Anesthesiology Clin N Am
21 (2003) 273–288

ANESTHESIOLOGY
CLINICS OF
NORTH AMERICA

Intravenous techniques in ambulatory anesthesia

Antoine Tesniere, MD, Frederique Servin, MD*

University Hospital Bichat Claude Bernard, Department of Anesthesiology, 46 Rue H Huchard, Paris, Cedex 18 75877, France

Recent advances in anesthetic and surgical techniques, combined with cost-containment concerns, have made day-case surgery increasingly popular. Day-case surgery differs significantly from classic in-patient surgery in that procedures are often shorter, less invasive, and less painful. Ambulatory anesthesia requires rapid recovery, good quality analgesia, decreased duration of care, and cost-effective techniques. Thus, anesthetic agents in day-case surgery should provide smooth and fast induction of anesthesia, rapid and pleasant recovery, and return to preoperative functional status with optimal postoperative analgesia and minimal side effects, such as postoperative nausea and vomiting (PONV). Several intravenous (IV) agents may fulfill these criteria and, therefore, ambulatory anesthesia can be achieved by a judicious combination of intravenous techniques, resulting in excellent postoperative outcome and comfort (Tables 1 and 2).

Because ambulatory patients expect to return to their preoperative functional state in the early postoperative period, anesthesiologists should strive to minimize discomfort. Obtaining patient satisfaction in this setting is an important objective for care providers. New techniques of administration have recently been developed to enhance patient comfort, reduce recovery times and length of stay and, therefore, outpatient surgery costs. Intravenous agents can be routinely used for induction and maintenance of anesthesia, for sedation, and for analgesia. This article reviews the pharmacology of intravenous anesthetic, sedative and analgesic agents, and the recent advances in the techniques of administration for ambulatory surgery.

* Corresponding author.
E-mail address: frederique.servin@bch.ap-hop-paris.fr (F. Servin).

0889-8537/03/$ – see front matter © 2003, Elsevier Inc. All rights reserved.
doi:10.1016/S0889-8537(02)00081-0

Intravenous hypnotic drugs

Thiopental

Thiopental is a barbiturate, characterized by a rapid onset and a short duration of action after a single dose (5–7 $mg.kg^{-1}$). It has a low elimination clearance [1] and therefore cannot be used for maintenance of anesthesia. It may also delay early recovery without modifying intermediate and late recovery after short procedures when compared with propofol [2]. Thiopental usually provides a pleasant induction of anesthesia with pain rarely (2%) on injection and few excitatory movements [3]. Arterial pressure may decrease because of peripheral venodilatation, a reflex increase in heart rate, and a decreased cardiac output. Apnea is frequent, followed by a dose-dependent decrease in patient ventilation and in physiologic response to hypoxemia. Extravasation of a thiopental solution can cause pain, erythema, and tissue damage. Anaphylactoid reactions with thiopental are rare and mild. Thiopental is a cost-effective drug for induction of anesthesia.

Methohexital

Methohexital is also a barbiturate, and its pharmacological properties are close to those of thiopental. It is more potent, and the induction doses are therefore lower (1–3 $mg.kg^{-1}$). It is eliminated much more quickly than thiopental [1] and, as a consequence, can be used as a continuous infusion for maintenance of anesthesia. Unfortunately, the high incidence of unwanted side effects associated with methohexital administration is one of the main downsides of this drug: excitatory movements, PONV, hiccup, cough, or even laryngospasm have been reported in about 20% of cases [3].

However, the cost of methohexital is low, and its use for induction in day-case surgery is cost-effective when compared with propofol [4].

Table 1
Examples of dosing regimens for the various anesthetic I.V. agents during general anesthesia in the ambulatory setting

	Induction bolus dose	Maintenance infusion rate	Maintenance intermittent boluses
Thiopentone	5–7 mg/kg	—	—
Methohexital	1–3 mg/kg	100–150 $\mu g.kg^{-1}.min^{-1}$	—
Midazolam	Not recommended as hypnotic agent in ambulatory general anesthesia		
Etomidate	0.3 mg/kg	—	—
Propofol	2–3 mg/kg	6–10 $mg.kg^{-1}\ h^{-1}$	—
Fentanyl	50–100 μg	—	25–50 μg
Alfentanil	0.5–1.5 mg	1–3 mg/h	0.2–0.5 mg
Remifentanil	1 μg/kg	0.1–0.25 $\mu g.kg^{-1}.min^{-1}$	—
Ketamine (analgesic)	0.1–0.2 mg/kg	5–10 $\mu g.kg^{-1}.min^{-1}$	—

Table 2
Examples of dosing regimens for the various anesthetic I.V. agents during conscious sedation in the ambulatory setting

	Induction bolus dose	Maintenance infusion rate	Maintenance intermittent boluses
Midazolam	1–5 mg	—	1–2 mg
Propofol	0.5–1 mg/kg	2–4 $mg.kg^{-1}.h^{-1}$	0.3–0.5 mg/kg
Fentanyl	25–50 μg	—	25–50 μg
Alfentanil	0.2–0.5 mg	0.5–2 mg/h	0.2–0.5 mg
Remifentanil	—	0.025–0.10 $\mu g.kg^{-1}.min^{-1}$	25 μg
Ketamine (analgesic)	0.1 mg/kg	2–4 $\mu g.kg^{-1}.min^{-1}$	—

Midazolam

Midazolam is a potent benzodiazepine. It is characterized by a slower onset of action than diazepam [5], an intermediary clearance (approximately 500 mL/min^{-1}), and a short elimination half life (2 hours).

Sedative effects are variable among patients, and recovery from midazolam sedation can be prolonged, accompanied by delayed recovery of superior functions [6] and persistent amnesia after awakening [7]. Complete recovery requires approximately 90 minutes after a single dose of midazolam 0.1 $mg.kg^{-1}$. As a consequence, midazolam is not used to induce or maintain loss of consciousness in outpatients, but rather as a premedicantion or in conscious sedation.

Cardiovascular side effects are rare and mild at the doses used for sedation, but can be significant for more important doses, specifically in hypovolemic patients.

Respiratory tolerance is usually acceptable, but delayed obstructive apnea may occur in some patients [9].

Etomidate

Etomidate is an imidazole derivative that provides good hemodynamic stability when used as an induction agent. Despite its suitable pharmacokinetic properties for day-case anesthesia [10], etomidate is seldom used in the ambulatory setting because of a high incidence of unwanted side effects. These include PONV [11], pain on injection, venous irritation, phlebitis, and excitatory movements. The incidence and severity of these effects can be partially reduced. Pain on injection can be prevented by prior injection of 1 to 2 mL of lidocaine 1% or the use of a lipid formulation, and abnormal movements may be attenuated by prior injection of fentanyl [12].

Propofol

Propofol is the drug of choice for induction and maintenance of day-case anesthesia and the most widely used intravenous agent for ambulatory anesthesia and sedation because of its favorable pharmacokinetic and pharmacodynamic properties in this specific setting. It can be used solely or as part of total intravenous anesthesia (TIVA), by intermittent boluses, or continuous or target-

controlled infusions (TCI). Propofol is characterized by a fast onset and a short duration of action. Equilibration half-life between plasma and effect site is less than 3 minutes [13]. Its short context-sensitive half-life, a high plasma clearance (equal or greater than liver blood flow), associated with a large volume of distribution, results in a fast awakening even after prolonged continuous infusions when propofol is used as sole anesthetic agent. In the absence of estimation of the decrement time, gross overdosage is possible and may delay recovery [14].

When used at subhypnotic doses, propofol provides an easily titrable level of sedation, with anxiolysis and amnesia similar to those of midazolam [15].

Hemodynamic effects of propofol are mainly consistent with a dose-dependent decrease in peripheral resistances, resulting in a decrease of approximately 30% in mean arterial pressure. They may partly be avoided by a slow speed of injection [16]. Its use is relatively contraindicated in hypovolemic patients.

Because of direct antiemetic properties [17], the incidence of PONV in the postanesthetic care unit (PACU) is low with propofol [18].

When propofol is used at low concentrations, its respiratory effects are moderate and allow spontaneous ventilation during maintenance of anesthesia and sedation.

Intraoperative analgesia

Blunting autonomic responses to noxious anesthetic and surgical stimuli with intravenous anesthetics alone requires high doses leading to increased cost and delayed recovery. The analgesic component of anesthesia is usually provided by specific drugs, mainly opioids, low-dose ketamine or local anesthetic agents. Opioids interact synergistically with hypnotics for sedation and hypnosis [19] but cause significant respiratory depression and increase the incidence of PONV [20]. Local and regional anesthetics, when available, are effective to suppress pain related to surgical procedures. Recent studies have also shown that a combination of propofol and ketamine infusion (9.4 $mg.mL^{-1}$ and 0.94–1.88 $mg.mL^{-1}$ for propofol and ketamine, respectively) was effective in decreasing opioid requirements without modifying recovery profiles for monitored anesthesia care [21].

Optimal opioid analgesia should provide a fast onset of the desired effect, an easy titration to the level of noxious stimulation, and allow a fast recovery after surgery without postoperative pain. Thus, optimal dose and timing of administration are important factors.

To maintain a continuous opioid effect, a constant concentration of opioid must be maintained at the site of action of the drug. The usual titration methods rely extensively on the use of clinical criteria to assess the adequacy of the analgesic state and on the pharmacokinetic properties of the drugs used.

Fentanyl and its congeners

Fentanyl is a widely used opioid for ambulatory anesthesia and monitored anesthesia care (MAC). Despite its cumulative potential, when used at low dosages

(25–100 μg) it does not unduly delay recovery and provides adequate early postoperative analgesia. It can also be used as rescue pain medication in the initial recovery phase, providing analgesia long enough to allow nonopioid analgesics with a slower onset to exert their effects. Like all opioids, it should be used by titration, taking into account its slow onset (time to peak effect 4 min) under close respiratory monitoring.

The main advantage of alfentanil is its rapid onset (time to peak effect 1.5 min), which facilitates titration based upon respiratory rate in spontaneously breathing patients. In this situation, a continuous infusion produces less perioperative unwanted effects than intermittent boluses [22]. In outpatients, alfentanil induces less PONV than fentanyl [23].

Sufentanil has a longer time to peak effect (around 6 min) than fentanyl. As a consequence, its titrability is low, and it offers no advantages over fentanyl in ambulatory anesthesia.

Remifentanil is a potent opioid analgesic with a short onset similar to that of alfentanil and a high metabolic clearance. Its main advantage in the ambulatory setting is a short context sensitive half-time (3–5 min), independent of the duration of infusion. Because of the relative absence of residual opioid effect, its use requires adjunctive analgesics to maintain adequate postoperative analgesia after painful procedures. This is often best achieved with a combination of nonopioid analgesics (multimodal analgesia) administered well before remifentanil discontinuation, often at induction of anesthesia or toward the end of surgery. Remifentanil can be administered as intermittent boluses or as a continuous infusion. Use of continuous infusions (0.025–0.15 $\mu g.kg.min^{-1}$) in patients undergoing extracorporal lithotripsy provided better intraoperative comfort but was associated with a higher rate of hypoxemia when compared with intermittent boluses (25 μg) [24].

Ketamine

Ketamine is a dissociative IV anesthetic that plays a significant role in analgesia and sedation for ambulatory surgery, mainly as an adjunct to other hypnotic drugs. It has sedative hypnotic properties resulting in a light dissociative sleep, but also has potent analgesic properties. Its clinical effects are mediated by noncompetitive antagonism at the N-methyl-D-aspartate and opioid receptors. Ketamine has a high plasma clearance of 17 $ml.kg^{-1}.min^{-1}$, with an elimination half-life of 153 minutes and is essentially metabolized to norketamine by the hepatic microsomal enzymes (CYP450). Norketamine is an active metabolite of ketamine, which is 30% as potent as ketamine, and hence can produce prolonged effects [25].

Ketamine has direct analgesic properties at plasma concentrations significantly lower than those producing loss of consciousness (100–200 $ng.ml^{-1}$ for analgesic effects, corresponding roughly to a 5–10 $\mu g.kg^{-1}.min^{-1}$ infusion) [26]. Ketamine can be safely administered at low doses (2–4 $\mu g.kg^{-1}.min^{-1}$) with continuous infusions of propofol during monitored anesthesia care for

ambulatory procedures, allowing a reduction in opioid doses and unwanted effects. Moreover, ketamine may attenuate propofol-induced hypoventilation and provide earlier recovery of cognition [27]. Adjunctive use of ketamine during propofol sedation provides significant analgesia and minimizes the need for supplemental opioids when given at subhypnotic doses [21]. Simultaneous use of small doses of ketamine with morphine enhances opioid pain relief [28]. Given before the end of surgery in ambulatory procedures, ketamine allows a reduction of approximately 40% in morphine requirements without altering the recovery profile [28].

Intravenous techniques

Appropriate administration techniques are important to fully benefit from the pharmacological properties of the intravenous agents.

Total intravenous anesthesia (TIVA)

Total intravenous anesthesia (TIVA) involves induction and maintenance of anesthesia with intravenous drugs alone. In TIVA, hypnosis can theoretically be achieved with many agents (barbiturates, benzodiazepines, etomidate, ketamine, or propofol). Because of its superior pharmacokinetic and pharmacodynamic properties, propofol has gained increased popularity for TIVA in ambulatory surgery. Propofol TIVA provides the ability to enhance patient's satisfaction when compared with inhalational techniques, and results in a clinically relevant reduction in PONV when compared with isoflurane/nitrous oxide anesthesia [29].

TIVA is often associated with the administration of nitrous oxide, which does not delay recovery and may be used to decrease the requirement for the more expensive intravenous drugs. Nitrous oxide has been accused of increasing the incidence of PONV, but this assertion has recently been challenged [30]. Because nitrous oxide inhibits the NMDA receptor, it might reduce tolerance and hyperalgesia caused by opioid administration and thus improve postoperative pain control [31].

The objective of any form of administration is to maintain an appropriate concentration of anesthetic drugs at the site of action in the CNS. Choosing an appropriate method of administration is important in TIVA. Intermittent bolus injections of drugs may result in high peak plasma concentration, and therefore high concentrations at effect site, with possible unwanted effects. Depending on the drug administered and the time intervals between boluses, boluses can also result in significant accumulation. With continuous infusions of short-acting drugs, anesthesia can be maintained with a high degree of safety, precision, and titratability.

Propofol administration may be guided by the results from population studies that indicate the infusion rates needed to sustain a constant plasma or effect site concentration [19]. Infusion rates requirements decrease over time as muscle and

fat tissue depots equilibrate with a given plasma concentration. Various monitors, such as the bispectral index (BIS™), may further guide infusion rates. Its use allows a downtitration of hypnotic drugs doses and may promote earlier awakening [32].

Target-controlled infusion (TCI)

New techniques of continuous infusions use pharmacokinetic models to predict the patient plasma and effect site concentrations from the infusion scheme and allow the anesthesiologist to target a chosen concentration, the device calculating the appropriate infusion scheme to achieve this concentration [33]. Thus, the anesthesiologist deals directly with the concentration/effect relationship.

TCI rapidly achieves and maintains a predefined plasma or effect site concentration of the anesthetic drug. Appropriate target concentrations change with interindividual pharmacodynamic variability and with the nature of the surgery. When an appropriate target concentration for achieving the desired clinical endpoint is chosen, TCI delivery systems perform better than manual systems [34]. Currently, TCI devices are approved in many countries, but only for propofol administration.

Monitored anesthesia care

Monitored anesthesia care (MAC) is used for patients who require supervision of vital signs and administration of sedative/anxiolytic drugs to supplement local infiltrations or regional anesthesia, or to provide sedation during unpleasant diagnostic procedures. It usually describes an anesthetic state ranging from conscious sedation to deep sedation without airway control.

MAC is most often achieved with IV drugs, alone or in combination, which can easily produce a range of hypnotic states from anxiolysis to loss of consciousness without major hemodynamic and respiratory depression. A wide variety of IV drugs have been used during MAC, including barbiturates, benzodiazepines, ketamine, propofol, opioid and nonopioid analgesics, and nitrous oxide.

Methohexital provides excellent intraoperative conditions with a rapid recovery when administered by intermittent bolus injections (10–20 mg) or as a variable rate infusion, but its use is associated with adverse effects, such as pain on injection, excitatory movements, antianalgesic effects, and PONV [35].

Benzodiazepines, mainly midazolam, are widely used during MAC because of their sedative, anxiolytic, and amnesic effects.

Ketamine has been used alone in MAC, but its administration has been associated with a great incidence of side effects, including psychic disturbances, varying from 5% to 30% [36]. Benzodiazepines have been used in combination with ketamine, and have proved their effectiveness in attenuating the psychomimetic effects of ketamine. This combination also provided effective intraoperative analgesia [37].

Propofol is probably the most suitable IV agent for MAC. Propofol as an induction agent offers better conditions for immediate awakening and faster recovery of cognitive function, with no significant differences at 24 and 72 hours when compared with thiopental [2]. When compared with midazolam infusions for sedation during procedures under local anesthesia, propofol use was associated with a more rapid recovery of cognitive functions and less postoperative sedation, drowsiness, and confusion [38]. Moreover, the quality of early and intermediate recovery after propofol sedation was superior to that obtained after benzodiazepines associated with flumazenil [8].

Propofol can depress the hypoxic ventilatory response and therefore coadministration of oxygen is usually recommended. The combination of propofol and small dose ketamine (3.7 ± 1.5 $\mu g.kg^{-1}.min^{-1}$) during MAC provides a reduction in the incidence of propofol-induced hypoventilation with a significant improvement in quality of recovery [27]. It also provides effective analgesia [39] and significant decreases in pain scores after discharge.

Although propofol has direct amnesic effects, a bolus of midazolam (2 mg IV) may be useful to enhance postoperative amnesia and anxiolysis without altering recovery profile [40]. Midazolam acts synergistically with propofol [41] and thus may reduce the propofol induction requirements. Nevertheless, this technique may impair postoperative recovery of swallowing reflexes more than propofol alone [42].

For office-based anesthesia, the use of propofol compared favorably with that of sevoflurane, with an improved recovery profile, greater patient satisfaction, and lower costs [43].

MAC is a cost-effective technique for outpatient surgery. Use of regional anesthesia as part of MAC for unilateral inguinal herniorrhaphy is associated with the shortest time to home readiness, lower pain scores at discharge, highest satisfaction at 24 hours follow-up, and the lowest costs when compared with general and spinal anesthesia [44].

In conclusion, MAC has become widely used throughout the world because of its efficacy in providing optimal intraoperative conditions, favorable recovery profile, pain management, and patient satisfaction with lower costs than general anesthesia.

Conscious sedation

Conscious sedation, defined as any degree of sedation ranging from anxiolysis to sleep with preservation of eyelash reflex and purposeful reaction to verbal or mild physical stimulation, allows many medical or surgical procedures with good perioperative anxiolysis and amnesia and without requiring mechanical ventilation. Subanesthetic doses of intravenous drugs are often used to provide sedation for procedures performed under local or regional anesthesia. As such, conscious sedation is part of MAC.

Sedation, which is a specific form of TIVA, can be achieved with many IV drugs.

The interest of propofol for conscious sedation was demonstrated at the early stages of clinical use of that drug. Mackenzie et al [45] studied the adequacy of propofol in sedation combined with local anesthesia and found that continuous infusion at subhypnotic doses (3–4 $mg.kg^{-1}.h^{-1}$) was safe, efficient, and accompanied by an impressively rapid awakening with low incidence of postoperative side effects. In patients requiring general anesthesia during these procedures, the infusion rate was increased (10 $mg.kg^{-1}.h^{-1}$) to induce loss of consciousness.

Sedation with propofol can be achieved with intermittent boluses (10 mg), continuous infusion (25–100 $\mu g.kg^{-1}.min^{-1}$), or TCI (1–2 $\mu g.ml^{-1}$). The overall quality of sedation, intraoperative conditions, and clinical recovery profiles are similar with the three techniques, but the use of infusions (manually controlled or TCI) decreases the number of interventions necessary to administer supplemental doses and therefore allows more time to monitor the patients [46].

Patient-controlled sedation

During day-case surgery, patients' anxiety, level of stimulation, and type of procedures vary widely, thus inducing a broad range of sedative dosage requirements. New techniques of administration for IV sedation during MAC have thus been developed to meet this interindividual variability. Patient-controlled sedation (PCS) devices deliver a predefined bolus of IV drug during a defined time, with or without a lockout interval (eg, propofol 0.3 $mg.kg^{-1}$ over 5 sec, without lockout period) [47].

Ng et al [47] compared anesthesiologist-controlled administration of midazolam and patient-controlled administration of propofol. The results of this randomized study showed that PCS administration of propofol was associated with a better cooperation of patients and a higher endoscopist satisfaction. Time for awakening and discharge was shorter with propofol than with midazolam, with a higher overall patient satisfaction in the PCS group.

When compared with TCI administration of propofol, PCS showed similar quality of sedation, intraoperative conditions, and high levels of patient satisfaction in a crossover study during dental procedures in anxious patients [48].

Patient-controlled TCI may be a further interesting step in the delivery of sedation: when the patient activates the TCI device, the target is increased (eg, by 0.2 $\mu g.ml^{-1}$ steps). If the patient has not activated the device for a certain time, the target concentration drops automatically. The advantages of such a system would be a stable level of sedation and an almost ideal control with nearly no risk of oversedation [49].

Advantages of intravenous techniques

Advantages of intravenous anesthesia in ambulatory surgery can result from the administration technique or the pharmacological properties of the IV drugs, specifically propofol.

When only intravenous drugs are used, specifically with conscious sedation, no sophisticated anesthesia machines or vaporizers are required, and the respiratory equipment can be kept at a minimum. If inhalational techniques are used, the cost of the less-soluble volatile agents and the necessity to maintain a low level of pollution in the operating theater require a circle circuit with online measurement of volatile anesthetic end tidal concentrations.

Propofol effect site concentration as estimated by TCI devices is a good predictor of loss of consciousness [50], whereas blood concentration and *a fortiori* end tidal anesthetic concentrations are not good predictors unless a steady state is reached, which is seldom the case with short ambulatory procedures [51]. If effect site anesthetic drug concentration is not available, hypnosis level may be estimated through analysis of spontaneous or evoked EEG activity.

Monitoring the hypnotic component of anesthesia has undergone recent changes with the analysis of the bispectral index of the EEG (BIS™, Aspect Medical Systems, Newton, MA). BIS™ has demonstrated a significant correlation with the level of responsiveness and the loss of consciousness during anesthesia with propofol, midazolam, and isoflurane [52]. Moreover, BIS monitoring proved its effectiveness in reducing anesthetic drugs consumption when compared with standard general anesthesia for propofol and sevoflurane [53]. When used during propofol and alfentanil TCI, it allowed a significant reduction of propofol doses without intraoperative modifications, compared with standard clinical practice, and a faster recovery [32].

BIS™ value is a better predictor of the level of sedation than end tidal sevoflurane concentration [51]. Therefore, BIS™ monitoring for day-case surgery is an effective way to reduce anesthetic drugs doses and delayed awakening and to improve recovery. However, the economy of reduced drug costs achieved with BIS™ monitoring must be balanced with the price of the disposable sensors, and the result may differ in various countries as well as in the duration of surgery [53].

Preventing PONV is one priority in ambulatory patients, as PONV has been rated by patients and anesthesiologists as the second and third most frequent and important adverse effects to avoid [54], and has also been recognized as one of the main factors contributing to prolonged stay after ambulatory surgery [55] or unintended return to hospital [56]. Still, PONV incidence remains high in ambulatory surgery, and is responsible for increased costs, delays in home readiness, hospital return, and patient discomfort.

Several studies have demonstrated the antiemetic effect of propofol when used as an induction bolus or as a maintenance agent for general anesthesia or MAC. Eriksson et al [57] showed that propofol used by continuous infusion provided a lower incidence of PONV than an association of desflurane and prophylactic ondansetron (20% versus 40%) for outpatient gynecological laparoscopy. Similarly, propofol administered through patient-controlled devices at repeated doses of 20 mg in PACU [58] has proven its effectiveness to treat PONV.

This ability to reduce the incidence of PONV allows indirect savings by improving speed and quality of recovery and avoiding the use of adjuvant drugs and

thus may counterbalance the higher acquisition costs of propofol when compared with inhalational agents [59]. The difference in direct drug cost has been narrowed by the marketing of propofol generic formulations [60].

Patient satisfaction is a major concern for the anesthesiologist in ambulatory surgery, especially when short and minor surgical procedures are performed. The quality of recovery offered by propofol and the pleasant mood described by the patients may be directly related to the pharmacological action of the drug. Pain and colleagues have found that propofol, unlike methohexital, induced a pleasant affective state in rats at subanesthetic doses and during recovery from anesthetic doses [61]. D'Haese et al [62] showed that the use of propofol was associated with higher mood status scores in female patients when compared with methohexitone. This positive change in mood after propofol administration remains only partly understood, but is certainly an important point contributing to the patients' well-being and satisfaction after ambulatory procedures.

In reviewing the numerous studies published over the past few years, propofol has obviously become an extremely valuable agent for diagnostic and therapeutic procedures performed in the ambulatory setting.

Limits of intravenous techniques

Intravenous techniques in ambulatory anesthesia have limitations that need to be clearly understood to prevent their consequences.

The use of a specific equipment, such as pumps able to deliver very low (less than 1 ml/h) and very high (greater than 1000 ml/h) infusion rates, is mandatory to ensure a proper titration of anesthesia. Dead space between the stopcock and the indwelling catheter should be as small as possible, and a one-way valve will best avoid a backflow of the anesthetic agent in the main infusion line. It is not possible with intravenous agents to keep the same syringe for successive patients and therefore drug waste will frequently occur.

Other limitations are mainly the result of pharmacokinetic properties of the agents and to the fact that direct drug concentration measurements are not available. The relationships between infusion rates and adequate effect-site concentrations are not readily available and, even in the presence of predicted concentrations, a good understanding of the pharmacokinetic model implemented in the device and of its covariates is necessary to adapt the dosage to the individual patient. A good example is the elderly patient, in whom initial distribution of drugs is impaired, leading to concentrations higher than expected, and therefore to an increased incidence of overdosage at induction of anesthesia. This overdosage may increase the incidence of hemodynamic unwanted side effects [63]. Therefore, propofol induction doses should be reduced in elderly patients by approximately 40%, even for achieving conscious sedation [64]. When using TCI, if age is not a covariate incorporated in the model used, the initial predicted concentrations will be grossly underestimated in elderly patients.

One way to overcome this problem is to monitor spontaneous or evoked EEG parameters when titrating IV hypnotics.

Changes in volume of distribution and redistribution of drugs after prolonged continuous infusion may lead to a significant accumulation in obese patients. This redistribution may result in unpredictable delay in awakening after prolonged continuous infusion, and, therefore, continuous infusion of propofol may not be the optimal anesthesia regimen for this specific population [65].

Macario et al [54] have shown that pain on propofol injection, and behavioral troubles such as fatigue, confusion, and somnolence were ranked highly as clinical outcomes to avoid.

Pain on injection with propofol occurs in 28% to 90% of patients [66], even with low-dose propofol infusions used for sedation. The use of a low dose of lidocaine reduces the pain resulting from propofol injection. Despite contradictory results [67], it seems that doses as low as 0.1 mg/kg lidocaine are effective in reducing the incidence of propofol pain on injection [68]. This dose was equally effective when given simultaneously with propofol or as a pretreatment dose 20 seconds before the injection of propofol. Pain on propofol injection should be systematically prevented to avoid patient discomfort because effective and low-cost techniques exist.

Costs related to propofol use in TIVA have often been considered a major drawback when compared with inhalational techniques, especially desflurane and sevoflurane [69]. To reduce excessive costs related to propofol use in TIVA, a concomitant administration of 65% nitrous oxide has been evaluated. In office-based surgery, this adjunct allowed a reduction in propofol requirement, without increasing PONV or altering recovery profiles [70]. The use of a propofol/nitrous oxide combination is therefore a cost-effective alternative to propofol alone in ambulatory surgery. This association has also shown its effectiveness to improve recovery profiles and patient satisfaction and to decrease costs when compared with inhalational techniques with a sevoflurane/nitrous oxide association in fast-track office-based anesthesia [43].

Summary

The growing importance of ambulatory surgery during the past decade has led to the development of efficient anesthetic techniques in terms of quality and safety of anesthesia and recovery. In these challenging objectives, intravenous techniques have played an important role, as they provide safe, efficient, and cost-effective anesthesia in the ambulatory setting. Among the numerous intravenous drugs, propofol, with its fast and smooth onset of action, short duration of action, and low incidence of postoperative side effects appears to be the anesthetic of choice in this situation.

The recent development of new techniques of administration (such as TCI, monitored anesthesia care, or patient-controlled sedation) and monitoring (such as the BIS™ and the availability of “hit and run” drugs such as remifentanil) will

further optimize intraoperative conditions and recovery, thus allowing faster home readiness in the ambulatory setting.

References

[1] Hudson RJ, Stanski DR, Burch PG. Pharmacokinetics of thiopental and methohexital in surgical patients. Anesthesiology 1983;59:215–9.

[2] Kern C, Weber A, Aurilio C, Forster A. Patient evaluation and comparison of the recovery profile between propofol and thiopentone as induction agents in day surgery. Anaesth Intensive Care 1998;26:156–61.

[3] Whitwam JG. Methohexitone. Br J Anaesth 1976;48:617–9.

[4] Sun R, Watcha MF, White PF, et al. A cost comparison of methohexital and propofol for ambulatory anesthesia. Anesth Analg 1999;89:311–6.

[5] Bührer M, Maître PO, Crevoisier C, Stanski DR. Electroencephalographic effects of benzodiazepines. II. Pharmacodynamic modeling of the electroencephalographic effects of midazolam and diazepam. Clin Pharmacol Ther 1990;48:555–67.

[6] Kanto J, Aaltonen L, Himberg JJ. Midazolam as an intravenous induction agent in the elderly. A clinical and pharmacokinetic study. Anesth Analg 1986;65:15–20.

[7] Fragen RJ, Caldwell NJ. Awakening characteristics following anesthesia induction with midazolam for short surgical procedures. Arzneimittelforschung 1981;31:2273–5.

[8] Ghouri AF, Ruiz MA, White PF. Effect of flumazenil on recovery after midazolam and propofol sedation. Anesthesiology 1994;81:333–9.

[9] Montravers P, Dureuil B, Desmonts JM. Effects of intravenous midazolam on upper airway resistances. Br J Anaesth 1992;68:27–31.

[10] Craig J, Cooper G, Sear JW. Recovery from day case anesthesia: comparison between methohexitone, althesin and etomidate. Br J Anaesth 1982;54:447–51.

[11] Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162–84.

[12] Helmers J, Adam A, Giezen J. Pain and myoclonus during induction with etomidate. A double-blind, controlled evaluation of the influence of droperidol and fentanyl. Acta Anaesthesiol Belg 1981;32:141–7.

[13] Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90:1502–16.

[14] McLeskey CH, Walawander CA, Nahrwold ML, et al. Adverse events in a multicenter phase IV study of propofol: evaluation by anesthesiologists and postanesthesia care unit nurses. Anesth Analg 1993;77:S3–9.

[15] Veselis RA, Reinsel RA, Feshchenko VA, Wronski M. The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. Anesthesiology 1997;87:734–6.

[16] Peacock JE, Lewis RP, Reilly CS, Nimmo WS. Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. Br J Anaesth 1990;65:346–52.

[17] Borgeat A. Subhypnotic doses of propofol possess direct antiemetic properties. Anesth Analg 1992;74:539–41.

[18] Joo HS, Perks WJ. Sevoflurane versus propofol for anesthetic induction: a meta-analysis. Anesth Analg 2000;91:213–9.

[19] Vuyk J, Hennis PJ, Burm AGL, et al. Comparison of midazolam and propofol in combination with alfentanil for total intravenous anesthesia. Anesth Analg 1990;71:645–50.

[20] Avramov MN, White PF. Use of alfentanil and propofol for outpatient monitored anesthesia care: determining the optimal dosing regimen. Anesth Analg 1997;85:566–72.

[21] Badrinath S, Avramov MN, Shadrick M, et al. The use of a ketamine-propofol combination during monitored anesthesia care. Anesth Analg 2000;90:858–62.

[22] Ausems ME, Vuyk J, Hug Jr CC, Stanski DR. Comparison of a computer-assisted infusion

versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 1988;68:851–61.
[23] Langevin S, Lessard MR, Trepanier CA, Baribault JP. Alfentanil causes less postoperative nausea and vomiting than equipotent doses of fentanyl or sufentanil in outpatients. Anesthesiology 1999; 91:1666–73.
[24] Sa Rego MM, Inagaki Y, White PF. Remifentanil administration during monitored anesthesia care: are intermittent boluses an effective alternative to a continuous infusion? Anesth Analg 1999;88:518–22.
[25] Grant IS, Nimmo WS, McNicol LR, Clements JA. Ketamine disposition in children and adults. Br J Anaesth 1983;55:1107–11.
[26] Idvall J, Ahlgren I, Aronsen KR, Stenberg P. Ketamine infusions: pharmacokinetics and clinical effects. Br J Anaesth 1979;51:1167–73.
[27] Mortero RF, Clark LD, Tolan MM, et al. The effects of small-dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. Anesth Analg 2001;92:1465–9.
[28] Suzuki M, Tsueda K, Lansing PS, et al. Small-dose ketamine enhances morphine-induced analgesia after outpatient surgery. Anesth Analg 1999;89:98–103.
[29] Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth 2002;88:659–68.
[30] Arellano RJ, Pole ML, Rafuse SE, et al. Omission of nitrous oxide from a propofol-based anesthetic does not affect the recovery of women undergoing outpatient gynecologic surgery. Anesthesiology 2000;93:332–9.
[31] Jevtovic-Todorovic V, Todorovic SM, Mennerick S, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med 1998;4:460–3.
[32] Gan TJ, Glass PS, Windsor A, et al. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. Anesthesiology 1997;87:808–15.
[33] van den Nieuwenhuyzen MC, Engbers FH, Vuyk J, Burm AG. Target-controlled infusion systems: role in anaesthesia and analgesia. Clin Pharmacokinet 2000;38:181–90.
[34] Passot S, Servin F, Allary R, et al. Target-controlled versus manually-controlled infusion of propofol for direct laryngoscopy and bronchoscopy. Anesth Analg 2002;94:1212–6.
[35] Doze VA, Westphal LM, White PF. Comparison of propofol with methohexital for outpatient anesthesia. Anesth Analg 1986;65:1189–95.
[36] White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. Anesthesiology 1982;56:119–36.
[37] Deng XM, Xiao WJ, Luo MP, et al. The use of midazolam and small-dose ketamine for sedation and analgesia during local anesthesia. Anesth Analg 2001;93:1174–7.
[38] White PF, Negus JB. Sedative infusions during local and regional anesthesia: a comparison of midazolam and propofol. J Clin Anesth 1991;3:32–9.
[39] Frey K, Sukhani R, Pawlowski J, et al. Propofol versus propofol-ketamine sedation for retrobulbar nerve block: comparison of sedation quality, intraocular pressure changes, and recovery profiles. Anesth Analg 1999;89:317–21.
[40] Taylor E, Ghouri AF, White PF. Midazolam in combination with propofol for sedation during local anesthesia. J Clin Anesth 1992;4:213–6.
[41] McClune S, McKay AC, Wright PM, et al. Synergistic interaction between midazolam and propofol. Br J Anaesth 1992;69:240–5.
[42] D'Honneur G, Rimaniol JM, el Sayed A, et al. Midazolam/propofol but not propofol alone reversibly depress the swallowing reflex. Acta Anaesthesiol Scand 1994;38:244–7.
[43] Tang J, Chen L, White PF, et al. Recovery profile, costs, and patient satisfaction with propofol and sevoflurane for fast-track office-based anesthesia. Anesthesiology 1999;91:253–61.
[44] Song D, Greilich NB, White PF, et al. Recovery profiles and costs of anesthesia for outpatient unilateral inguinal herniorrhaphy. Anesth Analg 2000;91:876–81.
[45] Mackenzie N, Grant IS. Propofol for intravenous sedation. Anaesthesia 1987;42:3–6.

[46] Newson C, Joshi GP, Victory R, White PF. Comparison of propofol administration techniques for sedation during monitored anesthesia care. Anesth Analg 1995;81:486–91.
[47] Ng J, Kong CF, Nyam D. Patient-controlled sedation with propofol for colonoscopy. Gastrointest Endosc 2001;54:8–13.
[48] Oei-Lim VL, Kalkman CJ, Makkes PC, Ooms WG. Patient-controlled versus anesthesiologist-controlled conscious sedation with propofol for dental treatment in anxious patients. Anesth Analg 1998;86:967–72.
[49] Henderson F, Absalom AR, Kenny GN. Patient-maintained propofol sedation: a follow up safety study using a modified system in volunteers. Anaesthesia 2002;57:387–90.
[50] Wakeling HG, Zimmerman JB, Howell S, Glass PS. Targeting effect compartment or central compartment concentration of propofol: what predicts loss of consciousness? Anesthesiology 1999;90:92–7.
[51] Ibrahim AE, Taraday JK, Kharasch ED. Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. Anesthesiology 2001;95:1151–9.
[52] Glass PSA, Bloom M, Kearse L, et al. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane and alfentanil in healthy volunteers. Anesthesiology 1997; 86:836–47.
[53] Yli-Hankala A, Vakkuri A, Annila P, Korttila K. EEG bispectral index monitoring in sevoflurane or propofol anaesthesia: analysis of direct costs and immediate recovery. Acta Anaesthesiol Scand 1999;43:545–9.
[54] Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. Anesth Analg 1999;88:1085–91.
[55] Chung F, Mezei G. Factors contributing to a prolonged stay after ambulatory surgery. Anesth Analg 1999;89:1352–9.
[56] Marcus JR, Tyrone JW, Few JW, et al. Optimization of conscious sedation in plastic surgery. Plast Reconstr Surg 1999;104:1338–45.
[57] Eriksson H, Korttila K. Recovery profile after desflurane with or without ondansetron compared with propofol in patients undergoing outpatient gynecological laparoscopy. Anesth Analg 1996; 82:533–8.
[58] Gan TJ, El-Molem H, Ray J, Glass PS. Patient-controlled antiemesis: a randomized, double-blind comparison of two doses of propofol versus placebo. Anesthesiology 1999;90:1564–70.
[59] Eger EI, White PF, Bogetz MS. Clinical and economic factors important to anaesthetic choice for day- case surgery. Pharmacoeconomics 2000;17:245–62.
[60] Shao X, Li H, White PF, Klein KW, et al. Bisulfite-containing propofol: is it a cost-effective alternative to diprivan for induction of anesthesia? Anesth Analg 2000;91:871–5.
[61] Pain L, Oberling P, Sandner G, Di Scala G. Effect of propofol on affective state as assessed by place conditioning paradigm in rats. Anesthesiology 1996;85:121–8.
[62] D'Haese J, Camu F, Dekeyzer PJ, D'Haenen HA. Propofol and methohexitone anaesthesia: effects on the profile of mood state. Eur J Anaesthesiol 1994;11:359–63.
[63] Kazama T, Ikeda K, Morita K, et al. Comparison of the effect-site k(e0)s of propofol for blood pressure and EEG bispectral index in elderly and younger patients. Anesthesiology 1999;90: 1517–27.
[64] Kazama T, Takeuchi K, Ikeda K, et al. Optimal propofol plasma concentration during upper gastrointestinal endoscopy in young, middle-aged, and elderly patients. Anesthesiology 2000;93: 662–9.
[65] Juvin P, Vadam C, Malek L, et al. Postoperative recovery after desflurane, propofol, or isoflurane anesthesia among morbidly obese patients: a prospective, randomized study. Anesth Analg 2000; 91:714–9.
[66] Mangar D, Holak EJ. Tourniquet at 50 mm Hg followed by intravenous lidocaine diminishes hand pain associated with propofol injection. Anesth Analg 1992;74:250–2.
[67] Johnson RA, Harper NJN, Chadwick S, Vohra A. Pain on injection of propofol: methods of alleviation. Anaesthesia 1990;45:439–42.

[68] Gehan G, Karoubi P, Quinet F, et al. Optimal dose of lidocaine for preventing pain on injection of propofol. Br J Anaesth 1991;66:324–6.
[69] Boldt J, Jaun N, Kumle B, et al. Economic considerations of the use of new anesthetics: a comparison of propofol, sevoflurane, desflurane, and isoflurane. Anesth Analg 1998;86: 504–9.
[70] Tang J, Chen L, White PF, et al. Use of propofol for office-based anesthesia: effect of nitrous oxide on recovery profile. J Clin Anesth 1999;11:226–30.