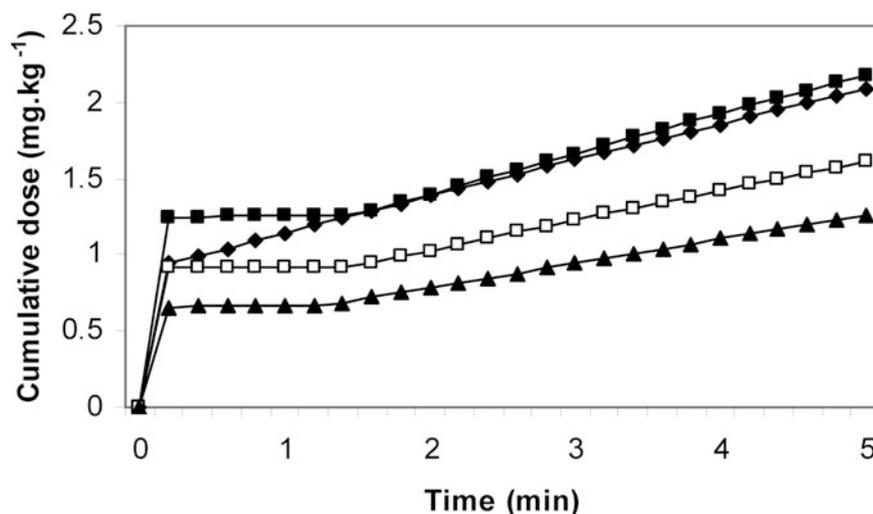
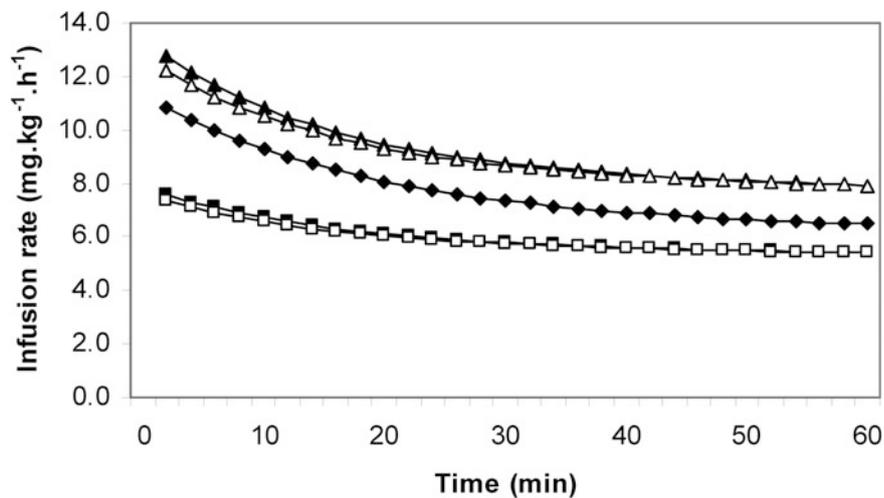


Fig. 2.9 Propofol infusion rates ($\text{mg kg}^{-1} \text{h}^{-1}$) delivered with Marsh model in blood concentration control (C_{bT} $3 \mu\text{g ml}^{-1}$) and the Schnider model in blood concentration (C_{bT} $3 \mu\text{g ml}^{-1}$) and effect control (C_{eT} $3 \mu\text{g ml}^{-1}$) in 50 year, 170 cm male subjects weighing 50 or 110 kg. *Filled triangle* 50 kg, Schnider C_{bT} , *open triangle* 50 kg, Schnider C_{eT} , *filled diamond* Marsh C_{bT} all weights, *filled square* 110 kg, Schnider C_{bT} , *open square* 110 kg, Schnider C_{eT}



set. Infusion rates with the Schnider model in the 50 kg subject are greater than those provided with the Marsh model and those in the 110 kg subject are lower, in both cases reflecting weight related changes in clearance (Table 2.3). In both Schnider simulations, the maintenance infusion rate in effect control mode is only marginally slower than with blood control and this difference disappears over time, in the absence of any change in target setting. Increases in rapid peripheral distribution and clearance (V_2 and Cl_2) in subjects younger than 53 years and decreases in older subjects influence the maintenance infusion rate for the first 30 min but thereafter, in a 70 kg subject, rate is similar to that provided by the Marsh model. The increase in clearance in female subjects seen with the Schnider model leads to greater infusion rates in females and, in terms of $\text{mg kg}^{-1} \text{h}^{-1}$, the influence is greater in heavier patients (Fig. 2.10).

The potential attraction of the Schnider model is that the incorporation of covariates for age, body weight and height attempts to explain and reduce inter-individual variability in propofol pharmacokinetics and improve the precision of the model in predicting the blood and effect-site propofol concentrations achieved. Effect-site propofol concentrations

cannot be measured but methodology for the evaluation of predictive performance of TCI systems has been described [18] whereby bias is described by the median performance error (MDPE) for an individual or group of patients and inaccuracy as the median absolute performance error (MDAPE) derived from comparisons of measured and predicted blood propofol concentrations. It has been suggested that MDPE should be no greater than 10–20 % and MDAPE in the region of 20–30 % for a TCI system to be deemed clinically acceptable [45]. While most studies evaluating predictive performance with both the Marsh and Schnider models have found group values for MDPE and MDAPE close to these ranges, group values being medians of medians in an individual patient probably provide an unrealistic picture of the large degree of pharmacokinetic variability between individuals in a group and within an individual over time. This variability becomes evident when one looks at the range of values contributing to the group and individual median values (Table 2.4) [46]. This shows that the benefits of the more complex Schnider model over the simpler Marsh model are limited as considerable inter-individual variability persists with both models. It has been confirmed that the Schnider model produces less

Fig. 2.10 Influence of gender and body weight on propofol infusion rates ($\text{mg kg}^{-1} \text{h}^{-1}$) in 50 year, 170 cm subjects with the Schnider model in blood concentration control (C_{bT} $3 \mu\text{g ml}^{-1}$). Filled diamond 50 kg female, open square 50 kg male, filled triangle 110 kg female, open triangle 110 kg male

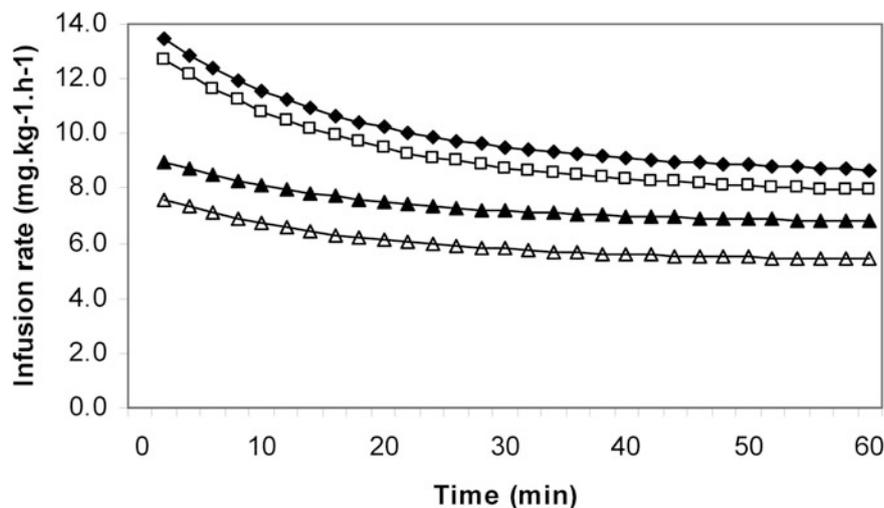
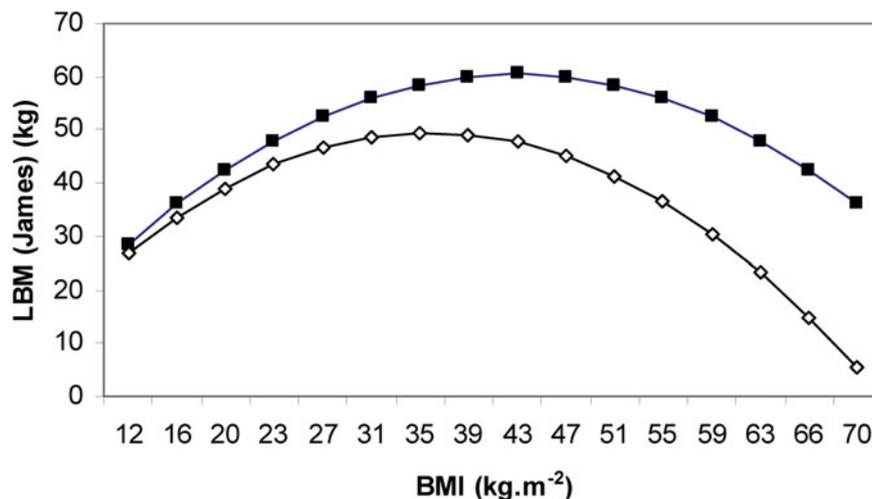


Table 2.4 Predictive performance of the Marsh and Schnider models for propofol as assessed by median performance error (MDPE %) and median absolute performance error (MDAPE %) with values given as the median and range of values encountered for individual patients in each study group

Model	Subjects	n	MDPE %	MDAPE %	Reference
Marsh	Major elective surgery patients	46	16.2 (–21–84)	20.7 (6.3–84)	[19]
Marsh	Orthopaedic or gynaecological surgery	10	–7 (–43–43) ^a	18.2 (8–53) ^a	[13]
Schnider	Healthy adult volunteers	18	1.8 (–34–74)	20.7 (11–74)	[46]
Marsh	Healthy control patients	9	2.3 (–32–33)	24.6 (11–37)	[47]
Schnider	Healthy control patients	9	–0.1 (–22–34)	23.6 (13–43)	[47]
Marsh	Major elective surgery patients	41	16 (–27–84)	26 (11–84)	[48]
Schnider	Major elective surgery patients	41	15 (–23–73)	23 (7–73)	[48]

^a10–90 percentiles

Fig. 2.11 Influence of body mass index (BMI kg m^{-2}) on lean body mass (LBM kg) in *filled square* male and *open diamond* female subjects, 160 cm height and bodyweight 30–180 kg as calculated with the James equation [38]



positive bias (measured concentrations greater than predicted) when the target concentration is steady or increasing, but the overall figure in a given patient is influenced by a trend towards negative bias at induction and positive bias at recovery or when a lower target is set [47, 48]. Opposite effects are seen with the Marsh model with positive bias at induction and negative bias during recovery. These differences are most likely a consequence of the marked difference in central compartment volume (V_1) with the two models (Table 2.2) as discussed earlier. More recent pharmacokinetic studies [49, 50] have demonstrated an influence of age on propofol clearance, an effect that was not observed in the Schnider model (Table 2.2). While there is merit in the development of pharmacokinetic models which attempt to take account of age and gender related changes in pharmacokinetics, patient characteristics such as age [28] and ASA status lead to marked differences in propofol pharmacodynamics, which influence the drug concentrations required to achieve a desired effect. On top of predictable trends, inter-individual variability in pharmacokinetics and pharmacodynamics account for the guidance that propofol target concentrations should be titrated to achieve the effect desired in any individual patient and limits the potential benefits of more complex models.

Lean Body Mass Calculation

The Schnider model for propofol, and the Minto model for remifentanyl, both incorporate lean body mass (LBM) as a covariate for the calculation of metabolic clearance and both use the equations described by James [38] to determine LBM. However, there are inconsistencies in these equations which in some circumstances lead to erroneous values [51].

The James equations based on weight (kg) and height (cm) for male and female subjects differ as follows:

$$\text{Males : LBM (kg)} = 1.1 \times \text{weight} - 128 \times (\text{weight}/\text{height})^2$$

$$\text{Females : LBM (kg)}$$

$$= 1.07 \times \text{weight} - 148 \times (\text{weight}/\text{height})^2$$

Body mass index (BMI) = weight (kg)/height (m^2) increases as body weight increases but increases more slowly if height also increases. Figure 2.11 illustrates the influence of body mass index on lean body mass as calculated by the James equation in male and female subjects of 160 cm height over the weight range of 30–180 kg. It can be seen that LBM reaches a maximum value and begins to decline at a BMI value around 35 kg m^{-2} in female subjects and about 42 kg m^{-2} in males.

Alternative methods to assess LBM based on measurement of antipyrine space or fat free mass (FFM) have been described by Hume [52] and Janmahasatian and colleagues [53], respectively, as follows:

$$\text{Hume : Males : LBM (kg)}$$

$$= 0.33929 \times \text{height (cm)} + 0.32810 \times \text{weight (kg)} - 29.533$$

$$\text{Females : LBM (kg)}$$

$$= 0.41813 \times \text{height (cm)} + 0.29569 \times \text{weight (kg)} - 43.2933$$

$$\text{Janmahasatian and colleagues : Males : FFM}$$

$$= \frac{9.27 \times 10^3 \times \text{Body wt (kg)}}{6.68 \times 10^3 + 216 \times \text{BMI}}$$

$$\text{Females : FFM} = \frac{9.27 \times 10^3 \times \text{Body wt (kg)}}{8.78 \times 10^3 + 244 \times \text{BMI}}$$

Both of these methods avoid the paradoxical decline in LBM in patients with high values for BMI and can be used to illustrate the differing consequences of the use of the James LBM

Fig. 2.12 Influence of method of calculation of lean body mass on propofol clearance ($\text{ml kg}^{-1} \text{min}^{-1}$) in a 160 cm, 40 year female subject. Filled diamond James [38], open triangle Janmahasatian [53] and filled square Hume [52] equations

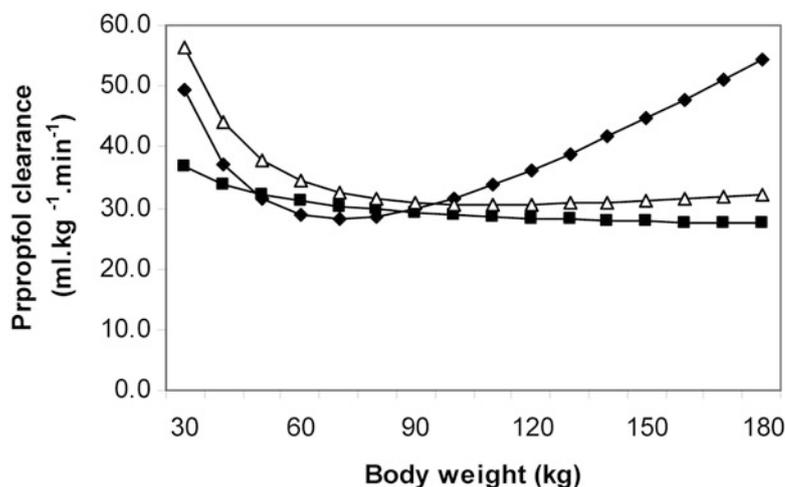
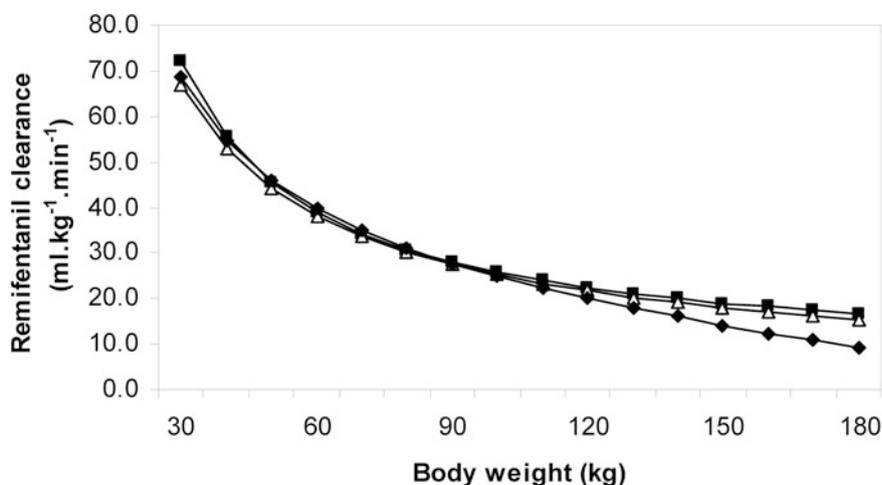


Fig. 2.13 Influence of method of calculation of lean body mass on remifentanyl clearance ($\text{ml kg}^{-1} \text{min}^{-1}$) in a 160 cm, 40 year female subject. Filled square Hume [52], open triangle Janmahasatian [53] and filled diamond James [38] equations



equations in the Schnider model for propofol and the Minto model for remifentanyl. In the Schnider model for propofol, clearance is influenced by both LBM and total body weight (TBW): $Cl_1 (1 \text{ min}^{-1}) = 1.89 + ((\text{TBW} - 77) \times 0.0456) + ((\text{LBM} - 59) \times -0.0681) + ((\text{Height} - 177) \times 0.0264)$. The consequence is that at BMI values greater than 35 kg m^{-2} in female patients, as calculated LBM begins to decrease, metabolic clearance begins to increase again, such that the infusion rates at a given target setting will increase with a potential risk of overdose.

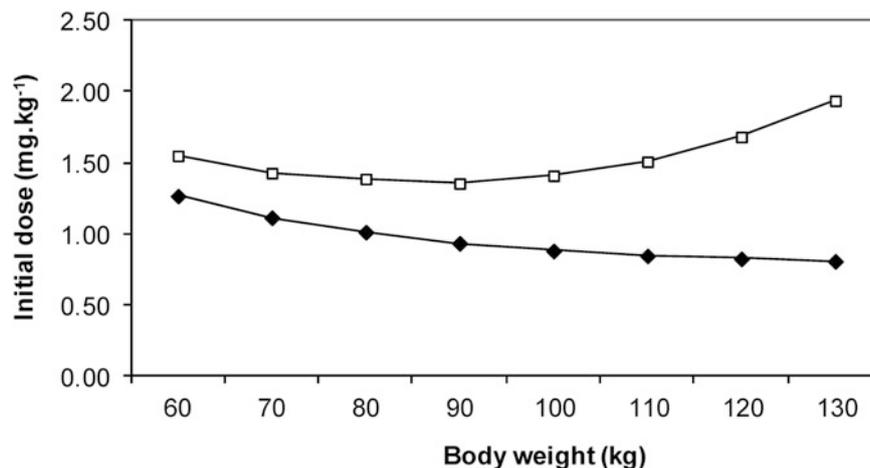
In the Minto model for remifentanyl, age and LBM are covariates for metabolic clearance: $Cl_1 (1 \text{ min}^{-1}) = 2.6 - 0.0162 \times (\text{Age} - 40) + 0.0191 \times (\text{LBM} - 55)$. Thus, in patients with high BMI, clearance in terms of 1 kg^{-1} decreases such that there is a potential risk of underdosage. However, in terms of $\text{ml kg}^{-1} \text{min}^{-1}$, the principal influence on infusion rate during maintenance of anaesthesia, the increase in propofol clearance with the Schnider model in a 40 year, 160 cm height, female patient of 180 kg would be 70 % in comparison with values predicted by the Hume and

Janmahasatian equations while the decrease in remifentanyl clearance in the same patient would be 40 % (Figs. 2.12 and 2.13). This problem highlights a failure to validate the performance of the proposed models over the whole range of potential patient input characteristics. Once recognised, the manufacturers of the Asena PK and Orchestra Base Primea open TCI systems introduced a compromise solution whereby inputs of body weight and height producing BMI figures above the point where the James equation calculates a declining LBM lead to clearance being calculated based on the maximum LBM for the patient's height. A similar procedure has been implemented in more recently introduced open TCI systems.

Different Implementations of Effect Control Software

At the time of their introduction in 2003 both the Asena PK and the Orchestra Base Primea open TCI pumps provided users with the option of controlling propofol blood or effect-site concentrations with the Schnider pharmacokinetic

Fig. 2.14 Influence of method of implementation of effect control TCI on initial propofol dose delivered in a 20 year, 170 cm female subject with the Schnider model at a target effect site concentration (C_{eT}) of $4 \mu\text{g ml}^{-1}$. *Open square* fixed T peak 1.6 min, *filled diamond* fixed k_{e0} 0.456 min^{-1}



model. However the implementation of the effect control facility in the Asena PK device calculated a k_{e0} for each patient based on a fixed time to peak effect of 1.6 min while the Base Primea pump used a fixed k_{e0} of 0.456 min^{-1} , both figures coming from the original publication by Schnider and colleagues [28]. With both methods, age has an influence on the size of the initial bolus delivered and the time of peak effect as a consequence of age related changes in rapid distribution. As such the greatest difference between the two methods is seen in younger patients. In a 20-year-old, 70 kg, 170 cm female subject, at a propofol effect site target concentration of $4 \mu\text{g ml}^{-1}$, the initial dose delivered with a fixed k_{e0} of 0.46 min^{-1} (predicted time to peak effect 1.36 min) is 1.11 mg kg^{-1} . In the same patient with time to peak effect fixed at 1.6 min ($k_{e0} = 0.32 \text{ min}^{-1}$), the initial dose delivered is 1.43 mg kg^{-1} , an increase of 28 %. The difference between the two methods becomes more marked as body weight increases as shown in Fig. 2.14. In the 60 and 70 kg patients, the difference between the two methods occurs principally because the illustration involves a young patient but, as body weight increases and clearance increases due to the complex influence of body weight and LBM, time to peak effect with a fixed k_{e0} decreases. Thus with the fixed time to peak effect method, a greater reduction in k_{e0} is required to achieve a time to peak of 1.6 min and this slower k_{e0} delivers a greater initial dose at the same target setting. As the disparity between the two methods, in the initial dose delivered over the weight range 80–100 kg increases from 37 to 60 %, while BMI remains below the point at which the James equation provides erroneous values for LBM, it is unlikely that this difference would be abolished by the use of an alternative method of LBM calculation.

The same problem does not occur with the Marsh model as an increase in body weight is not associated with any decrease in the predicted time to peak effect and effect control TCI at a target of $4 \mu\text{g ml}^{-1}$ with a fixed k_{e0} of 1.2 min^{-1} or a fixed time to peak effect of 1.6 min delivers

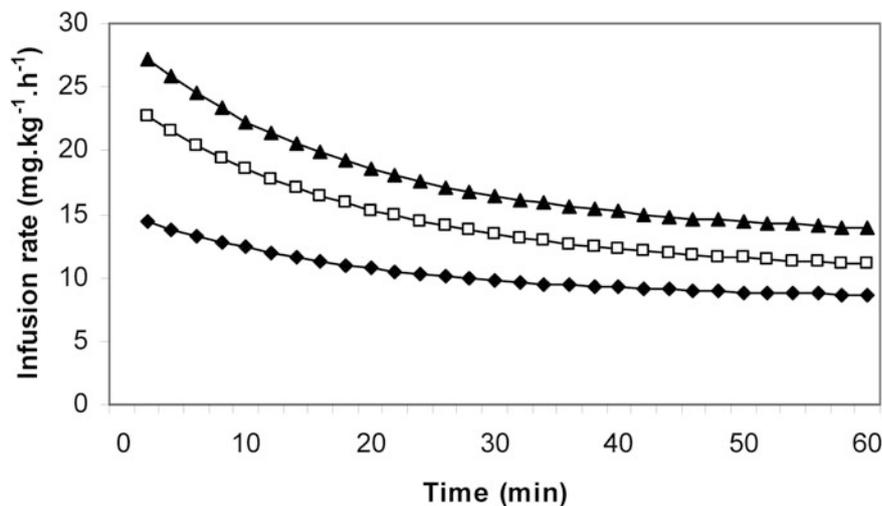
an initial dose of 1.4 mg kg^{-1} , independent of patient age or body weight.

Models for TCI in Children

Use of the Diprifusor TCI system is restricted to use in patients of 16 years of age or older as studies with this system have not been conducted in children and no guidance on propofol target concentration for use in children is provided in Diprivan (propofol) labelling. However, a number of studies of the pharmacokinetics of propofol in children have been published and the model described by Kataria and colleagues [54] and the ‘Paedfusor’ model have been incorporated in some open TCI systems.

The history of the ‘Paedfusor’ model is as follows: In 1997, discussions with Jürgen Schüttler and Martin White at the time of the ASA meeting in San Diego that year led to the production of a modified Diprifusor system with a pharmacokinetic model which required the calculation of clearance as a power function of body weight on the basis of the preliminary results of a population pharmacokinetic study with propofol which was later published [55]. Central compartment volume (V_1) at 458 ml kg^{-1} was much greater than the value of 228 ml kg used by the Marsh model in adults and to avoid a sudden step change in 16-year-old patients, V_1 is gradually decreased in 13- to 15-year-old patients. This system, which became known as a ‘Paedfusor’ was provided by Zeneca to Neil Morton in Glasgow who confirmed the ease of use of the system, clinical efficacy and absence of adverse effects when used for induction and maintenance of anaesthesia in healthy children aged 6 months to 16 years [56]. Further studies confirmed good predictive performance when this model was used in children of 1–15 years undergoing cardiac surgery or catheterization [57]. Anaesthesia was induced with an initial propofol target blood concentration of $5 \mu\text{g ml}^{-1}$ and was supplemented with a TCI infusion of alfentanil. Median performance error (MDPE) and median absolute performance error (MDAPE)

Fig. 2.15 Influence of pharmacokinetic model on propofol infusion rates delivered in a 20 kg child at a target blood concentration (C_{bT}) of $4 \mu\text{g ml}^{-1}$ with filled triangle Kataria, open square Paedfusor and filled diamond Marsh adult models



values of 4.1 % and 9.7 %, respectively, were determined. The full details of the Paedfusor model used in this study were provided in a subsequent publication [58]. Both the Kataria and Paedfusor models were found to achieve acceptable predictive performance in a study which compared eight paediatric pharmacokinetic models in healthy young children [59]. At a given target blood propofol concentration both models deliver greater initial doses and subsequent infusion rates than the Marsh adult model with the Kataria model delivering more than the Paedfusor model (Fig. 2.15). Another potential problem with commercial implementations of the Kataria model is that the study publication describes three different models and the same version of the model may not always be selected.

Use of Different Rate Constants to Predict or Control Effect Site Concentration

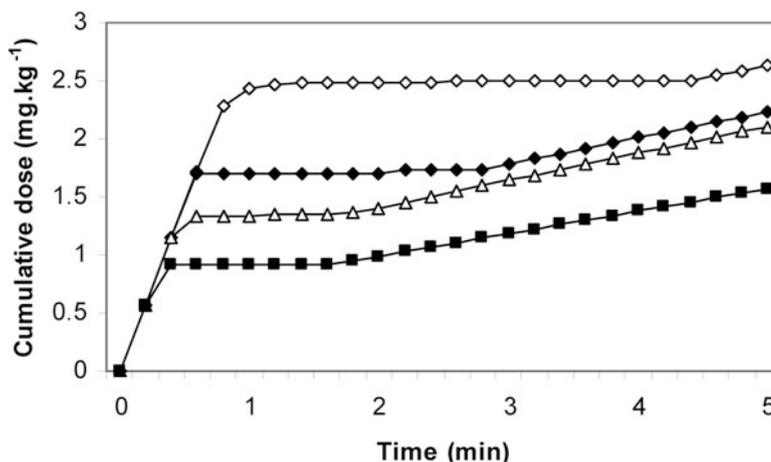
As mentioned earlier, the original submissions for ‘Diprivan’ (propofol) and ‘Ultiva’ (remifentanyl) to Medicines Authorities in Europe did not contain information on administration of these drugs by effect control TCI and no guidance on effect-site target concentrations was provided in drug labelling. An early modification of Diprifusor TCI software involved the incorporation of a blood brain equilibration constant (k_{e0}) of 0.26 min^{-1} , but only to allow the prediction of effect site propofol concentration. Despite the lack of regulatory approval from any Medicines Authority at the time in 2003 when open TCI systems began to be marketed, administration of propofol and remifentanyl by effect control TCI has become widely practised. Potential confusion arises from the incorporation of different k_{e0} values for effect control with the same drug as has occurred with propofol. The TCI devices provided by Arcomed AG allow a choice of time to peak effect of 1.6 min or 4 min with the Marsh model, Fresenius Kabi use a k_{e0s} of 0.456 min^{-1} for the Schnider model and 1.2 min^{-1} for the Marsh model in

their system, while Carefusion TCI pumps use a time to peak effect of 1.6 min for both models. AstraZeneca considered that a time to peak effect of 4 min was probably too slow, that a time to peak effect of 1.6 min was probably too fast, and only recently a modified version of the Diprifusor module incorporating an intermediate k_{e0} of 0.6 min^{-1} was approved. This value was determined on the basis of a detailed review of published studies in which propofol was given safely by effect control TCI with the Marsh pharmacokinetic model and a range of k_{e0} values. To update the Summary of Product Characteristics for ‘Diprivan’ with the provision of information on the administration of propofol by effect control TCI a Type II variation was submitted to Medicines Agencies in a selection of European countries. Despite the fact that, with the effect site target recommended for induction with this k_{e0} , the initial dose of propofol delivered would be less than that advised for induction with a manual bolus, and the widespread use of open TCI systems with a range of k_{e0} values, further prospective studies with this k_{e0} were requested. The only exception was Germany where the variation was approved.

The consequences of a range of k_{e0} values for the same drug are as follows:

1. With blood concentration control, the rate of increase in *predicted* effect site concentrations at induction and the rate of decrease in *predicted* effect site concentrations after a reduction in target or during recovery will be influenced. A faster k_{e0} or shorter time to peak effect predicting faster equilibrium between blood and effect site concentrations and vice versa for a slower k_{e0} or longer time to peak effect. However, at any given target setting, the actual rate of onset of effect and rate of recovery will be dependent on the rate of blood brain equilibration in the patient and unaffected by the prediction provided by any model k_{e0} .

Fig. 2.16 Influence of pharmacokinetic model and equilibration rate constant (k_{e0}) on cumulative dose of propofol delivered in a 50 year, 70 kg, 170 cm male subject at a target effect site concentration (C_{eT}) of $4 \mu\text{g ml}^{-1}$. *Open diamond* Marsh k_{e0} 0.26 min^{-1} , *filled diamond* Marsh k_{e0} 0.6 min^{-1} , *open triangle* Marsh k_{e0} 1.2 min^{-1} , *filled square* Schnider k_{e0} 0.456 min^{-1}



- With effect control administration, different k_{e0} s can have a marked effect not only on the rate at which predicted effect site concentrations increase and a desired effect-site target is achieved but also on the initial dose delivered at any particular target (Fig. 2.16); and that in return will influence the peak predicted blood concentration ($C_{b,CALC}$) achieved. With the Marsh model and a propofol effect site target of $4 \mu\text{g ml}^{-1}$ as used in Fig. 2.16, peak $C_{b,CALC}$ ranges from $5.5 \mu\text{g ml}^{-1}$ with a k_{e0} of 1.2 min^{-1} to $9.4 \mu\text{g ml}^{-1}$ with a k_{e0} of 0.26 min^{-1} . With the Schnider model and a k_{e0} of 0.456 min^{-1} , despite the administration of a smaller initial dose, peak $C_{b,CALC}$ reaches $13.3 \mu\text{g ml}^{-1}$, as a consequence of the smaller central compartment volume in this model. Thus it is imperative in any study which describes effect site concentrations at induction, that information on the model and k_{e0} used is provided to allow meaningful interpretation of any observations [60]. Once equilibrium between predicted blood and brain concentrations is achieved, the infusion rate of drug required to maintain a desired target is essentially similar to that which would be provided with blood concentration control, and the precision of the two systems at that point will be identical.

In summary, the regulatory approach adopted in the approval of second generation, open TCI systems, by providing different models for the same drug, inappropriate methods for the calculation of lean body mass, two different implementations of effect site concentration control, and a choice of different k_{e0} values for effect control, has led to a considerable degree of confusion. The skill of anaesthetists in titrating drug dosage to effect, and dealing with situations where potential overdosage or underdosage could occur, appears to have avoided serious safety issues. Some hospitals adopt a local policy to limit possible confusion by only allowing one model to be used, but problems may arise when trainees move from one institution to another.

Possible Ways Forward

The syringe recognition system used in the development of the Diprifusor TCI system prevents the possibility of the type of ‘drug swap’ error as described earlier. However, the Diprifusor approach has not been applied to other drugs and electronically tagged syringes are not available for generic preparations of propofol. The use of barcode technology to reduce drug administration errors is showing promising results [61, 62]. Universal compliance with these systems was not achieved, but perhaps one can envisage a future TCI pump where mandatory scanning of the drug to be infused, with a scanner as an integral part of the infusion device, would be required to allow the pump to operate.

It appears that the regulatory approach to clinical use of the technique of TCI and the approval of TCI devices will be dependent on the stage of development of the particular drug involved:

Drug Is Still Being Actively Marketed by the Originating Company

The benefit of the Diprifusor approach, also relevant to remifentanyl TCI, is that a single pharmacokinetic model was identified, clinical studies were performed with TCI, and with the involvement of medicines regulatory authorities, guidance on target drug concentrations, appropriate for use with the selected model was included in the drug labelling, now provided as the Summary of Product Characteristics (SPC) in Europe. Key elements in the Diprifusor development were the provision of a delivery performance specification and guidance for device manufacturers on patient age and weight limits deemed suitable for the pharmacokinetic model used. It is suggested

that this information should form part of the regulatory submission to a Medicines Authority for any new drug to be given by TCI. The major failing of the current route of approval of 'Open' TCI systems is that the essential requirements of Directive 93/42/EEC can be met, and conformance with full quality assurance procedures demonstrated, and yet TCI devices intended for the same purpose can deliver drug in quite different ways at the same target setting. As such it would seem appropriate that TCI drug delivery devices should be considered as a special case within the Directive and should require the Notified Body evaluating the documentation to consult with the manufacturer of the drug to be infused and a relevant Medical Regulatory Authority to ensure the delivery performance of the device conforms to that held by the Medicines Authority and to avoid the confusion caused by different models for the same drug. Three technical evaluation reports on commercial TCI devices were prepared for the UK Medicines and Healthcare products Regulatory Agency (MHRA) by Craig Davey at the Bath Institute of Medical Engineering. These are available at the following web site: <http://nhscep.useconnect.co.uk/CEPProducts/Catalogue.aspx> The report on 'Target controlled infusion (TCI) systems part two: Alaris Asena PK' includes the following statements: "It is interesting to note that while a high degree of accuracy is achieved, the different models will actually cause the pump to deliver [propofol] markedly differently from one another . . . It is beyond the scope of this report to judge the clinical effectiveness for any of the models . . ." The same comment is made in the report on the Fresenius Vial Base Primea and neither report identified the problems associated with the James calculation of lean body weight or the different implementations of effect control TCI.

Drug Is No Longer Actively Marketed by Originating Company

Propofol

The above approach, while desirable, may not be possible when pharmaceutical companies limit further development effort and expenditure once generic versions of their drug become available and at the same time relevant expertise within the company may have been lost. As such, the driving force for the introduction of TCI for a particular drug comes from the academic community and device manufacturers. In an attempt to resolve the problems highlighted in this chapter, the 'Open TCI initiative' was inaugurated at the time of the 14th World Congress of Anaesthesiologists in Cape Town in 2008, at a meeting hosted by Steve Shafer. This Initiative, now hosted on the web site of the World Society of Intravenous Anaesthesia at www.worldsiva.org has provided a forum for discussion and a focal point for the

collection of study data which has been used in the development of a general purpose pharmacokinetic model for propofol [49]. This model has shown good predictive performance in the subgroups of children, adults, elderly and obese patients contributing data to the study and with further prospective validation may prove to be the preferred model for propofol. If this proves to be the case, there is likely to be a third model added to the options of anaesthetists in Europe, as those familiar with their current preferred model may be reluctant to change their practice, at least in the short term.

On the other hand, in the USA, in the absence of any approved TCI device to date, there may be an opportunity to introduce the technique with a single pharmacokinetic model, thus avoiding the confusion of multiple models for the same drug. Extensive clinical experience has demonstrated that propofol can be safely administered by TCI. In the absence of any approved predicate device, it is likely that a Pre Market Approval (PMA) application will be required and linkage to clinical information in published studies could be provided by device manufacturers in the form of a delivery performance specification linking particular target settings to initial doses delivered (mg kg^{-1}) and subsequent infusion rate profiles ($\text{mg kg}^{-1} \text{h}^{-1}$) recognised as appropriate for propofol. To assist in training and familiarisation with these systems it would be appropriate for such delivery equivalence data to be provided in the device operating manual. Once one device is approved, the requirement for other manufacturers to demonstrate equivalence in a 510 K application would prevent the introduction of different models unless they complied with the approved delivery specification. With propofol now a generic drug, it likely that the onus on funding regulatory submissions and training programs for the introduction of TCI in the USA will fall on the medical device companies. One possible way forward may be for a number of medical device companies to co-fund the more complex PMA submission by one of their number on condition that other subscribers have preferential access to data to facilitate early 510 K submissions.

Other Drugs

For other drugs, both in the USA and elsewhere, it would be desirable for the academic community to reach a consensus on a preferred pharmacokinetic model and, particularly where publications describe different modelling approaches [39, 54], to define the parameters of the model. Again a delivery performance specification should be produced by the first device company developing a system for a particular drug to demonstrate drug delivery rates consistent with existing drug labelling and clinical experience and again this information should be included in the device operating instructions. It is suggested that the evaluation of the first such device submitted to a European Notified body should require that body to consult with the manufacturer of the

drug and a relevant Medical Regulatory Authority to ensure the delivery performance of the device conforms to approved drug labelling and subsequent device submissions for the same drug should be required to demonstrate equivalent delivery performance.

Conclusion

While a tightly controlled regulatory approach was adopted in the development of the Diprifusor TCI system, the regulation of open TCI systems in Europe, by allowing duplicate models for the same drug, has probably hindered the wider adoption of TCI by making the technique appear more complex and confusing. With the recent development of a general purpose pharmacokinetic model for propofol, there may be an opportunity for the USA to adopt a sound approach, despite the delay.

References

1. Stokes DN, Peacock JE, Lewis R, Hutton P. The Ohmeda 9000 syringe pump, the first of a new generation of syringe drivers. *Anaesthesia*. 1990;45:1062–6.
2. Glass PSA, Glen JB, Kenny GNC, Schuttler J, Shafer SL. Nomenclature for computer-assisted infusion devices. *Anesthesiology*. 1997;86:1430–1.
3. White M, Kenny GNC. Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia*. 1990;45:204–9.
4. Kenny GNC, White M. A portable target controlled propofol infusion system. *Int J Clin Monit Comput*. 1992;9:179–82.
5. Taylor I, White M, Kenny GNC. Assessment of the value and pattern of use of a target controlled propofol infusion device. *Int J Clin Monit Comput*. 1993;10:175–80.
6. Glen JB. The development of ‘Diprifusor’: a TCI system for propofol. *Anaesthesia*. 1998;53 Suppl 1:13–21.
7. Gray JM, Kenny GNC. Development of the technology for ‘Diprifusor’ TCI systems. *Anaesthesia*. 1998;53 Suppl 1:22–7.
8. Arundel PA. Interactive simulation of non-uniform bolus and infusion dosing in linear compartment models. *J Pharm Sci*. 1989;78:688–90.
9. Dyck JB, Shafer SL. Effects of age on propofol pharmacokinetics. *Semin Anesth*. 1992;11:2–4.
10. Tackley RM, Lewis GTR, Prys-Roberts C, Coats D, Monk CR. Computer controlled infusion of propofol. *Br J Anaesth*. 1989;62:46–53.
11. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth*. 1991;67:41–8.
12. Servin F, Cockshott ID, Farinotti R, Haberer JP, Winkler C, Desmots JM. Pharmacokinetics of propofol infusions in patients with cirrhosis. *Br J Anaesth*. 1990;65:177–83.
13. Coetzee JF, Glen JB, Wium CA, Boshoff L. Pharmacokinetic model selection for target controlled infusions of propofol. Assessment of three parameter sets. *Anesthesiology*. 1995;82:1328–45.
14. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg*. 1987;66:1256–63.
15. Struys M, Versichelen L, Rolly G. Influence of pre-anaesthetic medication on target propofol concentration using a ‘Diprifusor’ TCI system during ambulatory surgery. *Anaesthesia*. 1998;53 Suppl 1:68–71.
16. Servin FS, Marchand-Maillet F, Desmots JM. Influence of analgesic supplementation on the target propofol concentrations for anaesthesia with ‘Diprifusor’ TCI. *Anaesthesia*. 1998;53 Suppl 1:72–6.
17. Richards AL, Orton JK, Gregory MJ. Influence of ventilator mode on target concentrations required for anaesthesia using a ‘Diprifusor’ TCI system. *Anaesthesia*. 1998;53 Suppl 1:77–81.
18. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. *J Pharmacokinetic Biopharm*. 1992;20:63–94.
19. Swinhoe CF, Peacock JE, Glen JB, Reilly CS. Evaluation of the predictive performance of a ‘Diprifusor’ TCI system. *Anaesthesia*. 1998;53 Suppl 1:61–7.
20. Barvais L, Rausin I, Glen JB, Hunter SC, D’Hulster D, Cantraine F, d’Hollander A. Administration of propofol by target-controlled infusion in patients undergoing coronary artery surgery. *J Cardiothorac Vasc Anesth*. 1996;10:877–83.
21. Russell D, Wilkes MP, Hunter SC, Glen JB, Hutton P, Kenny GNC. Manual compared with target controlled infusion of propofol. *Br J Anaesth*. 1995;75:562–6.
22. McMurray TJ, Johnston JR, Milligan KR, et al. Propofol sedation using Diprifusor target-controlled infusion in adult intensive care unit patients. *Anaesthesia*. 2004;59:636–41.
23. White M, Engbers FHM, Schenkels MJ, Burn AGL, Bovill JG. The pharmacodynamics of propofol determined by auditory evoked potentials. Sydney: Abstracts World Congress of Anaesthesiology; 1996. P610.
24. White M, Schenkels MJ, Engbers FHM, et al. Effect-site modelling of propofol using auditory evoked potentials. *Br J Anaesth*. 1999;82:333–9.
25. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G. Comparison of plasma compartment versus two methods for effect compartment-controlled target-controlled infusion for propofol. *Anesthesiology*. 2000;92:399–406.
26. Thomson AJ, Nimmo AF, Engbers FHM, Glen JB. A novel technique to determine an ‘apparent k_{e0} ’ value for use with the Marsh pharmacokinetic model for propofol. *Anaesthesia*. 2014;69:420–8.
27. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology*. 1998;88:1170–82.
28. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology*. 1999;90:1502–16.
29. Thomson AJ, Morrison G, Thomson E, Beattie C, Nimmo AF, Glen JB. Induction of general anaesthesia by effect-site target-controlled infusion of propofol: influence of pharmacokinetic model and k_{e0} value. *Anaesthesia*. 2014;69:429–35.
30. Kazama T, Ikeda K, Numata K, et al. Assessment of use of “Diprifusor” target controlled infusion (TCI) of 1% Diprivan (ICI 35,868). *Anesth Resuscitation*. 1998;34:121–39.
31. Hu C, Horstman DJ, Shafer SL. Variability of target-controlled infusion is less than the variability after bolus injection. *Anesthesiology*. 2005;102:639–45.
32. Struys MM, De Smet T, Glen JB, Vereecke HE, Absalom AR, Schnider TW. The history of target-controlled infusion. *Anesth Analg*. 2016 (in press)
33. Shafer SL, Gregg KM. Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. *J Pharmacokinetic Biopharm*. 1992;20:147–69.

34. Jacobs JR, Williams EA. Algorithm to control "Effect Compartment" drug concentrations in pharmacokinetic model-driven drug delivery. *IEEE Trans Biomed Res.* 1993;40:993–9.
35. Enlund M. TCI: target controlled infusion or totally confused infusion? Call for an optimised population based pharmacokinetic model for propofol. *Ups J Med Sci.* 2008;113:161–70.
36. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl. I Model development. *Anesthesiology.* 1997;86:10–23.
37. Mertens MJ, Engbers FH, Burm AG, Vuyk J. Predictive performance of computer-controlled infusion of remifentanyl during propofol/remifentanyl anaesthesia. *Br J Anaesth.* 2003;90:132–41.
38. James WPT. Research on obesity. A report of the DHSS/MRC Group. London: Her Majesty's Stationery Office; 1976.
39. Gepts E, Shafer SL, Camu F, et al. Linearity of pharmacokinetics and model estimation of sufentanyl. *Anesthesiology.* 1995;83:1194–204.
40. Scott JC, Cook JE, Stanski DR. Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanyl. *Anesthesiology.* 1991;74:34–42.
41. Chae Y-J, Joe HB, Kim J-A, Lee W-I, Min S-K. Correction of target-controlled infusion following wrong selection of emulsion concentration of propofol. *Korean J Anesthesiol.* 2014;66:377–82.
42. Sistema Español de Notificación en Seguridad en Anestesia y Reanimación (SENSAR). [Incorrect programming of a target controlled infusion pump. Case SENSAR of the trimester]. *Rev Esp Anesthesiol Reanim.* 2014;61:e27–30.
43. Nimmo AF, Cook TM. Total intravenous anaesthesia; 18:151–8. http://www.nationalauditprojects.org.uk/NAP5_home#pt.
44. Chae Y-J, Kim J-Y, Kim D-W, Moon B-K, Min S-K. False selection of syringe-brand compatibility and the method of correction during target controlled infusion of propofol. *Korean J Anesthesiol.* 2013;64:251–6.
45. Schüttler J, Kloos S, Schwilden H, Stoeckel H. Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. *Anaesthesia.* 1988;43(Suppl):2–7.
46. Doufas AG, Bakhshandeh M, Bjorksten AR, Shafer SL. Induction speed is not a determinant of propofol pharmacodynamics. *Anesthesiology.* 2004;101:1112–21.
47. Glen JB, Servin F. Evaluation of the predictive performance of four pharmacokinetic models for propofol. *Br J Anaesth.* 2009;102:626–32.
48. Glen JB, White M. A comparison of the predictive performance of three pharmacokinetic models for propofol using measured values obtained during target-controlled infusion. *Anaesthesia.* 2014;69:550–7.
49. White M, Kenny GNC, Schraag S. Use of target controlled infusion to derive age and gender covariates for propofol clearance. *Clin Pharmacokinet.* 2008;47:119–27.
50. Eleveld DJ, Proost JH, Cortinez LI, Absalom AR, Struys MMRF. A general purpose pharmacokinetic model for propofol. *Anesth Analg.* 2014;118:1221–37.
51. Green B, Duffull S. Caution when lean body weight is used as a size descriptor for obese subjects. *Clin Pharmacol Ther.* 2002;72:743–4.
52. Hume R. Prediction of leanbody mass from height and weight. *J Clin Pathol.* 1966;19:389–91.
53. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clin Pharmacokinet.* 2005;44:1051–65.
54. Kataria BK, Sudha SA, Nicodemus HF, et al. The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology.* 1994;80:104–22.
55. Schüttler J, Ihmsen H. Population pharmacokinetics of propofol. *Anesthesiology.* 2000;92:727–38.
56. Varveris D, Morton NS. Target controlled infusion of propofol for induction and maintenance of anaesthesia using the paedfusor: an open pilot study. *Paediatr Anaesth.* 2002;12:589–93.
57. Absalom A, Amutike D, Lal A, White M, Kenny GNC. Accuracy of the 'Paedfusor' in children undergoing cardiac surgery or catheterization. *Br J Anaesth.* 2003;91:507–13.
58. Absalom A, Kenny G. 'Paedfusor' pharmacokinetic data set. *Br J Anaesth.* 2005;95:110.
59. Sepulveda P, Cortinez LI, Saez C, et al. Performance evaluation of paediatric propofol pharmacokinetic models in healthy young children. *Br J Anaesth.* 2011;107:593–600.
60. Glen JB. Propofol effect site concentrations: hunt the k_{e0} . *Anesth Analg.* 2013;117:535–6.
61. Merry AF, Webster CS, Hannam J, et al. Multimodal system designed to reduce errors in recording and administration of drugs in anaesthesia: prospective randomised clinical evaluation. *Br Med J.* 2011;343.
62. Jelacic S, Bowdle A, Nair BG, Kusulos D, Bower L, Togashi K. A system for anesthesia drug administration using barcode technology: the codonics safe label system and smart anesthesia manager™. *Anesth Analg.* 2015;121:410–20.



<http://www.springer.com/978-3-319-47607-0>

Total Intravenous Anesthesia and Target Controlled Infusions

A Comprehensive Global Anthology

Absalom, A.R.; Mason, K.P. (Eds.)

2017, XVIII, 824 p. 324 illus., 200 illus. in color. With online files/update., Hardcover

ISBN: 978-3-319-47607-0