Continuing Medical Education

Intravenous infusion anaesthesia and delivery devices

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During the past decade, major advances have taken place with regard to intravenous infusion anaesthesia. New opioid analgesics, iv anaesthetics, and muscle relaxants have become available, which are characterized by a rapid onset of action, short duration of clinical effect, and favourable side effect profiles. Optimal administration of these drugs is often best achieved by continuous infusion, rather than a more traditional technique of intermittent bolus administration. New concepts in pharmacokinetic modelling also provide an enhanced appreciation of the factors which determine rates of recovery upon discontinuation of an intravenous infusion. Pharmacokinetic principles guide rational selection of the iv anaesthetic drugs according to both procedure and patient-specific requirements. In addition, improvements in the new programmable syringe infusion pumps provide a degree of simplicity and accuracy in operation, which make iv infusion of one, two or three components of the anaesthetic state a simple and practical reality for most procedures. In this CME article, these issues will be reviewed according to the following outline: Historical considerations; Rationale for continuous infusion of iv anaesthetic drugs; Pharmacokinetic and pharmacodynamic considerations; Infusion schemes; New techniques, new indications; IV anaesthetic delivery systems; Pharmacoeconomic considerations; Conclusions.

Au cours de la dernière décennie, l'anesthésie intraveineuse par perfusion continue a réalisé des progrès considérables. De nouveaux analgésiques morphiniques, agents iv et myorelaxants ont vu le jour. Ces produits sont caractérisés par un début d'action rapide, des effets de courte durée et un profil d'effets secondaires favorable. L'administration optimale de ces drogues est souvent réalisée par perfusion continue plutôt que par la technique traditionnelle des bolus intermittents. Les derniers modèles pharmacocinétiques assurent une meilleure évaluation des facteurs qui déterminent la vitesse de récupération après l'arrêt de la perfusion intraveineuse. Les principes pharmacocinétiques dirigent la sélection rationnelle de l'anesthésique iv adaptée à l'intervention et aux besoins spécifiques du patient. De plus, les améliorations apportées aux nouveaux pousse-seringue programmables assurent simplicité et précision pour le contrôle par perfusion iv d'une, de deux ou des trois composantes de l'état anesthésique pour la plupart des interventions. Dans cette mise à jour, ces sujets seront traités sous le schéma suivant: Historique; Rationnel de la perfusion iv continue d'anesthésiques; Considérations pharmacocinétiques et pharmacodynamiques; Plans de perfusion; Nouvelles techniques, nouvelles indications; Systèmes d'administration iv d'anesthésiques; Considération pharmacoéconomiques; Conclusions.

Key words
ANAESTHETICS: intravenous;
ANAESTHETIC TECHNIQUES: continuous infusion, intravenous;
EQUIPMENT: infusion pumps.

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Historical considerations

The first record of medication having been administered via the intravenous route dates as far back as 1657, when Sir Christopher Wren injected opium into humans, using a quill and bladder. By rendering his subjects unconscious, Wren can be credited with having been the first person to administer an *iv* anaesthetic. More than two centuries later, Frances Rynd developed a hypodermic needle, and the production of a functional syringe in the mid-1800's allowed Alexander Wood, in 1853, to be the first to employ a needle *and* syringe technique for *iv* drug administration. Within two decades (1870's), Pierre-Cyprien Ore described the use of *iv* choral hydrate to

provide anaesthesia for surgery, and thus the technique of intravenous delivery of anaesthetic drugs was established.

In the current century, *iv* opioid analgesics and sedative-hypnotics evolved a role as essential components of "balanced" anaesthetic techniques. During the 1930's, the introduction of thiopentone provided a major improvement in the choice of *iv* induction agents. The availability of this short-acting barbiturate also prompted several individuals to explore the administration of this drug for both induction *and* maintenance of general anaesthesia. As early as 1944, Dr. Pico attested that "the administration of intravenous anaesthesia by the continuous drip method is becoming more popular."[1] His report describes a simple system for delivery of a 1% solution of thiopentone by continuous infusion, "administered to meet the desired plane of anaesthesia".[1] An interesting observation is Dr. Pico's early recognition of the need to *titrate* the rate of drug infusion. Although this technique was practised by some, major disadvantages of prolonged recovery due to drug cumulation, and the relative imprecision of the delivery system, precluded its more widespread use.

The next major development in intravenous anaesthesia occurred in the provision of anaesthesia for cardiac surgery. Lowenstein used morphine 1–2 mg · kg^{-1} for cardiac valvular surgery, and found that it produced good haemodynamic stability in patients with limited circulatory reserve, but did not reliably produce amnesia in patients with normal ventricular function.[2] Larger doses of morphine were found to produce unconsciousness, but vasodilation associated with histamine release proved to be a major drawback. It was not until several years later that opioid anaesthesia became popularized, with the introduction of high-dose fentanyl, followed soon after by high-dose sufentanil techniques. The advantages of fentanyl (25–100 μg · kg^{-1} *iv*) and sufentanil (5–25 μg · kg^{-1} *iv*) include the ease of administration and inherent cardiovascular stability of these drugs. However, the problems of pre-bypass myocardial ischaemia, and hypertension during sternotomy, led to the realization that opioid analgesics, even in very high doses, do not ensure complete anaesthesia. In addition, prolonged respiratory depression, necessitating routine postoperative ventilation, preclude the use of this technique for most non-cardiac surgery. Currently, infusion of moderate doses of opioid analgesics, supplemented with inhalational agents, benzodiazepines, and more recently propofol, are favoured to provide anaesthesia for cardiac surgery.

The 1970's also saw the introduction of shorter-acting *iv* anaesthetic drugs, including althesin and ketamine. Althesin was withdrawn from the market because of severe anaphylactoid reactions in some patients. Ketamine, which has combined analgesic and amnestic properties, is capable of providing total intravenous anaesthesia. A high incidence of dysphoria in the early recovery period precluded its more widespread use. However, the use of ketamine, in combination with propofol, is now being re-explored as a combined technique for total intravenous anaesthesia (TIVA).

For administration of intravenous anaesthetic drugs by continuous infusion, it was not until the 1980's that infusion techniques in anaesthesia became both accurate and practical. The world-wide introduction of new, short-acting *iv* drugs such as propofol and alfentanil, and advances in computer technology, were the driving forces leading to the introduction of modern intravenous infusion techniques, which have become established as part of routine anaesthetic practice in the 1990's.

Rationale for continuous infusion of *iv* anaesthetic drugs

Anaesthetists have well recognized the advantages of the modern flow-compensated anaesthetic vaporizers, which provide reliable and accurate administration of potent inhalational agents independently of fresh gas flow rates. Key to vaporizer use is the ability to provide drug delivery, in a manner which is continuous and easily titratable, by simple adjustment of the vaporizer dial. In certain respects, intravenous infusion anaesthesia shares similarities with inhalational anaesthesia, including the need for user-friendly, accurate, and flexible delivery systems. Administration of *iv* anaesthetic drugs by infusion provides for greater stability of drug concentration within the plasma, and hence at effector sites, than can be achieved with an incremental bolus technique. By minimizing the fluctuations in serum concentration resulting from multiple drug boluses, infusion of *iv* anaesthetics, opioid analgesics, and muscle relaxants, minimizes the relative overdosing and underdosing during the time course of drug administration. Infusion techniques thus tend to provide a smooth intra-operative course characterized by enhanced cardiovascular stability, and, with appropriate titration, facilitate rapid and uneventful emergence from general anaesthesia. Patients tend to awaken rapidly at the end of surgery in a relatively pain-free state, and with minimal or no coughing on the endotracheal tube. Titrated according to individual patient needs, infusion techniques may also reduce drug requirements by as much as 25–30% when compared with repeated bolus administration of these agents.[3] Other *potential* advantages include a lower incidence of side effects, shorter recovery times, and decreased drug costs. The desirable characteristics of *iv* anaesthetic drugs suitable for administration by continuous infusion are outlined in Table I.

TABLE I Desired characteristics of *iv* anaesthetic drugs suitable for administration by continuous infusion

1 Water soluble
2 Rapid onset of action
3 Short duration of clinical effect
4 High clearance rate
5 Minimal tendency for cumulation
6 No active metabolites
7 High therapeutic index
8 Minimal side effects
9 Cost-effective

Pharmacokinetic and pharmacodynamic considerations

Pharmacokinetic principles

Although an in-depth knowledge of pharmacokinetics and pharmacodynamics is not essential for successful application of infusion techniques in clinical practice, a basic appreciation of the underlying principles is important. *Pharmacokinetics* is the process whereby various variables are used to construct models to assess what happens to drug concentrations within the plasma, allowing prediction of drug concentrations over time. More simply stated, pharmacokinetics provides a mathematical description of "what the body does to the drug." Most sedative-hypnotic and opioid analgesic medications have a time-concentration profile which can be described by the following equation:

$$Cp(t) = Ae^{\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where Cp(t) is the plasma concentration at time t; where A, B and C are the so-called fractional coefficients describing the relative contributions of each exponential term; and where α, β and γ are the rate constants corresponding to rapid distribution half-life, slow-distribution half-life, and the elimination half life, respectively. From this equation, it is apparent that a drug's elimination half-life ($t_{1/2}\beta$) is only one of several components which determines the rate at which drug concentration declines within the plasma, and correspondingly, within the *effect site* (the biophase, or site of drug action), once the infusion is discontinued.

This concept is important, in order to allow for a better appreciation of the factors which influence clinical rates of recovery, following termination of *iv* drug infusions. One approach is to describe the basic priniples of drug disposition by the process of *compartment modelling*. In this model, the concentration of drug in the central compartment depends on the amount of drug delivered to the compartment, its volume, and the rate of drug removal from the compartment. Using a pharmacokinetic-dynamic model, Shafer and Varvel have simulated the time necessary to achieve a 50% decrease in drug concentration of the opioid analgesics, following infusions of up to eight hours (Figure 1).[4] In their study, the percentage changes in concentration, rather than the absolute concentrations, were simulated to permit comparison of the relative opioid concentration, independently of drug potency. This method of analysis demonstrates that alfentanil is associated with the most rapid decline in *effect site* concentration, but only when infusions are prolonged, lasting beyond six to eight hours. In contrast to earlier thinking, Shafer's work demonstrated that, for infusions of less than eight hours, the decrease in effect site concentration of sufentanil is actually more rapid than that of alfentanil, despite the two-fold difference in elimination half-life of these drugs (three to four hours for sufentanil vs one to three hours for alfentanil). The explanation lies in the very large "slow" distribution compartment for sufentanil, which continues to fill even after the infusion is discontinued, contributing to the decrease in plasma (and effect site) concentrations. Infusion of fentanyl is associated with much longer recovery times than either sufentanil or alfentanil, except when very low serum concentrations are maintained during the course of drug administration.

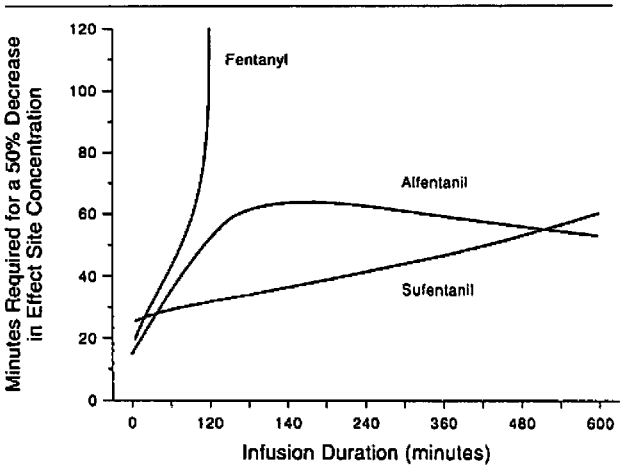

FIGURE 1 A simulation of the time necessary to achieve a 50% decrease in drug concentration (or plasma) after variable-length intravenous infusions of fentanyl, alfentanil, and sufentanil. (From *Shafer SL, Varvel JR.* Pharmacokinetics, pharmacodynamics and rational opioid selection. Anesthesiology 1991; 74: 53–63, with permission).

Pharmacokinetic modelling also helps to explain the extremely rapid emergence from propofol anaesthesia. Propofol's high clearance rate of 1.5–2.0 $L \cdot min^{-1}$ exceeds hepatic blood flow, and the drug's high lipid solubility results in sequestration in fat following long infusions. These properties result in a rapid decrease in propofol concentration following prolonged administration, regardless of infusion duration. Rapid recovery is

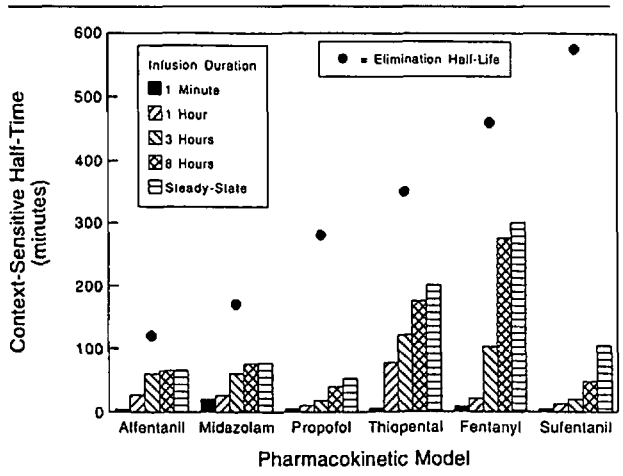

FIGURE 2 Context-sensitive half-times (bars) after terminating a 1 min, 1 hr, 3 hr, 8 hr or steady state BET-type infusion, relative to the elimination half-life (dots), computed from each pharmacokinetic model. (From *Hughes MA, et al.* Context-sensitive half-times in multicomponent pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992; 76: 334–41, with permission).

also seen within minutes following prolonged infusions (hours to days) of propofol when administered for ICU sedation, a recently-approved indication.

Another approach to *quantitate* the relative importance of elimination and redistribution processes on recovery times, is to model the time required for drug concentration to decrease by 50% following an infusion scheme designed to maintain a fixed drug concentration for a specified time (the so-called "context"). This concept has been recently referred to as the *context-sensitive plasma half-time*, and provides a much more relevant descriptor of post-infusion kinetics than elimination half-life.[5] The context-sensitive half-times of the opioid analgesics and sedative hypnotics, for infusions lasting one minute, one, three and eight hours, and at a steady state, are shown in Figure 2. Using this approach, one can predict that following infusions of three hours in duration, the times required for a 50% decrease in plasma concentration for equipotent infusions of sufentanil, alfentanil, and fentanyl, would be approximately 27 min, 55 min, and 120 min, respectively. By comparison, the very high clearance rate of propofol results in a context-sensitive half time of approximately 20 min following a three hour infusion of this drug. In general, appropriate titration of infusion rates should result in drug plasma concentrations which have declined to within 10–20% of the desired "emergence threshold" towards the end of surgery. Nevertheless, the times required for a 50% decrease in plasma concentration provide a *relative* comparison of recovery times.

Several other factors need to be addressed when applying this information clinically. The first is that, due to frequently-changing levels of autonomic stimulation, infusions during general anaesthesia are generally *not* titrated in a manner to achieve steady-state conditions. In addition, the frequency and size of supplemental bolus doses will impact on actual recovery time. Furthermore, even if one could produce a precise plasma concentration of a drug such as alfentanil, there is still a three–fivefold inter-individual variability in the amount of drug necessary to suppress the response to any given stimulus. Thus, the rate of recovery following administration of *iv* anaesthetic drugs by continuous infusion will be influenced not only by the drug's pharmacokinetic behaviour, but also by how well the drug has been titrated intraoperatively.

These concepts can be extended further by considering remifentanil, a new opioid analgesic currently under development. A "μ agonist' with typical opioid pharmacology, remifentanil has a rapid plasma-effect site equilibration (like alfentanil), and a potency similar to that of fentanyl. The most remarkable feature of remifentanil, however, is its extremely brief duration of action, due to rapid metabolism ($t_{1/2}\beta$ = 10–20 min) by non-specific esterases in both tissues and plasma. Although the terminal elimination half-life of remifentanil is similar to that of alfentanil, the overall decrease in plasma concentration of remifentanil is more rapid. This is because terminal elimination half-life accounts for only a very small fraction of the overall decrease in the drug concentration over time. Computer simulation shows that the duration of drug infusion has almost no influence on the time required for a 50% decrease in plasma or effect site concentration.[6] Furthermore, no dosage adjustments appear to be required for patient age, sex, or body weight. The extremely rapid decrease in plasma and effect site concentrations of remifentanil may be useful in decreasing the likelihood of undesirable opioid side effects postoperatively (respiratory depression), and avoiding drug cumulation with repeat bolus injections or prolonged infusions. In this regard, the drug may be more "forgiving" than the other members of the fentanyl "family." However, the very rapid clearance of remifentanil would require the substitution of either a longer-acting opioid at the end of the procedure, or continuing the infusion postoperatively (at a reduced rate) to prevent rapid onset of pain following surgery.

Pharmacodynamic principles

The other major aspect to consider when infusing drugs during anaesthesia is *pharmacodynamics*, which defines the relationship of the pharmacological effect in the body to a given concentration of drug (i.e., "*what the drug does to the body*"). In this regard, the plasma can be thought of as a conduit for intravenous drugs to reach

TABLE II Therapeutic serum concentrations: sedative-hypnotics and opioid analgesics

	Propofol ($\mu g \cdot ml^{-1}$)	*Midazolam* ($ng \cdot ml^{-1}$)	*Fentanyl* ($ng \cdot ml^{-1}$)	*Sufentanil* ($ng \cdot ml^{-1}$)	*Alfentanil* ($ng \cdot ml^{-1}$)
Major surgery	3–8	150–300	4–10	0.25–1.0	300–500
Minor surgery	2–6	100–200	2–5	0.5–1	150–300
Skin incision	2–6		3–6	0.25	200–300
Spontaneous ventilation	<2	-	<1–3	<0.5	<200–250
Analgesia/awakening	0.8–1.5	100–150	1–2	?	50–100
Sedation	1–3	50–120	-	-	-

Therapeutic ranges of serum concentrations of the commonly used sedative-hypnotics and opioid analgesics when combined with 70% N_2O.

their effect sites. Due to differences in physiochemical properties (pKa, protein binding), drugs differ in the times they require to reach peak effect. This can be measured by assessing the degree of hysteresis, or lag time, of the concentration-effect relationship (i.e., *kinetic-dynamic dissociation*). In one such experiment, Scott *et al.* found that alfentanil equilibrates between the blood and the CNS biophase approximately five times more rapidly than does fentanyl.[7] This is due primarily to the different pKa's of the drugs, with alfentanil being almost 90% unionized at physiological pH, compared with 9% for fentanyl. Accordingly, alfentanil equilibrates extremely rapidly with the CNS biophase (reaching peak effect within 90–120 sec), providing early, and more intense effects than either fentanyl or sufentanil, which both require five to six minutes to reach peak effect.

Such information helps to explain the fact that fentanyl is only four times as potent as alfentanil when given as a bolus, but is 60 times more potent when steady-state plasma concentrations are compared (Table II). Minimal kinetic-dynamic dissociation also results in relatively lower drug requirements, and considerably shorter recovery times for alfentanil when compared with single equipotent boluses of either fentanyl or sufentanil (Figure 3).[4] However, the extremely rapid termination of effect seen after *iv* injections of alfentanil may not be seen when very large doses are given, or after relatively prolonged infusions; situations in which the effects of rapid equilibration of the biophase are lost.

One additional aspect to consider when titrating *iv* anaesthetic drugs is *pharmacodynamic variability*, which provides a measure of the differences in clinical response from one patient to another for a given drug concentration. Variability can be measured relative to the *CP50*, which is the plasma concentration of a drug at which 50% of patients do not respond to a given stimulus. This is similar to the concept of MAC for inhaled anaesthetics. One difference is that CP50 values have been defined for different levels of stimulation for several drugs (e.g., alfentanil and propofol), emphasizing the need for different plasma concentrations for different levels of autonomic stimulation. This observation forms the pharmacological basis for recommending that optimal administration of *iv* anaesthetic drugs by continuous infusion should be done using variable rate infusions, with periodic supplemental boluses as required, adjusted to both individual requirements and the varying levels of stimulation intra-operatively.

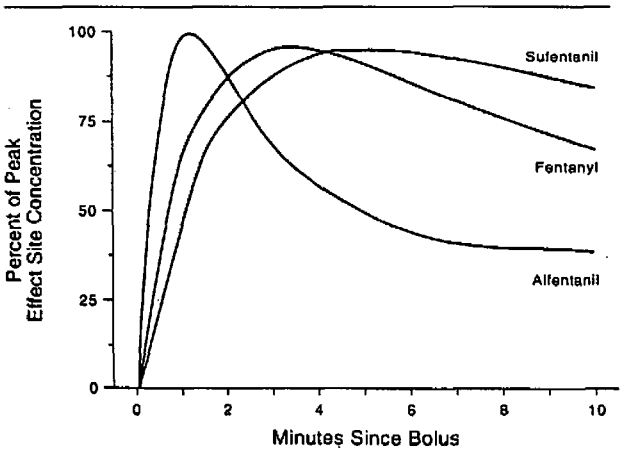

FIGURE 3 Effect site opioid concentrations over time after a bolus injection, as a percentage of peak effect site concentration. (From *Shafer SL, Varvel JR.* Pharmacokinetics, pharmacodynamics and rational opioid selection. Anesthesiology 1991; 74: 53–63, with permission).

Infusion schemes

Infusions schemes are derived from a knowledge of the desired target plasma concentrations, and the pharmacokinetic variables of the given drug. The ranges of therapeutic serum concentrations of the opioid analgesics and sedative-hypnotics are outlined in Table II. From a practical perspective, the desired plasma concentration for any drug can be achieved using the following calculation:

Administered dose = CP × Vd,

where CP is the desired concentration within the central compartment, and Vd is the volume of distribution. In order to maintain the desired concentration, an infusion, which delivers drug at a rate equal to its rate of removal from the central compartment, is required, as follows:

Infusion rate = Cp × Vc × Clearance,

where Vc is the volume of the central compartment. The problem with using such a scheme in the clinical setting is that drugs equilibrate at different rates within the body. Thus, if the drug's volume of distribution at steady state is used to calculate the loading dose, then the initial drug concentration will be much greater than desired, and may result in side effects (e.g., hypotension with alfentanil or propofol.) If instead, the volume of distribution of the central compartment is chosen to calculate the initial dose, then a decline in drug concentration will be apparent following the loading dose (resulting in light or inadequate anaesthesia), and it will require approximately four to five elimination half-lives to reach 96% of the desired plasma concentration, when the drug infusion is maintained at a constant rate. To accommodate this problem, there are two basic approaches to the administration of *iv* anaesthetics by continuous infusion. The first is to modify the infusion regimen necessary to achieve and maintain a fixed, or "target", plasma concentration of drug. To be accurate, this approach must take into consideration multiple pharmacokinetic variables, including the drug's rapid and slow distribution times, the total body *and* central compartment volumes of distribution, as well as the drug's elimination half-life. One method to incorporate all such information is to employ a "BET" scheme, where "B" represents the size of the Bolus or loading dose, "E" represents the steady-state rate of infusion according to drug's Elimination, and "T" represents an exponentially-declining rate of infusion to accommodate for drug Transfer from the central to peripheral compartments. However, to be accurate, a BET-type regimen can only be accomplished using computer-controlled administration, and such devices will not be commercially available for several years.

A second, more practical approach is to use the method described by Wagner, which employs a two-step infusion scheme[8] that is more suited to the use of current calculator syringe pumps. With this scheme, an initial rapid infusion is administered to fill the volume of distribution of the central compartment, followed by a maintenance infusion determined by the desired central compartment drug concentration and the drug's rate of clearance. The infusion can then be supplemented with periodic bolus doses as required throughout the procedure, with or without altering the rate of infusion. In general, with most regimens, the infusion should be discontinued a short time before the completion of surgery, in order to allow drug concentration to decline below the threshold for spontaneous ventilation (opioid analgesics), to approach the threshold for awakening (propofol, midazolam), or to facilitate reversal of paralysis (neuromuscular blocking drugs).

TABLE III Dose ranges for infusion anaesthesia

Drug	*Loading dose* ($\mu g \cdot kg^{-1}$)	*Maintenance infusion rate* ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
Opioid analgesics		
Alfentanil		
- BAL	15–30	0.25–1.5
- TIVA	30–50	0.75–2.0
Sufentanil		
- BAL	0.1–0.3	0.25–0.5*
- TIVA	0.3–0.5	0.5–1.0*
Sedative/Hypnotics		
Propofol		
- MAC	250–500	10–50
- BAL	1000–2000	50–150
- TIVA	1000–2000	120–200
Midazolam		
- MAC	25–100	0.25–0.75
- TIVA	50–150	0.5–1.5
Ketamine		
- MAC	500–1000	10–20
- BAL	1500–2500	25–75
Muscle relaxants		
Succinylcholine	500–1000	50–150
Atracurium	0.25–0.50	4–8
Vecuronium	0.05–0.1	0.5–1.5
Mivacurium	0.20–0.25	5–10

*$\mu g \cdot kg^{-1} \cdot hr^{-1}$ (for sufentanil only).
Dose ranges for the opioid analgesics, sedative-hypnotics, and muscle relaxants which are most suitable for administration by continuous infusion. MAC = dose ranges for monitored anaesthesia care (MAC) sedation, BAL = dose ranges for balanced anaesthesia; TIVA = dosage ranges for total intravenous anaesthesia.

Currently-recommended infusion schemes are based on calculations from pharmacokinetic variables as well as on empiric considerations. In Table III, regimens for the opioid analgesics, *iv* anaesthetic drugs, and neuromuscular blocking drugs are listed. In addition, practical aspects which need to be taken into consideration are provided in Table IV. The essential principles are as follows:

(i) the infusion rate should be variable, rather than constant, in order to facilitate titration of drug concentration (and hence, drug effect), and adjusted according to both individual patient requirements and the varying levels of stimulation throughout surgery. In general, infusion rates should be decreased over time to prevent drug cumulation.

TABLE IV Practical aspects of *iv* infusion anaesthesia

1 Before starting the infusion, ensure that drug catheters are connected to the *iv* tubing, that air has been purged, that syringes are loaded, that pump settings are correct, and that alarms are inactive.
2 Prepare syringes with slightly less than the anticipated amount of drug required for the entire procedure, so that additional drug can be added, rather than discarded, towards the end of the procedure, to minimize drug wastage.
3 Infuse through a T-piece connected to the *iv* catheter to minimize dead space.
4 Check repeatedly for adequate flow of carrier fluid, as TIVA can become "NIVA" (no intravenous anaesthesia), with the patient awake in minutes following interruption of drug flow, for any reason.
5 Hypotension during induction can be minimized by giving the loading doses of opioid and propofol slowly.
6 Begin with high initial rates of infusion, then decrease the rate over time, to avoid overdose. If propofol is being infused for TIVA, do not decrease the rate below 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until near the end of surgery.
7 Signs of light anaesthesia can be treated using supplemental boluses of propofol, midazolam and/or opioid analgesic, with or without increasing the rate of infusion.
8 Movement is a good sign of light anaesthesia, so avoid complete paralysis. The easiest way to do this for a long procedure, while maintaining adequate surgical relaxation, is to infuse the neuromuscular blocking drug.
9 A reasonable time sequence for terminating a properly titrated infusion is – opioid: 15–20 min prior to the end of surgery; muscle relaxant: 5–15 min prior to the end of surgery; propofol: 5–10 min prior to the end of surgery. Once the propofol is discontinued, be prepared to give small boluses (10–30 mg *iv prn*).
10 Reduce infusion rates by 25–50% for elderly patients, or for those who have been heavily premedicated.

(ii) The use of a continuous infusion does not preclude the use of periodic bolus doses. Boluses are used throughout the anaesthetic, with or without altering the rate of infusion, in order to increase the plasma drug concentration rapidly to respond to either actual or anticipated increases in surgical stimulation. This technique is particularly valuable with small doses of alfentanil and propofol, because of their rapid onset of effect, and rapid redistribution.

(iii) One, two or three components of the anaesthetic state, (amnesia, analgesia, muscle relaxation) may be administered by continuous infusion. This may be done as either part of a balanced technique with nitrous oxide and/or a potent inhalational agent, or with air/oxygen to provide total intravenous anaesthesia.

(iv) Infusion techniques should be done with dedicated infusion pumps in order to ensure accurate infusion rates, and avoid cumbersome calculations in the operating rooms. Computer-assisted delivery devices will soon be commercially available, and may further simplify and improve administration of *iv* anaesthetics by continuous infusion.

New techniques, new indications

Benzodiazepines are the most commonly prescribed drugs for conscious sedation. Midazolam provides several advantages for this indication, including absence of pain on injection, and relatively short context-sensitive half-times, which predict more rapid recovery than with other benzodiazepines. Practically speaking, midazolam can be administered using either an intermittent bolus technique, or by continuous infusion for conscious sedation. Recently, midazolam has been approved for administration by infusion for ICU sedation. Although there is considerable variability in both pharmacokinetics and infusion requirements in different ICU populations, dose-response relationships occur over a relatively narrow range for individual patients, as with most sedative-hypnotics and opioid analgesics. Practically speaking, the rate of infusion can be adjusted, as required, according to the level of sedation. Recovery generally occurs within one to three hours following discontinuation of the infusion.[9]

Recently, propofol has been approved for "MAC (Monitored Anaesthesia Care) Sedation," which is achieved by continuous infusion at rates between 10–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This method of conscious sedation is particularly beneficial if the patient must occasionally interact with the surgeon, and for the very anxious day surgery patient, where a deep level of sedation may be desired, while at the same time allowing for prompt recovery. Patients may occasionally become excitable during MAC sedation with propofol. To minimize such occurrences, it is useful to administer a small dose of midazolam (1–2 mg) as part of the sedation regimen. Another recently-introduced concept is "patient-controlled sedation," which permits the patient to adjust his or her own level of sedation analogous to patient-controlled analgesia. When using this technique, it must be emphasized that propofol is a potent respiratory depressant, and should be administered only by anaesthetists or physicians skilled in airway management.

Propofol is now also approved for ICU sedation. The high clearance of propofol results in a rapid decrease in plasma concentration, and hence recovery that occurs within minutes, even after infusions lasting many days. This allows for awakening of patients at regular intervals, and permits frequent assessment of neurological status. Full consideration of the benefits of propofol vs midazolam for ICU sedation is beyond the scope of this article, but cost is a major concern with these new indications. Further clinical experience and detailed pharmacoeconomic studies will be required to determine the most appropriate applications for this new indication. Finally,

propofol is also now approved for use in paediatric anaesthesia. The propofol dose in infants and children for induction of anaesthesia is 2.5–3.0 mg · kg^{-1}, but maintenance infusion rates are similar to those for adults.

Total intravenous anaesthesia (TIVA) is a technique whereby the components of general anaesthesia (amnesia, analgesia and muscle relaxation) are administered in combination, without the use of nitrous oxide or potent inhalational agents. The most obvious indications for TIVA include situations where it is either awkward or impossible to administer anaesthetic gases (e.g., rigid bronchoscopy), and where the use of nitrous oxide is precluded (e.g., gas-containing spaces such as emphysematous bullae), or when inhalational anaesthetics are contra-indicated (e.g., malignant-hyperthermia susceptible individuals). Although propofol is the most appropriate primary anaesthetic drug for TIVA, small increments of midazolam (1–2 mg *iv* q 1h) may be useful to supplement this technique. As neither drug has inherent analgesic properties, an opioid analgesic is necessary, for which alfentanil and sufentanil are preferred. TIVA can be performed with spontaneous or assisted ventilation for very short procedures, but in general it is easier to use controlled ventilation with the aid of a muscle relaxant. A recent trend is the use of propofol in combination with ketamine. It appears that the combination of propofol/ketamine provides acceptable haemodynamic stability, and that propofol prevents the dysphoria and other recovery problems associated with ketamine administered alone.

Another development is the recent interest in administration of muscle relaxants by continuous infusion. Availability of new, short- and intermediate-acting non-depolarizing drugs (mivacurium and rocuronium), greater ease of titration using the new delivery systems, and the ability to provide a more stable level of neuromuscular block for longer procedures, are the primary motivating factors for infusion of these drugs. In general, muscle relaxant infusions should be adjusted to maintain one or two twitches of the train-of-four response of the peripheral nerve stimulator (Table III). With vecuronium, it is important to realize that the terminal slope (elimination phase) of the time-concentration profile begins late in the first hour, after the clinical effects of the drug have dissipated. However, with larger doses or continuous infusions of vecuronium, the plasma concentration-time curve changes in a manner that leads to progressively longer recovery times. This phenomenon occurs to a much lesser extent with atracurium because of its short elimination half-life (≈20 min compared with ≈70 min for vecuronium), which results in a more constant rate of infusion when the level of block is relatively deep (Figure 4). Despite these differences, infusions of both atracurium and vecuronium are characterized by their ease of administration, and ability to be rapidly reversed with an appropriate dose of anticholinesterase drug.[10] For shorter procedures, and in the outpatient setting, mivacurium will play an important role. The unique characteristic of this drug is its very brief duration, due to rapid metabolism by plasma cholinesterase ($t_{1/2}\beta$ = 9–10 min). Because of its rapid spontaneous recovery (T_1 25–95% = 10 min), it has been suggested that reversal of mivacurium may not be necessary. Before adopting such a recommendation, however, careful evaluation of both monitored and clinical variables of recovery of neuromuscular function must be performed.

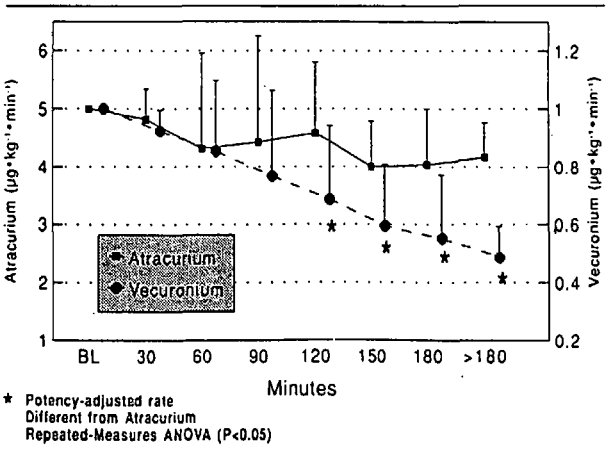

FIGURE 4 The mean infusion rates of atracurium and vecuronium required to maintain 90–95% suppression of the single twitch height during balanced anaesthesia. (From *Martineau RJ, et al.* Cumulation and reversal with prolonged infusions of atracurium and vecuronium. Can J Anaesth 1992; 39: 670–6, with permission).

IV Anaesthetic delivery systems

A most important factor which has contributed to the ever-increasing popularity of *iv* infusion anaesthesia, is the current availability of programmable syringe infusion pumps which have been specifically designed for intraoperative use. Amongst current technology, *calculator pumps* are devices capable of automating simple calculations from information entered by the user. *Smart pumps* are systems which use complex mathematical equations, which cannot be achieved by manual administration, to allow for targeting of set plasma concentrations. *Closed loop controllers* and *pharmacokinetic model-driven infusion pumps* are examples of smart pumps which will be commercially available within the next several years.

Manual infusion devices

GRAVIMETRIC CONTROLLER PUMPS

A controller infusion device regulates the rate of flow

caused by gravity. The simplest example of such a device is the CAIR clamp, which is supplied with most *iv* tube sets. By varying the radius of the *iv* tubing, the rate of flow can be adjusted by knowing the volume of each drop (60 drops/ml for a typical microdrip set), and the drip rate. However, this process is tedious and relatively inaccurate, and provides no feedback of information regarding the amount of drug administered. Furthermore, the rate of administration which such an infusion apparatus is very dependent on the flow rate of the main intravenous line, which usually undergoes many adjustments throughout the operative course, and may at times be under pressure during rapid fluid administration. Thus, such delivery systems are generally not considered appropriate for regulating the infusion rates of the potent intravenous anaesthetic drugs.

To provide greater accuracy with a gravimetric controller, non-volumetric pumps may be used, which rely on drop counting to calculate the volume infused. A drop counter is coupled to a device controlling the orifice of the infusion tubing. The drop counter measures the drop rate, and continuously adjusts the tubing orifice to maintain the specified infusion rate through a feedback mechanism. Although these pumps are much more accurate than devices which use a simple CAIR clamp, the volume of each drop is affected by the characteristics of the solution. This would be a particular problem when infusing more viscous medications such as propofol.

POSITIVE DISPLACEMENT PUMPS

Volumetric, or positive displacement infusion pumps, obviate many of the foregoing problems. These devices are capable of pumping against pressure, using either a peristaltic or piston action. Most commercially-available pumps for administration of *iv* anaesthetic drugs employ a piston mechanism driven by a screw motion, although peristaltic pumps with either a linear or rotary mechanism also exist. Many devices require a special administration set, whereas syringe pumps tend to be much more practical in the setting of the operating room. The desired features of such devices are listed in Table V.

With calculator pumps, the user needs simply to set the body weight and desired rate of infusion, and the pump microprocessor automatically calculates the actual infusion rate, as a given volume per unit time. Infusion rates are then adjusted as required, either by simple adjustment of a dial, or by entering the new desired rate of infusion. This process avoids the necessity of performing tedious calculations and minimizes the likelihood of human error if infusion rates are miscalculated. The Bard Alfentanil Infuser™ was the first commercially available calculator pump, and was co-marketed in the late 1980's with alfentanil, at the time when this drug was introduced into clinical practice. The pump was specifically designed for the infusion of alfentanil at a concentration of 500 $\mu g \cdot ml^{-1}$. Using a 60 ml syringe, the pump is capable of infusing alfentanil at rates between 0.25–3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, adjusted to body weight, as well as delivery bolus doses between 5 $\mu g \cdot kg^{-1}$ and 100 $\mu g \cdot kg^{-1}$. A microprocessor also provides a continuous display of cumulative dose of drug delivered. Despite the major advances of this delivery system, the obvious limitation is its specificity for alfentanil or other drugs which have a concentration of 500 $\mu g \cdot ml^{-1}$. Fortunately, a number of new infusion devices has become commercially available:

TABLE V Desired features of infusion devices for intra-operative use

1 Accurate (±2% of set rate)
2 User-friendly
3 Versatile – able to function with:
  (a) A number of drugs
  (b) A range of drug concentrations
  (c) Different-sized syringes
4 Bolus and infusion modes available
5 Operating range from 1–1500 $ml \cdot hr^{-1}$
6 Occlusion and low volume alarms incorporated
7 Air detection
8 Display of drug administered and infusion rate
9 Lightweight and compact
10 Electrically safe, but unaffected by electromagnetic fields
11 Digital interface (RS232 port) for external automated control
12 Reasonable price

Bard InfusOR™

Because of the limitations with the Alfentanil Infuser, Bard developed the InfusOR pump, which is capable of delivery a wide variety of drugs by means of a series of electromagnetic templates. The templates modify the control of the internal driving mechanism, while the pump maintains the same four-dial configuration as the original Alfentanil Infuser. The pump also operates with either 20 ml or 60 ml syringes. The size of the syringe to be used, and the concentration of drug to be administered, are specified on the templates, which are available for over 15 drugs. When the template is placed on the pump and the pump is turned on, the LCD displays the number of the template being "read" in order to confirm the proper functioning of the device. The InfusOR is small and lightweight, and operates using 4 "C" size batteries which last approximately 150 hr at average rates of infusion. The pump has a single alarm light, but provides separate coded messages for each malfunction on the LCD display.

Baxter Autosyringe AS20GH and AS40A

Shortly after the introduction of the Bard pump, Baxter

Inc. developed a positive displacement syringe infusion pump which incorporates a user interface with soft keys, that functions more like a calculator than the Bard System. The model AS20GH, which was co-marketed with propofol when this drug was introduced to Canada in 1990, requires that the user enters the patient's body weight, the drug concentration, and the desired rate of infusion by using the pump's soft keys. Advantages of this pump include the fact that any drug concentration can be set, and the pump also functions in either a dose/weight/time or volume/time mode. There are separate alarms for high pressure, low syringe volume, internal system failure, and battery status. However, this pump is cumbersome for administration of bolus doses, as it requires the pressing of two keys simultaneously to deliver the bolus, and is limited to a maximum bolus rate of 360 ml · hr^{-1}.

The AS20GH has now been replaced with a new version of the Baxter pump, model AS40A. This pump also has a soft key interface by which a range of body weights and drug concentrations can be entered. Several important features of this pump make it a much more practical device than its predecessor. The new features include clear, user-prompted programming with accelerated access features, automatic rate calculation, automated delivery of intermittent doses, and the ability to accept all syringe sizes from 1–60 ml. In addition, new safety features are incorporated, including a syringe detection system to ensure proper syringe placement, and two independent microprocessors to monitor and control infusion processes for consistent delivery.

Medfusion 2010 and 2010i

The Medfusion systems are a series of calculator infusion pumps which have many features similar to those of the Baxter AS40A. The most recent Medfusion pump, model 2010*i*, can accommodate programming of up to 60 drugs over a wide range of concentrations, to delivery at rates between 0.1–360 ml · hr^{-1}. Bolus doses can be easily and rapidly administered at any time during the infusion, and the number of alarms has been expanded. In general, the programming features of both the AS40A and Medfusion 2010*i* provide major advances for intraoperative infusion of anaesthetic drugs. In addition, both pumps can be fitted with an RS232 port to allow computer interfacing for pharmacokinetically-driven drug administration, when such systems become commercially available within the next several years.

MULTICHANNEL PUMPS

In addition to efforts directed to making syringe infusion pumps both smaller and more user-friendly, there are now several multichannel pumps which permit simultaneous infusion of three or four drugs. This allows one to more easily co-administer a sedative-hypnotic, opioid analgesic, and muscle relaxant, whether in combination with nitrous oxide and/or potent inhalational agents as part of a balanced anaesthetic technique, or to provide TIVA. Examples include the Omniflow, which is the first pump to combine the convenience of four channels with calculator capabilities. Syringes and/or fluid bags can be used with such a device, and four separate infusions can be given simultaneously using a single *iv* line. One potential problem with such a system is the possibility of incompatible drug mixing. The Minimed III® infusion pump is an even more compact three channel infusion pump that will soon be upgraded to a calculator pump.

PHARMACOKINETICALLY-DRIVEN INFUSION SYSTEMS

As drug effect is determined by drug concentration, considerable effort has been applied to the development of delivery devices which are capable of rapidly achieving and maintaining a desired or set concentration within the effect site. New terms for such systems include computer-assisted continuous infusion devices (CACI), or computer-controlled infusion pumps (CCIP). These systems incorporate a computer with the infusion device, to control the drug's rate of infusion continuously in order to maintain more accurately the desired drug concentration. This is done by linking a host computer to an infusion pump via a communication port (RS232 port on currently available pumps). The computer is used to provide a pharmacokinetic simulation of infusion requirements, incorporating all of the pharmacokinetic variables for the selected drug. In practice, one simply enters the target or desired concentration of the patient's body weight, and the computer provides a simulation, targeted toward the desired concentration. The difference between the predicted concentration and the desired target concentration is used to update the infusion rate constantly which is then communicated back to the infusion pump via the RS232 port. At the same time, the infusion rate administered is also communicated to the infusion pump, so that a new predicted plasma concentration can be calculated and updated every few seconds (Figure 5).

Practically speaking, the value of pharmacokinetically-driven infusion devices lies in their ability to achieve and maintain a given depth of anaesthesia more rapidly and easily, with intravenous medications, than can be achieved using a manual infusion scheme. This is analogous to the simplicity of turning up or down the vaporizer dial with the inhalational anaesthetic drugs, according to the desired end-tidal gas concentration. One obvious limitation of such systems is that the "target" concentration may vary considerably from the true plasma concentration, which cannot be measured "on line," as are end-

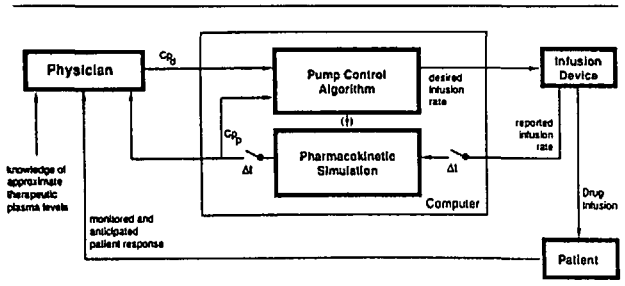

FIGURE 5 Generalized control diagram for computerized pharmacokinetic model-driven delivery of intravenous drugs. Cp_d is the desired plasma drug concentration, Cp_p is the plasma drug concentration predicted by the pharmacokinetic simulation, and Δt is the sampling interval. (From *Jacobs JR.* Algorithm for Optimal linear model-based control with application to pharmacokinetic model-driven drug delivery. IEEE Transactions on Biomedical Engineering, 1990; 37: 107–9.) © 1990 IEEE.

tidal concentrations of the inhalational anaesthetics. Discrepancies may also arise because the pharmacokinetic data are generally derived from population pharmacokinetics, and may be at variance with individual pharmacokinetic variables. Nevertheless, several studies of pharmacokinetically-driven infusion devices have been reported, which show an accuracy of approximately ±30% for such systems when using propofol, fentanyl and alfentanil.[11] It is expected that commercially available devices will be available in Canada within the next two to three years.

Pharmacoeconomic considerations

A final, and increasingly important matter to address when considering new anaesthetic techniques, is the issue of costs. In the past several years, it has become apparent that, in order to determine overall benefits of *iv* infusion anaesthesia, a number of factors, including drug acquisition costs, must be evaluated. Recently, the new science of *pharmacoeconomics* has emerged to describe and analyze the costs of drug therapy to health care systems and society.[12] This new research is used to identify, measure and compare the costs, risks, and benefits of programmes, services or therapies, and to determine which alternatives produce the best outcome for the resources invested. Thus, the purpose of pharmacoeconomics is not to identify the least expensive therapy, but to identify the total cost of treatment. In addition to hospital pharmacy costs, assessments need to be made of alternative treatments, and consumption of other aspects of health care. Furthermore, risks and complications resulting from the type of treatment need to be considered.

With regard to cost-effectiveness of *iv* infusion anaesthesia, considerable attention has been focused on propofol since this drug was introduced in Canada in 1991. Although propofol infusions for maintenance of anaesthesia will increase costs of this class of drugs, the technique may lead to savings in other areas. For example, it has recently been shown that for outpatient surgery, propofol/nitrous oxide anaesthesia provides a considerable reduction in recovery time, a decreased incidence of postoperative nausea and vomiting, and a decrease in nursing workload, compared with patients who receive thiopentone/isoflurane anaesthesia.[13] In order for savings to be realized, however, discharge must be geared to specific recovery criteria rather than a designated time, and flexibility and mobility of the nursing staff must be assured. Interestingly, recent reports of pharmacy costs for anaesthetic drugs show an overall decrease since the introduction of propofol.[14] For the muscle relaxants, other data suggest that despite improved haemodynamic stability of pipercuronium and doxacurium, these new drugs are not cost-effective when compared with pancuronium.[15] In contrast, in the United States, acquisition costs of relaxation with mivacurium are comparable to the costs of atracurium and vecuronium, for short procedures. If mivacurium also reduces the requirement for anticholinesterase drug for reversal, a further saving may be realized, in addition to the possibility of reducing the incidence of post-operative nausea and vomiting. These aspects, however, have yet to be evaluated.

Additional expenses of infusion anaesthesia include the costs of the delivery devices. Current pumps cost approximately $3,000–$3,500. Thus, the financial impact of supplying each operating room with one or two pumps can be considerable. However, if these devices do provide for more efficient drug utilization, their costs can be readily justified. Furthermore, these costs could eventually be off-set by decreasing slightly the number of vaporizers ($4,000–$6,000/vaporizer) in circulation within each department. It is increasingly apparent that economic considerations have become part of clinical decision-making. The pharmacoeconomic evaluation of modern intravenous anaesthetic techniques is just beginning, and will be the focus of considerable future research.

Conclusions

The new short-acting, potent intravenous anaesthetic drugs provide the ability to rapidly alter the depth of anaesthesia, according to both individual patient needs and varying levels of surgical stimulation, while also facilitating prompt and smooth recovery. These essential aspects may provide benefits for a wide range of surgical procedures of varying duration, including outpatient procedures. Optimal administration of the new sedative-hypnotics, opioids, and neuromuscular blocking drugs can be achieved by administration of continuous variable rate infusions, with supplemental periodic bolus doses as

required, according to the varying levels of intraoperative surgical stimulation. To facilitate drug administration, the new calculator syringe infusion pumps provide enhanced simplicity and user-friendliness, while also being flexible and accurate in operation. The next generation of infusion devices will incorporate pharmacokinetically-driven algorithms, to provide even more clinical information and greater ease-of-use. Further trials, more clinical experience, and cost-benefit considerations will determine the ultimate role of intravenous infusion techniques in the clinical practice of anaesthesia.

Acknowledgments

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Appendix I

Simplified glossary of terms related to iv infusion anaesthesia

1 *Bolus, Elimination, Transfer (BET) Regimen:* An algorithm infusion of intravenous anaesthetic drugs designed to achieve and maintain a stable plasma drug concentration. "B" represents the size of the Bolus or loading dose, "E" represents the steady-state rate of infusion according to drug's Elimination, and "T" represents an exponentially-declining rate of infusion to accommodate for drug Transfer from the central to peripheral compartments. To be accurate, a BET-type regimen can only be accomplished using a computer-controlled delivery device.

2 *Calculator pumps:* infusion devices which are capable of automating simple calculations from information entered by the user.

3 *Closed-Loop Delivery:* A technique whereby the rate of drug delivery is constantly adjusted by feed-back mechanism of a measured physiological variable, without operator intervention.

4 *Computer-Assisted Continuous Infusion (CACI):* Use of a computer for pharmacokinetic model-driven infusion of *iv* anaesthetic drugs or adjuvants, designed to achieve and maintain rapidly the set plasma concentration entered by user. In this way, the level of anaesthesia is adjusted simply by re-setting the desired plasma concentration, but does not imply closed-loop delivery. CACI is an example of a "smart pump".

5 *Computer-Controlled Infusion Pump (CCIP):* Same as: computer-assisted continuous infusion pump (CACI).

6 *Context-Sensitive Plasma Half-Time:* The computer-simulated time required for the concentration of an intravenous anaesthetic drug to decrease by 50% following an infusion scheme designed to maintain a constant plasma concentration for any given time period (the so-called "context").

7 *Cp50:* Plasma concentration of an intravenous drug required to either achieve or attenuate a physiologic response to a given stimulus in 50% of individuals (analogous to minimal alveolar concentration).

8 *Cumulation:* The tendency for drug concentration to increase within the plasma following repeated bolus administration or during prolonged infusion. The rate of cumulation depends on the rate of drug administration, and the rate of drug removal from the body's central compartment, as determined by elimination and redistribution processes.

9 *Effect Site:* The physiological site of drug action (e.g., the *brain* is the effect site of *iv* anaesthetic drugs, whereas the *neuromuscular junction* is the effect site of muscle relaxants). In general, is possible to measure drug plasma concentrations, but not effect-site concentrations.

10 *Intravenous Anaesthesia:* Anaesthesia employing opioid analgesics and sedative-hypnotics by either bolus or infusion techniques, with *or* without nitrous oxide and/or low concentrations of potent inhalational anaesthetics.

11 *Intravenous Infusion Anaesthesia:* The technique of administering one or more intravenous medications by continuous infusion as part of a balanced anaesthetic regimen, in combination with nitrous oxide and/or potent inhalational agents.

12 *Kinetic-Dynamic Dissociation:* The time-lag between drug concentration and drug effect (e.g., alfentanil equilibrates extremely rapidly with the CNS, and therefore exhibits less kinetic-dynamic dissociation than do either fentanyl or sufentanil).

13 *Pharmacodynamics:* The relationship between drug concentration and physiological effect (i.e., what the drug does to the body).

14 *Pharmacokinetics:* The mathematical description of the time course of drug concentration within the body (i.e., what the body does to the drug).

15 *Smart Labels:* Drug-specific magnetic templates which attach to the front of Bard syringe infusion pumps, and set the internal driving mechanism to adjust for the range of available drug concentrations and desired rates of infusion, for the anaesthetic drugs and muscle relaxants.

16 *Smart Pumps:* Pumps which use complex mathematical equations, which cannot be achieved by manual administration, to allow for targeting of set plasma concentrations. *Closed loop controllers* and *pharmacokinetic model-driven infusion pumps* are

examples of smart pumps which will be commercially available within the next several years.

17 *Soft Key Interface:* A key system for syringe infusion pumps, analogous to that on hand-held calculators, that allows the user to enter patient data, and select the drugs to be infused, and desired rates of infusion and bolus injections.

18 *Total Intravenous Anaesthesia (TIVA):* A technique of general anaesthesia using sedative-hypnotic and opioid analgesic combinations (with or without muscle relaxants), in the absence of potent inhalational agents or nitrous oxide. Air/oxygen or oxygen alone may be used during either spontaneous or controlled ventilation with TIVA. Total intravenous anaesthesia may be administered by either bolus or infusion regimens.

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Self-assessment Questionnaire

FOR EACH OF THE FOLLOWING QUESTIONS, SELECT THE ONE BEST ANSWER.

1 Which of the following factors is *least likely* to alter the pharmacokinetics of intravenous anaesthetic drugs?
- A Drug interaction.
- B The stress response to surgery.
- C Method of drug administration; i.e., infusion *vs* bolus technique.
- D Changes in body temperature.
- E Cardiopulmonary bypass.

2 Similarities of infusion *vs* inhalational anaesthesia include all but which *one* of the following?
- A Both approaches require expensive equipment (delivery devices).
- B Both techniques require incorporation of pharmacokinetics into the design of dose regimens, to allow for rapid attainment of stable effect site concentrations.
- C Continuous background administration of one drug can be used to reduce the dose requirements of the titrated drug, for both inhalational and *iv* infusion techniques.
- D Overpressurization may be considered analogous to administration of a loading dose of an *iv* drug, to rapidly achieve the desired initial concentration.
- E On-line measure of drug concentration can be used to guide the rate of drug administration with either technique.

3 Regarding pharmacokinetically-driven infusion systems, which of the following statements is *true*?
- A Rate settings are entered on the basis of $\mu g \cdot kg^{-1} \cdot min^{-1}$.
- B Knowledge of individual pharmacokinetic variables is required.

C Variability in plasma drug concentrations would tend to be greater than with manual methods of administration.
D The rate of drug infusion is constantly adjusted to maintain a set target plasma concentration.
E Accuracy of current systems is around ±3%.

4 Minimal safety features of syringe infusion pumps would necessarily include each of the following *except*:
A Air detection.
B Versatile syringe size.
C High pressure alarm.
D Near end-of-syringe alarm.
E Near end-of-battery alarm.

5 Which one of the following statements is true?
A The therapeutic concentration of propofol for minor surgery is between 2–6 $ng \cdot ml^{-1}$.
B Sufentanil is approximately five times more potent than fentanyl.
C The CP50 for spontaneous ventilation with alfentanil is around 500 $ng \cdot ml^{-1}$.
D Awakening from propofol occurs at plasma concentrations around 1 $\mu g \cdot ml^{-1}$.
E Midazolam has little influence on propofol requirements during total intravenous anaesthesia.

FOR EACH OF THE FOLLOWING QUESTIONS, SELECT THE MOST APPROPRIATE CHOICE ACCORDING TO THE FOLLOWING POSSIBLE ANSWERS.
A if only 1, 2 and 3 are correct
B if only 1 and 3 are correct
C if only 2 and 4 are correct
D if only 4 is correct
E if all are correct

6 Potential advantages of infusion *vs* bolus administration of *iv* anaesthetic drugs include:
1 A decrease in total drug requirement per unit time.
2 A decreased incidence of side effects.
3 Increased cardiovascular stability.
4 Increased variability of drug concentration within the effect site.

7 Which of the following factors determines the rate of clinical recovery following termination of an *iv* infusion of midazolam?
1 The duration of administration.
2 The context-sensitive plasma half-time of the drug.
3 The size and number of boluses administered.
4 The age of the patient.

8 When comparing the times required for a 50% decrease in effect site concentration, under what conditions is alfentanil a shorter-acting opioid analgesic compared with sufentanil?
1 Following administration of a single *iv* bolus.
2 Following a 3 hr infusion.
3 Following a 10 hr infusion.
4 Always, due to the shorter elimination half-life of alfentanil.

9 The most effective manual infusion scheme for administration of an opioid analgesic during balanced anaesthesia with nitrous oxide/midazolam would include which of the following?
1 Administration of a loading dose followed by a relatively high initial rate of infusion.
2 Avoidance of supplemental bolus dosing.
3 Progressively decreasing the rate of infusion over time.
4 Discontinuing the infusion 30–45 min before the end of surgery.

10 Which of the following statements is/are true.
1 The high clearance rate of propofol suggests the presence of extra-hepatic sites of metabolism for this drug.
2 For alfentanil, the CP50 for spontaneous ventilation is greater than the CP50 providing residual analgesia at the end of surgery.
3 Propofol minimizes dysphoria associated with the use of ketamine.
4 Compared with vecuronium, atracurium demonstrates a greater tendency for cumulation during prolonged infusion.

ANSWERS

1	C	2	E	3	D	4	B	5	D
6	B	7	E	8	B	9	A	10	A