

Recent advances in intravenous anaesthesia

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Efforts to develop new hypnotic compounds continue, although several have recently failed in development. Propofol has been reformulated in various presentations with and without preservatives. Pharmacokinetic and pharmacodynamic differences exist between some of these preparations, and it is currently unclear whether any have substantial advantages over the original presentation. The use of target-controlled infusion (TCI) has been extended to include paediatric anaesthesia and sedation. Application of TCI to remifentanyl is now licensed. Linking of electroencephalogram (EEG) monitoring to TCI for closed-loop anaesthesia remains a research tool, although commercial development may follow. The availability of stereoisomer ketamine and improved understanding of its pharmacology have increased non-anaesthetic use of ketamine as an adjunct analgesic. It may be useful in subhypnotic doses for postsurgical patients with pain refractory to morphine administration.

Br J Anaesth 2004; **93**: 725–36

Keywords: anaesthetics i.v., etomidate; anaesthetics i.v., ketamine; anaesthetics i.v., ORG21465; anaesthetics i.v., ORG25435; anaesthetics i.v., propofol; anaesthetics i.v., THRX-918661; analgesics opioid, remifentanyl

Intravenous anaesthesia (IVA) is now well established in most areas of anaesthetic provision and is the preferred technique for some. This review assesses the present status of IVA, describes recent and forthcoming developments, and addresses various related controversies and their implications. Intravenous anaesthetics have other uses beyond the induction and maintenance of anaesthesia, and recent developments of relevance to clinicians are also summarized. Material for this review was gathered from literature searching, attendance at meetings and personal communication with experts in the field. Priority has been given to developments since 2000. The content has been constrained to clinical developments and late-stage animal work with possible relevance to man.

New drugs

Attempts to develop new water-soluble i.v. agents for use in man have not been successful. Two Organon compounds, ORG 21465 and 25435, were both rejected in phase 1 clinical trials because of unwanted effects, including excitation and tachycardia, and disappointing pharmacokinetics leading to slow recovery after prolonged infusion.^{102 103 106} Other novel water-soluble anaesthetics exist which perform well in rodents but which for various reasons have not been tested in man.¹⁸ The success of remifentanyl and its esterase metabolism has encouraged other attempts at developing

compounds with very rapid metabolism. THRX-918661, a sedative-hypnotic agent being developed by Theravance (Theravance, South San Francisco, CA, USA), is an allosteric modulator of the GABA_A receptor which is hydrolysed by esterases to an inactive metabolite. In rat and guinea-pig whole blood the compound is rapidly hydrolysed ($t_{1/2}$ 0.4 and 0.1 min respectively). After discontinuing a 3 h continuous i.v. infusion in rats, the parent compound was only detectable for 5 min.⁵⁰ When the compound was administered to pigs by continuous i.v. infusion, recovery was faster than with propofol.³⁴ However, rapid metabolic deactivation combined with modest potency require that a large mass of drug be infused to produce a therapeutic effect (1.5 mg kg⁻¹ min⁻¹ to maintain anaesthesia in a pig), and this might impede clinical development. If the ultrarapid recovery from THRX-918661 anaesthesia is confirmed in man, this agent will have a clinical profile distinct from other hypnotics. Whether such abrupt emergence is clinically advantageous is unknown. Certainly, this compound raises the theoretical question of whether it is possible for an i.v. anaesthetic agent to wear off too quickly. In any case, speed of emergence could presumably be controlled by tapering rather than discontinuing the infusion. The structure of THRX-918661 is described as a commercial secret, but a

[†]Declaration of interest. Professor Sneyd is an Advisory Board member for Organon Inc. and has received research funding from AstraZeneca.

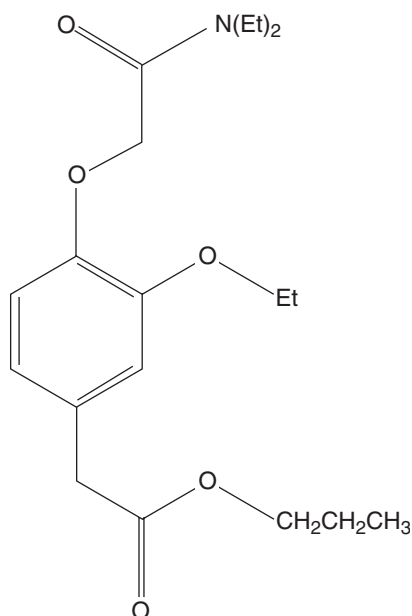


Fig 1 THRX-918661 is a short-acting novel i.v. anaesthetic agent which has been evaluated in various animal models.^{16,34,50} Its formula is probably [4-[(N,N-diethylcarbamoyl)methoxy]-3-ethoxyphenyl]acetic acid propyl ester. A likely structure is shown.⁵¹

recent US patent application⁵¹ includes the formula [4-[(N,N-diethylcarbamoyl)methoxy]-3-ethoxyphenyl]acetic acid propyl ester and a structure (Fig. 1) which appear to describe the compound.

Propofol

After its launch in 1986, propofol rapidly became the most commonly used i.v. anaesthetic agent, with thiopental, ketamine and etomidate reserved for specific indications. So ubiquitous has propofol IVA become that it is simpler to list its contraindications than to describe the techniques for which it is suited.

When should propofol not be used? The only absolute indication to propofol is allergy and this appears to be rare. Although Laxenaire^{58,59,65} has described several cases of propofol allergy, its overall incidence appears to be very low and the drug is well tolerated by most patients, including those allergic to eggs. Alternative induction agents also cause serious adverse reactions.¹⁵

Several groups have studied propofol for induction and maintenance of anaesthesia during Caesarean section; neonatal scores and neurobehavioural measures were inferior when propofol was used in comparison to thiopental and inhalational agents respectively.^{26,130} Propofol is not licensed for use in obstetric anaesthesia.

Parkinson's disease is a common condition, yet there is remarkably little information to guide anaesthetists on which, if any, i.v. agent to use for these patients. A limited number of case reports suggest that Parkinson's disease may

be worsened by propofol,⁷⁵ presumably due to dopaminergic effects. However, the ability of propofol to diminish or abolish Parkinsonian tremor yet induce myoclonic movements is hard to understand.⁵ Clearly, we need to know more about these aspects of propofol pharmacology; meanwhile, the drug should be used cautiously in patients with movement disorders. Excitatory events following propofol administration are well described if not well understood,¹⁰¹ and thiopental may be a better choice for patients with epilepsy who hold a driving license.¹⁰⁵

Haemodynamic changes following propofol administration are well detailed and are generally moderated by a reduction in dose and slower administration,⁷⁸ combined with adequate fluid administration. In practice, propofol is commonly co-administered with other drugs, some of which have vagotonic effects, particularly opioids. However, although frequent, bradycardia associated with propofol anaesthesia seldom has serious consequences.⁴⁷

Old drugs in new clothing: propofol revisited

Whilst the original 1 and 2% presentations of propofol in soya oil remain popular, there have been a number of attempts at reformulation. The basic presentation³⁸ supports bacterial growth,⁸⁸ and has been supplemented with EDTA (ethylene diamine tetraacetic acid)⁴² or sulphite,⁹⁹ the manufacturers of rival formulations arguing whether sulphite causes allergic reactions, especially in atopic or asthmatic patients. When the sulphite and EDTA formulations were administered to 40 current, long-term smokers, total respiratory system resistance was increased in the patients treated with the sulphite-containing formulation. But changes in inflation pressure were not significant,⁸⁴ suggesting that sulphite has some effect on the tracheobronchial system of patients with reactive airways. However, the clinical significance of these small changes is unclear.

Sulphite supports the peroxidation of lipids in soybean oil emulsions,¹² and this may cause the infusion to develop a yellowish discoloration during use.¹³ The addition of sulphite also lowers the pH of the propofol formulation and may compromise the stability of the oil-in-water emulsion, leading to an increase in the number and size of large-diameter lipid droplets in the ampoule.

In Europe, propofol continues to be safely used without supplementary preservatives and it is clear that when the drug is prepared using a proper aseptic technique and not stored beyond recommended guidelines, then bacterial contamination is not a clinical issue. Whether the added preservatives are clinically important in standard anaesthetic practice is probably debatable, but different considerations may apply for critically ill patients with organ dysfunction receiving prolonged propofol infusions.¹³¹

Propofol in different lipids

The standard propofol formulation contains 10% soya oil as long-chain triglycerides. Triglyceride concentrations

increase in a proportion of patients after propofol administration. Changing the emulsion in which propofol is presented might have favourable effects on the plasma triglyceride profile. An emulsion containing long- and medium-chain triglycerides (Propofol-Lipuro[®]) reduced the incidence of pain on injection from 14.7 to 2.7% (lidocaine was not given).⁸² When used to maintain anaesthesia in volunteers, their plasma triglyceride concentrations did not rise.¹²⁵ Whether these 'advantages' are of any real clinical importance remains to be determined. In critical care, however, things seem to be different. When a similar comparison between standard (long-chain triglyceride) propofol and the long- and medium-chain mixture was made using 2% formulations, similar propofol concentrations and equivalent levels of sedation were achieved. But there was no difference in plasma triglyceride concentrations between the two groups and the recovery time was prolonged in patients receiving the new formulation.¹¹³ Thus, the reformulation not only failed to confer any advantage, it actually reduced clinical performance. However, the study was a small one and differences in patient characteristics may also have influenced the outcome.

Another propofol-containing emulsion based on medium-chain triglycerides (AM149 1%) caused pain on injection in 93% of subjects as well as thrombophlebitis and seems unsuitable for further development.⁷⁷

Propofol prodrug

Propofol phosphate is a water-soluble propofol prodrug which is enzymatically converted to propofol, formaldehyde and inorganic phosphate. The compound produces sedation and anaesthesia in a range of animal species.¹⁴ However, the onset of hypnotic effect ranged from a minute to several minutes and was much slower than for propofol. When the compound was administered to volunteers as a 10-min infusion, two of the nine subjects reported an unpleasant sensation of burning or tingling in the anal and genital region. Modelling suggested that, after a bolus injection of propofol phosphate, the peak blood propofol concentration would occur more than 5 min later and context-sensitive half-times would increase substantially after prolonged infusions.³⁵ The effects of formaldehyde and formate (to which the formaldehyde is converted) have not yet been fully investigated in man. Whilst the prodrug approach renders the compound water-soluble and may reduce pain on injection, it is clinically counterintuitive to modify a drug in such a way as to slow its onset of action when almost the entire focus of anaesthetic drug development has been to achieve the opposite.

Water-soluble propofol analogues

A substantial number of water-soluble anaesthetics have been prepared with structures derived from that of propofol.^{4,27,116} These have been tested in rodents as bolus injections and in some cases by infusion for closed-loop

computer-controlled maintenance of anaesthesia. These laboratory projects indicate that the potential remains for new propofol-derived drugs but their commercialization remains uncertain.

Non-lipid formulations of propofol

Cyclodextrins are widely used as solubilizing agents in pharmaceutical practice. Cyclodextrins are ring sugar molecules which form guest-host complexes, the guest compound (in this case propofol) migrating between the hydrophilic centre of the cyclodextrin molecule and the water-soluble phase. This allows compounds which are sparingly soluble in water to be presented in an injectable format. After injection, the guest (propofol) migrates out of the cyclodextrin into the blood, where it is protein-bound and, in small amounts, dissolves. Adjustment of the size of the cyclodextrin ring and the addition of side-chains allows cyclodextrins to be developed with specific binding characteristics. Propofol has recently been evaluated in a cyclodextrin-based formulation (Fig. 2). When administered to isoflurane-anaesthetized pigs, the pharmacokinetic and pharmacodynamic effects of conventional and cyclodextrin formulated propofol were similar and further clinical investigation may be appropriate.³² This study was, however, a small and preliminary investigation and extrapolation of these findings to man is not appropriate without additional supporting information.

Polysorbate 80 is a non-ionic surfactant derived from sorbitol which is used widely as an additive in foods, pharmaceutical preparations and cosmetics as an emulsifier, dispersant or stabilizer. A polysorbate formulation of propofol has been tested in goats but was associated with haemodynamic instability and prolonged apnoea.¹⁹

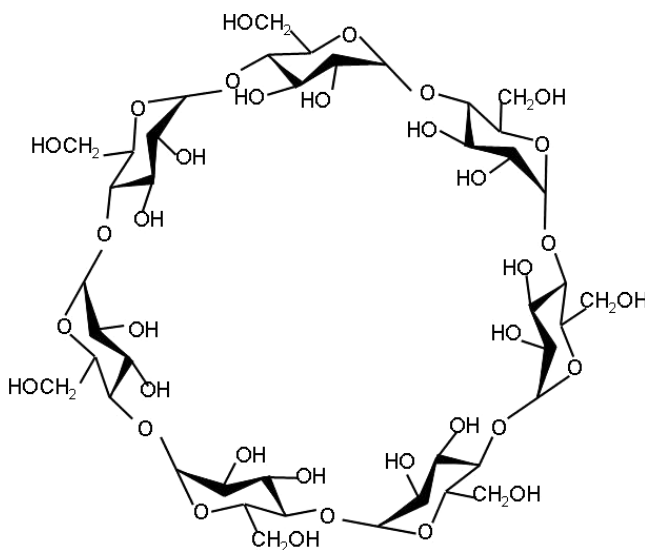


Fig 2 Sulfobutyl ether- β -cyclodextrin (Captisol), a polyanionic β -cyclodextrin derivative with a sodium sulfonate salt separated from the lipophilic cavity by a butyl ether spacer group. Captisol has been used as a lipid-free vehicle for propofol.³²

Another aqueous formulation of propofol may exist but details are sketchy. The use of a 'vegetarian' formulation of propofol, Cleofol® (Themis Medicare, Vapi, Gujarat, India), has been described in a patient from the Jain community of India.⁷⁰ No details of the supposedly aqueous formulation are available, nor are any supporting volunteer or preclinical data.

More drug, less fat

Attempts have been made to reduce the amount of fat given to patients receiving propofol. Increasing the concentration of propofol from 10 to 60 mg ml⁻¹ reduced the total amount of fat received by sedated patients in intensive care and was also associated with lower triglyceride concentrations than in patients receiving the standard formulation.⁵⁷ Another version of propofol emulsion has been described with the soya oil content reduced to 5%, i.e. half that of the original presentation. When this formulation was given to outpatients, the pharmacodynamic effects were unchanged but the incidence of pain on injection was increased from 9% (with the original formulation) to 39%, despite pretreatment with lidocaine.¹⁰⁸ A summary of the formulations of propofol is given in Table 1.

Propofol and pain on injection

Although important to patients given propofol, this has been partially addressed by the preadministration of lidocaine.⁹⁷ Notwithstanding this well-established practice, investigators continue to study alternative and sometimes bizarre ways of addressing the problem (Table 2). Medline now lists many studies on the topic, perhaps reflecting the relative ease with which such investigations can be conducted.

Propofol and nausea and vomiting

Intravenous anaesthesia with propofol has long been associated with a modest reduction in postoperative nausea and vomiting.^{104 115} Apfel and colleagues⁸ used a complex multifactorial crossover design to evaluate in detail the relative contributions of the hypnotic agent, opioid selection and various antiemetics. This study confirmed that replacing an inhaled anaesthetic agent with propofol does reduce postoperative nausea and vomiting (PONV) by roughly the same amount as a single antiemetic. Further, addition of one or more antiemetics to a propofol anaesthetic does reduce PONV.⁹ Recent consensus guidelines for managing PONV include i.v. anaesthesia with propofol as part of a multimodal strategy to reduce baseline risk in susceptible patients.³⁶

Propofol pharmacokinetics

Understanding of the pharmacokinetics and pharmacodynamics of propofol has improved with a comprehensive remodelling of pooled data, drawing together information from a number of clinical trials and specific modelling for children and the elderly.⁹³ However, the interpretation and applicability of the data for the elderly has been disputed¹²³ and defended.⁹⁴ The pharmacokinetics of propofol in critically ill children have also been described in detail.⁸⁵ Pharmacokinetic parameters from four different models are summarized in Table 3. The major difference between the models is the size of the central compartment, which affects the predicted concentrations achieved by propofol infusions. These differences are illustrated in Figure 3. Differences between models also affect their predictions for the decline in blood propofol concentrations when an infusion is stopped. Context-sensitive half-time is a clinically useful

Table 1 Formulations of propofol

Characteristics	Trade name	Manufacturer	References
Propofol 1% and 2% in 10% soya oil with or without EDTA	Diprivan, Disoprivan	AstraZeneca	38, 42
Propofol 6% in 10% soya oil			57
Propofol 1% and 2% in 10% soya oil with or without sodium sulphite	Various	Various	99
Propofol 1% and 2% in 10% long and medium chain triglycerides	Propofol Lipuro	Braun medical	82, 125
'A new galenic formulation of propofol'	AM149	Amrad	77
Propofol phosphate	Aquavan	Guildford Pharmaceuticals	35
Propofol polysorbate			19
Propofol 1% in 5% soya oil with or without EDTA	Ampofol	Amphastar Pharmaceuticals	108, 109
Propofol 1% in sulfobutyl ether-β-cyclodextrin (Captisol)		CyDex Corporation	32

Table 2 Methods to alleviate or modify pain on injection⁹⁷ with propofol which have been evaluated in randomized controlled trials

Local anaesthetics	Technique modifications	Antiemetics	Analgesics	Anaesthetic agents	Other drugs
Lidocaine	5 μm filter	Metoclopramide	Fentanyl	Nitrous oxide	Ephedrine
EMLA cream	Carrier fluid	Granisetron	Ketorolac	Thiopental	Magnesium sulphate
Prilocaine	Large vein	Dolasetron	Tramadol	Ketamine	Neostigmine
Lidocaine tape	Speed of injection	Ondansetron	Nafamostat mesilate		Clonidine
Lidocaine iontophoresis	Aspiration of blood	Metoclopramide	Alfentanil		Nitroglycerin

Table 3 Parameter values from four, three-compartment pharmacokinetic models (calculated for a 20 kg child aged 5 yr). Parameters for a child are shown because all models offer predictions for this weight whereas smaller children and adults are not addressed by all models. V_1 is the volume of the central compartment, and K_{10} is the rate constant describing clearance from the central compartment, and k_{12} , k_{13} , k_{21} , k_{31} are micro rate constants between compartments. Thus, k_{12} is the micro-constant between compartments 1 and 2. The Marsh⁶¹ and Gepts³⁷ Diprifusor model is based primarily on adult data and describes a smaller central compartment than the Schuttler⁹³ and Paedfusor¹ models, which are based on data collected from children. The Rigby-Jones postcardiac surgery model⁸⁵ has an even larger central compartment

Parameter value	Marsh ⁶¹ and Gepts ³⁷ (Diprifusor)	Schuttler ⁹³ 20 kg, 5 yr	Paedfusor ¹ 20 kg	Rigby-Jones ⁸⁵ 20 kg
V_1 (ml kg ⁻¹)	228	384	458	584
k_{10} (min ⁻¹)	0.119	0.073	0.062	0.038
k_{12} (min ⁻¹)	0.112	0.135	0.114	0.0274
k_{13} (min ⁻¹)	0.042	0.06	0.042	0.023
k_{21} (min ⁻¹)	0.055	0.05	0.055	0.012
k_{31} (min ⁻¹)	0.0033	0.00174	0.0033	0.0012

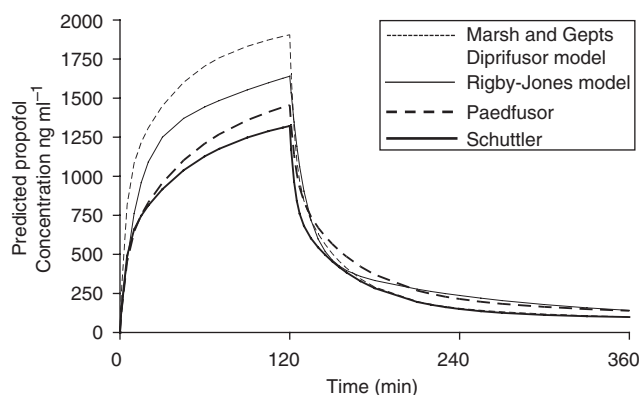


Fig 3 Predicted blood propofol concentrations after a 120 min infusion of propofol 4 mg kg⁻¹ h⁻¹ into a 20 kg child aged 5 yr. Four pharmacokinetic models are compared. Plots represent, from top to bottom: Marsh⁶¹ and Gepts³⁷ Diprifusor model, mostly based on adult data; Rigby-Jones⁸⁵ model, postcardiac surgery; Paedfusor;¹ and Schuttler.⁹³ Thick solid line shows pooled analysis including data from healthy children.

output of pharmacokinetic modelling,¹¹ and the differences in predictions of context-sensitive half-time between the models are illustrated in Figure 4.

Target-controlled infusion of propofol

Introduction of prefilled and 'tagged' propofol syringes and commercial equipment led to the rapid popularization of target-controlled infusion (TCI) in most parts of the world except the USA. Adoption in the USA appears to be almost indefinitely delayed despite evident safety and efficacy across the rest of the world.³¹⁻³³ Theoretical developments associated with TCI continue, and improved blood sampling in clinical trials used for model-building may further improve the fit between predicted and measured

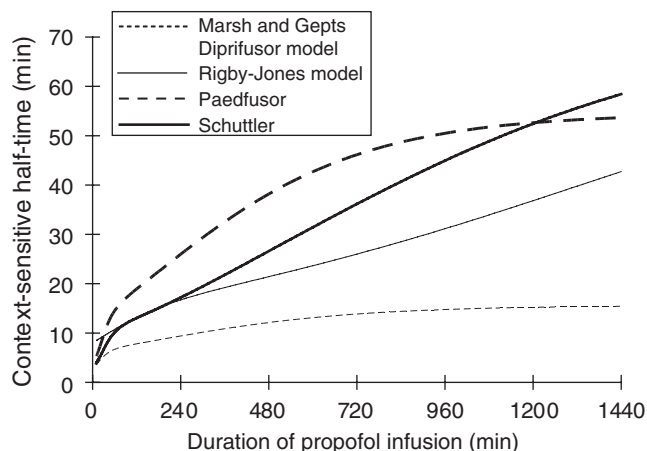


Fig 4 Context-sensitive half-times after propofol infusions of various lengths into a 20 kg child aged 5 yr. Plots represent, from bottom to top: Marsh⁶¹ and Gepts³⁷ Diprifusor model, mostly based on adult data; Rigby-Jones⁸⁵ model, paediatric, postcardiac surgery; Paedfusor;¹ and Schuttler.⁹³ Thick solid line shows pooled analysis including data from healthy children.

blood concentrations. Further enhancement of the basic pharmacokinetic modelling in standard TCI allows the inclusion of additional covariates, such as body surface area. However, it is unclear whether their inclusion will improve the clinical utility of TCI. A further supplement to TCI is the computation and presentation of predicted effect site concentrations^{29,124} and/or effect-site decrement time.⁹² However, it is unclear whether clinicians find this information useful or incorporate it into their daily practice. The availability of effect site models for propofol allows comparisons between two forms of TCI, namely plasma- and effect-site-targeted. If the correct value of k_{e0} is selected, the effect site model can predict loss of consciousness¹²⁴ and be used to maintain anaesthesia effectively.¹¹¹

Certainly, effect compartment targeting is both effective and safe. When anaesthesia was induced and maintained by TCI using either a plasma compartment model or one of two effect compartment models, loss of consciousness occurred earlier, without hypotension, when the effect site was targeted.¹¹¹ However, this study was undertaken in healthy female patients (ASA physical status I or II) who were scheduled for day surgery. When the effect site is targeted, higher plasma concentrations are achieved during induction of anaesthesia, and this might induce hypotension in elderly patients or those with cardiovascular compromise.

The recent emergence of generic target-controlled infusion apparatus from various manufacturers carrying proper CE marking will allow clinicians to use cheap, unbranded propofol in daily clinical practice without recourse to the effective but unlicensed research systems, notably STAN-PUMP and RUGLOOP, which are available to researchers and enthusiasts via the internet.⁹⁸ These new systems also offer the possibility of choosing different pharmacokinetic models and increased covariate input.

Analysis of pharmacokinetic data from paediatric studies has allowed the establishment of a separate model for TCI of propofol into children, the so-called Paedfusor,¹ although this application and the associated model are not licensed for general use. The original report of the 'Paedfusor' describes its application in 29 children aged 1–15 undergoing elective cardiac surgery or cardiac catheterization.¹ The pharmacokinetic model differs from that in the commercially available adult system, the Diprifusor, in that the size of the central compartment is proportionately larger. Performance of the system was clinically satisfactory. However, the degree to which the model is suitable for the general paediatric population requires further evaluation.

Closed loop anaesthesia with propofol

Using derivatives of the electroencephalogram (EEG) as a measure of hypnotic effect and a model of drug distribution, it is possible to use feedback control to alter the rate of propofol administration and maintain a constant level of sedation or anaesthesia. Various implementations of closed loop control have been described as research projects in rats^{6,117,120} and in man.^{2,66,112} Some commercial development is in hand, but it is currently unclear whether closed loop systems will move into mainstream clinical practice.

Propofol pharmacodynamics

Detailed clinical studies demonstrate that effect-site modelling^{48,100} can be usefully applied to concepts other than hypnosis, and the rates of equilibration of the effect sites for haemodynamic disturbance and sedation are different. Kazama and colleagues used TCIs to rapidly attain and maintain stable plasma propofol concentrations in adult patients.⁵⁴ The half-time for the plasma–effect site equilibration of the bispectral index (BIS) was around 2.3 min, regardless of age. In contrast, the half-times for systolic arterial blood pressure were 5.7 min for patients aged 20–39 yr and 10.2 min for those aged 70–85 yr. These observations endorse the common clinical practice of cautious drug administration in the elderly with generous allowance of time for hypnotic and haemodynamic effects to develop.

Improved understanding of patient response to propofol dosing has been translated into a predictive model which relates predicted induction dose to age, lean body mass and central blood volume.¹³⁴ However, although theoretically attractive, it is unclear whether such modelling will improve patient satisfaction, safety or outcome beyond standards achievable by careful titration to effect. A historic limitation of pharmacokinetic and pharmacodynamic modelling is the limited ability to extrapolate beyond the population from whom the data underpinning the model was drawn. Theoretical advances now allow data from separate studies to be combined into enhanced models with broader applicability,⁶⁹ and this should inform the development of clinical systems.

Clinicians are accustomed to reducing doses of propofol in patients who are undergoing haemorrhage or partly resuscitated from trauma. Recently, the effect of haemorrhagic shock on propofol anaesthesia has been explored in detail in a pig model. In animals which had been bled and then resuscitated, the measured propofol concentration increased by 20%, whereas in those which had not been resuscitated the concentration increased by 375%.⁵⁵ These findings build on earlier observations that the initial arterial concentrations of propofol after i.v. administration are inversely related to cardiac output.¹¹⁹

Etomidate

Etomidate has been evaluated in an oral transmucosal formulation in dogs and in man. In dogs, the bioavailability was reported as 16.6%.¹³³ In man, the formulation used had a bitter taste and absorption was non-linear, with decreased absorption at higher doses. Nevertheless, clinically relevant plasma concentrations and clinical effects were reported.¹¹⁰ Transmucosal delivery of etomidate is therefore feasible but it is unclear whether this will prove clinically useful, given the well known side-effects of the agent.

Ketamine

Although ketamine is an old drug, it remains a focus for research.

Chronobiology of ketamine

When mice are anaesthetised with ketamine, their sleep time is increased by approximately 35% if they receive the drug at 22.00 h (when these nocturnal animals are maximally active), compared with similar doses given at 10.00 h (when they are normally inactive).⁹⁰ This effect is associated with a single gene, although whether the relationship is causal or more complex is not currently clear.³⁰ Although the relevance of this information to clinicians may not be obvious, it illustrates nicely the potential for genetic information to inform practice—perhaps future TCI systems will incorporate genetic covariates in the model-building process.

Ketamine and brain injury

Historically, anaesthetists have regarded ketamine as contraindicated in patients with brain injury as the drug may increase intracranial pressure and alter haemodynamics. Recently, interest in the *N*-methyl-D-aspartate (NMDA) receptor at which ketamine acts has encouraged re-evaluation of this old drug. When ketamine was administered to adults with traumatic brain or spinal cord injury, systemic haemodynamics were unaltered but the effects on intracranial pressure were not reported.⁴³ Other workers compared sedation with midazolam–sufentanil and midazolam–ketamine

in brain-injured patients and found both combinations effective.²¹ Importantly, no significant differences were observed between the two groups in the mean daily values of intracranial pressure and cerebral perfusion pressure, and the numbers of intracranial pressure elevations were similar in both groups.

Stereoisomers of ketamine

Clinical research in anaesthesia has recently addressed the pharmacological differences between optical isomers of anaesthetic drugs.⁷⁴ Although ketamine was originally presented as a racemic mixture of two isomers (S+ and R-), separation of the two optical isomers has allowed investigation of their individual properties. The S+ isomer is 3–4 times as potent as an analgesic with a faster clearance than R-; thus, S+ ketamine is the useful enantiomer. Recently, research interest^{80 127} has focused on the single S+ enantiomer. However, this may be as much a reflection of commercial interest (the S+ enantiomer is significantly more expensive than generic racemic ketamine) as of real clinical advantage.

Ketamine with local anaesthetics

When preservative-free S+ ketamine is added to caudal bupivacaine, the duration of analgesia is extended but its intensity is not.^{62 126} Interest in this use of ketamine is growing and in a recent survey 32% of UK paediatric anaesthetists reported using epidural ketamine.⁸⁹

Ketamine as an adjunct analgesic

Ketamine has been evaluated as an adjunct to other analgesics with inconsistent results. When low-dose ketamine, 0.25 mg kg⁻¹, was given to surgical patients whose pain was poorly controlled with i.v. morphine, pain scores improved dramatically. Ketamine-treated patients also experienced less PONV and other side-effects than those receiving placebo.¹²⁸ However, when patients undergoing anterior cruciate ligament repair received S+ ketamine in addition to standard prescriptions of opioids, no benefit was seen.⁴⁹ The pharmaceutical compatibility of morphine and ketamine mixture has been evaluated and found to be stable for at least 4 days.⁹¹ However, the addition of ketamine to morphine patient-controlled analgesia has limited value.^{72 83 118} In a rat model, ketamine attenuated acute tolerance to morphine and also prevented rebound hyperalgesia.⁵⁶ These findings may be relevant to the intraoperative use of remifentanyl, where tolerance to analgesia may develop.¹²¹ The addition of an intraoperative ketamine infusion to patients anaesthetized with remifentanyl and desflurane reduced opioid consumption and decreased early postoperative pain.³⁹ The use of ketamine in chronic pain has recently been reviewed.⁴⁴ The authors found little evidence to support this use, and suggested ketamine be

reserved as a third-line drug for patients in whom routine pharmacotherapy has failed.

Ketamine and propofol

Adding ketamine to a propofol infusion for sedation during breast surgery under local anaesthesia reduced the requirement for supplementary opioids but there was a dose-related increase in nausea, vomiting and the need for airway support amongst patients receiving higher doses of ketamine.¹⁰

Remifentanyl

Remifentanyl is now well established for maintenance of anaesthesia, with a number of trials illustrating its safety and efficacy.^{45 87} Nevertheless, the high price of remifentanyl and its rapid elimination have, in practice, restricted its use to procedures where intense preoperative opioid effect (and associated haemodynamic stability) may be combined with mild or moderate postoperative pain. Such procedures include, but are not limited to, neurosurgery and ear nose and throat procedures. Satisfactory postoperative analgesia after remifentanyl infusion can be provided by continuing the infusion at a lower rate,²² or with a multimodal approach using locoregional techniques or administration of morphine,^{23 67} preferably 30–40 min before the end of surgery.⁷¹ Lower doses of remifentanyl can also be used to maintain anaesthesia in spontaneously breathing patients,^{73 79} although it is hard to see why this is a useful technique, given the ease of use and lower costs associated with other agents, including fentanyl and morphine.

Several pharmacokinetic sets for remifentanyl have been described, and one⁶⁸ implemented as a self-contained TCI system for remifentanyl—a ‘Remifusor’.⁴⁶ Although ambitious claims have been made for remifentanyl TCI, including improved haemodynamics and reduced drug consumption,²⁸ published studies are unconvincing and there is so far no clear case for TCI rather than manually controlled remifentanyl infusion.¹⁰⁷ Indeed, remifentanyl is an easy drug to use and TCI may simply increase equipment cost without demonstrable patient benefits. As TCI remifentanyl has recently been licensed in Europe, we will have the opportunity to see if it becomes a favoured technique with clinicians. More clinical studies with clinically comparable infusion schemes are needed to resolve whether TCI remifentanyl is a useful and important technique.

Remifentanyl and intubation

Remifentanyl attenuates the haemodynamic response to tracheal intubation and a combination of propofol and remifentanyl may permit tracheal intubation without the use of a muscle relaxant.^{40 41 60 129} However, the clinical need for this technique is unclear. In particular, the consistent intubating conditions offered by a neuromuscular blocker remain unequalled by the propofol–remifentanyl combination.³

Remifentanil sedation in intensive care

Remifentanil has been used as an adjunct sedative in critically ill adults,^{7,24,25} and this indication is now included in the product licence. Recently, the pharmacokinetics of the major metabolite, remifentanil acid have been described and modelled.⁸¹ During prolonged infusions of remifentanil, the principal metabolite, remifentanil acid, accumulates and may attain concentrations up to 100 times higher than the parent drug. Nevertheless, the metabolite is of very low potency and even after prolonged remifentanil infusion into patients with severe renal impairment, prolongation of μ -opioid effects seems unlikely.

Obstetric use of remifentanil

Obstetric use of remifentanil has theoretical attractions, given the rapid elimination of the drug and the possibility of allowing relatively generous opioid administration to the mother, the rapid clearance allowing an alert and fully functional neonate. Current experience ranges from case reports^{64,96,114} to small clinical trials.^{20,76,86} Overall, it appears that remifentanil can be used safely in obstetric applications, although whether it has real advantages in terms of patient safety, satisfaction or other outcomes, especially in comparison with neuroaxial techniques, remains to be demonstrated. Remifentanil is licensed for induction and maintenance of general anaesthesia; however, there is currently no licensing information about obstetric use.

Case reports of successful remifentanil administration to high-risk obstetric patients, including those with cardiomyopathy,⁶³ mitral valve disease,⁹⁵ pre-eclampsia⁵² and acoustic neuroma.¹⁷ However, caution should be used in interpreting these individual clinical experiences as publication and author bias may hinder reporting of less successful therapeutic experiments.

When remifentanil was infused into a selected group of patients undergoing elective Caesarean section under epidural anaesthesia at a low (analgesic) dose of $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$, typical opioid effects were seen in the mother whilst remifentanil rapidly crossed the placenta without deleterious effects on the neonate.⁵³ Concentrations of the remifentanil metabolite remifentanil acid in the umbilical artery were higher than those in the umbilical vein, suggesting continued metabolism of the drug in the fetus. However, investigators only obtained fetal blood at a single time point (delivery). For the labouring parturient, the use of patient-controlled remifentanil might combine the safety of patient control with a rapid onset of analgesic effect due to the pharmacokinetic and pharmacodynamic properties of the drug.

A dose-finding study of remifentanil patient-controlled analgesia during labour recommended a bolus dose of $0.4 \mu\text{g kg}^{-1}$ given over 1 min with a lockout time of 1 min.¹²² Individual parturients varied widely in their rate of (self) drug administration. Potentially serious side-effects included episodes of respiratory depression and desaturation. Pain scores fell sharply during the period of remifentanil administration

and increased promptly when it was discontinued. The authors conclude that remifentanil was potentially effective for obstetric analgesia by patient-controlled administration, although its side-effects may limit its use.¹²²

Adenosine

When either remifentanil or adenosine was added to desflurane–nitrous oxide anaesthesia, intraoperative haemodynamic stability was acceptable. However, two of the eight patients randomized to adenosine developed bronchospasm. Compared with remifentanil, intraoperative use of adenosine was associated with a decreased requirement for opioid analgesics during the first 24 h after operation.¹³² The doses of adenosine used in this study averaged 1400 mg for 171 min of anaesthesia. At current prices (£4.63, €6.61 for 6 mg in the UK NHS) the observation is interesting but unaffordable.

Conclusions

Research continues to extend the scope of i.v. anaesthesia and to find novel applications for old drugs. Increasing familiarity with the necessary clinical techniques of i.v. anaesthesia and their theoretical underpinnings will probably increase their use. Future drug development in anaesthesia is likely to be determined by commercial imperatives. In a clinical environment dominated by inexpensive generic propofol formulations, the likely return on pharmaceutical company investment may be insufficient to fully explore all the opportunities suggested by basic science and laboratory research. In particular, the exploitation of genomics and the opportunity to customize individual patients' pharmacotherapy to their genotype may prove unaffordable in anaesthesia. To date, development of i.v. hypnotics and opioids has focused on short-acting drugs. Opportunities exist to address other characteristics, including water solubility, pain on injection, haemodynamic disturbance and therapeutic index. The latter is especially important if sedative and hypnotic compounds are to be used by non-anaesthetists. Advances in administration, including TCI, drug interaction modelling and closed loop anaesthesia will offer clinicians enhanced information and therapeutic choices, and may make the use of current agents simpler and safer. Claims made for such developments must be rigorously evaluated and commercial hype distinguished from demonstrable clinical enhancement.

Acknowledgement

Ann Rigby-Jones kindly provided the simulations shown in Figures 3 and 4.

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