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Review

Total intravenous anaesthesia in day case surgery

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The use of total intravenous anaesthesia (TIVA) has increased in the UK over the past few years, and in some units 30% of anaesthetics are administered this way¹. The true value of any anaesthetic technique should be evaluated by examining the various advantages or disadvantages in terms of cost, pharmacological profile and ease of use of the technique in everyday practice. Table 1 lists the agents currently available for TIVA in a day case setting and this review will compare these agents with one another, in addition to making a direct comparison with the volatile anaesthetic agents. Finally, the recovery profile of these agents will be considered and an overview of the advantages and disadvantages of TIVA will then be formulated.

Intravenous anaesthetic agents – induction, maintenance and recovery aspects

Day case anaesthesia primarily concerns the recovery of patients to street fitness, and it should be the goal of anaesthetists to provide quality recovery. The recovery aspects of the commonly used induction agents will be compared, before examining their role in the maintenance of anaesthesia. Other important factors such as premedication and analgesic regimes may also have a significant effect on recovery and perioperative complications.

Intravenous induction agents

In the UK propofol is the most popular day case anaesthetic induction agent, but the place of other agents such as thiopentone, methohexitone, and etomidate should be

considered. Few studies have compared these agents with ketamine in a day unit setting. Comparison of induction half-lives may tempt anaesthetists to draw conclusions concerning recovery performance, but because a large proportion of the induction action of these agents is related to redistribution and not to metabolism, this may not be an easy comparison to make.

When propofol is compared to other induction agents for short operative procedures there is, indeed, evidence that there is no delay in recovery or alteration in post-operative co-ordination². One series has shown that discharge time was unrelated to the induction agent used, including results with thiopentone³. However psychomotor impairment may occur for up to 5 h following thiopentone compared with 1 h with propofol^{4,5}. This is supported by further work claiming a significant difference in sitting up and street fitness times, together with a reduced incidence of postoperative nausea and vomiting (PONV) in the propofol group⁶. Furthermore propofol compares favourably with methohexitone, again producing a faster recovery profile, although at 4 h no differences between thiopentone, methohexitone or propofol were observed⁷. It has also been recorded that propofol patients may display a better sense of wellbeing compared to other agents, but whether this is attributable directly to the agent itself or to the lack of PONV or barbiturate 'hangover' remains unclear⁸.

When propofol was compared to thiopentone in children it was noted that in children under 5 yr only the

Table 1. Agents suitable for total intravenous anaesthesia (with half-lives)

Propofol	3-4.8 h
Methohexitone	4 h
Thiopentone	11.5 h
Etomidate	75 min
Ketamine	2.5 h

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time to spontaneous eye opening was shorter after propofol. However in children aged 5–11 yr, times of spontaneous eye opening, name giving and discharge were shorter after propofol induction. These results showed that propofol hastened early recovery in children undergoing day case surgery, but earlier discharge occurred only in older children⁹.

Intravenous agents for maintenance

The recovery aspects of intravenous agents when used for anaesthesia or sedation will now be examined. Various studies have looked at intravenous agents in comparison with each other, but perhaps the most interesting topical debate arises when the recovery aspects of intravenous anaesthetic agents are compared to their volatile anaesthetic counterparts.

When propofol, methohexitone and midazolam were compared to propofol for sedation, the vigilance and concentration of the subjects were worse in the midazolam and methohexitone groups¹⁰. There is, however, evidence that premedication with midazolam before sedation with propofol may increase anxiolysis and sedation without affecting discharge from the recovery room¹¹. Indeed the use of midazolam premedication before general anaesthesia does not appear to alter the patients' ability to reach street fitness times in the day surgery environment¹².

When propofol and thiopentone were compared as maintenance agents for brief surgical procedures, the recovery in both memory and psychomotor performance was superior in the propofol group. The subjective feelings of tiredness, drowsiness and alertness were significantly worse in the thiopentone group even at 24 h¹³. This is not surprising owing to the different pharmacology of these agents and the known potential for accumulation with thiopentone.

Methohexitone, etomidate and althesin have been studied in day surgery, and it was found that recovery from methohexitone appeared to be the fastest. It was interesting to note that in this study it was found to be too difficult to produce good operating conditions with etomidate and this agent yielded the highest complication rate¹⁴. Finally, a series comparing propofol and methohexitone for outpatient anaesthesia found that propofol produced fewer side effects, e.g. hiccough and PONV, and the recovery times for awakening and ambulation were shorter in the propofol group¹⁵.

Throughout the literature review the common theme when comparing the intravenous agents against one another for maintenance in day surgery was not a question of recovery. Etomidate has important side-effects such as a 30% PONV rate, a high incidence of pain on injection with venous sequelae, a potent suppression of cortisol synthesis and difficulty in producing good operating conditions. Ketamine may be associated with postoperative hallucinations and emergence phenomena, and methohexitone has a high incidence of airway complications. Thiopentone, used for induction, may produce similar discharge times to propofol but barbi-

urate 'hangover' effects still remain. It would appear that propofol provides a superior recovery profile as shown by psychomotor tests, but although discharge times are similar, perhaps a better recovery quality tilts the balance towards the use of propofol.

A comparison of induction agents against one another indicated that the incidence of side-effects and complications perioperatively was lower when propofol was used. This ought to be an important consideration for all anaesthetists discharging day cases early into the community.

Recovery aspects of TIVA compared to volatile anaesthetic maintenance

The important question in day case anaesthesia today is whether to advise the use of TIVA with propofol, or the continued use of established or newer volatile anaesthetic agents. Interestingly, when propofol TIVA is compared to an anaesthetic comprising thiopentone or halothane induction coupled with halothane maintenance in children, the TIVA group produced the slowest recovery and there was no difference in recovery if thiopentone was used for induction compared to halothane¹⁶. However, when TIVA recovery was compared to an enflurane anaesthetic, the immediate recovery was shorter in the propofol group if thiopentone was used for induction. There would again appear to be an increase in wellbeing noted in the TIVA group, but the time to reach discharge criteria was often the same in both groups (except in Miller¹⁷). In these series there was an increased incidence of PONV in the enflurane group¹⁸.

When propofol TIVA was compared to isoflurane maintenance, conflicting papers revealed only minor differences in psychomotor test results at up to 1 hr^{19–22}. Following minor gynaecological surgery there were no psychometric test differences after 60 min or fit-for-discharge times. Again a higher incidence of PONV was noted in the isoflurane groups. If isoflurane is used to supplement TIVA immediate recovery was slower and the incidence of PONV was higher, although discharge times remained the same²³. However, when propofol was used to finish major cases using isoflurane, immediate recovery tended to be faster but the incidence of PONV was still higher than with TIVA alone²⁴. In a direct comparison between TIVA and isoflurane in major cases, extubation times were longer in the TIVA groups but recovery times appeared to be similar²⁵.

Newer agents such as sevoflurane may offer smooth inhalational characteristics and a 30% faster immediate recovery when compared to propofol. However, the incidence of PONV was higher, and in the intermediate phase of recovery awareness, confusion and co-ordination were similar²⁶. Desflurane produced a high incidence of airway complications when used for an inhalational induction, but did offer rapid recovery even after exceptionally long surgery and minimal metabolism. Desflurane was faster than propofol in the early phase of recovery but by 2 h psychomotor test times were equal. Perhaps of more relevance were the equal 'street fitness' times, but the incidence of

PONV was higher in the desflurane group (50%) compared with the propofol group (12%)²⁷⁻³⁰.

After all the evidence produced in this review article the debate is still open as to which anaesthetic agent should be used for day case anaesthesia. Although desflurane produces the most consistent early recovery, there is little evidence to support significant variations in the time to street fitness with any particular anaesthetic technique. Indeed there was a remarkable similarity with many recovery tests at 60-120 min following the cessation of general anaesthesia. However, there is no doubt that PONV is associated with volatile anaesthesia and therefore propofol TIVA deserves to be seriously considered for maintenance, based on its production of quality recovery with minimal perioperative sequelae.

Important considerations for TIVA

So far in this review the intraoperative and recovery performances offered by propofol produces the best pharmacological profile for use in TIVA. However, other issues need to be considered, especially if propofol TIVA is to be recommended.

Pollution

One of the main advantages of TIVA is the absence of operating theatre pollution. Potential atmospheric environmental effects exist with volatile anaesthetic agents and hepatotoxicity may also occur with some agents. Nitrous oxide has been used for over a century for its analgesic and minimal alveolar concentration (MAC) sparing effects but potential hazards may arise. It may cause expansion of closed gas spaces, e.g. air in the bowel, pleural cavity or middle ear, and this may directly affect anaesthesia or surgery. Nitrous oxide disturbs vitamin B12 synthesis through inhibition of the enzyme methionine synthetase and may interface with folic acid metabolism and the production of DNA³¹; prolonged exposure over 6 h may produce a megaloblastic anaemia. In addition, a condition similar to subacute degeneration of the spinal cord has been reported in dentists and in individuals addicted to nitrous oxide. Teratogenic effects from prolonged nitrous oxide exposure have been observed in pregnant rats³², although there is no evidence that similar effects occur in man. Nitrous oxide may therefore be harmful both to patients and staff through occupational exposure either during anaesthesia, especially paediatric anaesthesia, or during the recovery period. Perhaps if strict guidelines, as set down by the Control of Substances Hazardous to Health (COSHH), were to be vigorously enforced the continuing use of nitrous oxide may be limited.

Toxicity and repeated anaesthetic agent exposure

Although there may be a lack of hepatotoxicity associated with TIVA, doubts remain as to the safety of

propofol sedation in children. Published evidence points to five deaths of children from respiratory tract infections following sedation with propofol³³. Correspondence indicated that the lipid solvent may be implicated if propofol was given long term, and suggested that lipid given without glucose would explain acidosis, ketosis and death in small children. Propofol is unlicensed for the anaesthesia of children under 3 yr but this may be explained on the grounds of liability vs. profit margins for the manufacturer. Manufacturers will not carry out research on the use of drugs in the very young, and the older anaesthetic agents now used for infants have been licensed retrospectively. Some paediatric anaesthetists do use propofol for young children and neonates, and work with infants has shown a larger volume of distribution and increased clearance with a resultant increase in requirements³⁴. As is the case with all drugs, patients may occasionally experience allergic reactions to propofol or the egg phosphatide and soya bean oil solvent. Perhaps in this section on toxicity it should be remembered that propofol TIVA is a safe method of anaesthesia for susceptible malignant hyperpyrexia patients.

Awareness and depth of anaesthesia

Awareness is a major fear among anaesthetists, and reports divide the subject into true unconsciousness, awareness with information processing but no recall and fully conscious awareness. Modern vaporisers may alarm when nearly empty, and with the increased use of vapour monitoring during anaesthesia, episodes of awareness should be avoided. With TIVA reliable venous access is vital, especially with paralysed patients, and to date there is no monitor relating plasma levels of drug to the depth of anaesthesia. Individual propofol ranges are extremely wide compared to the standard deviations surrounding the MAC₅₀ and MAC₉₅ (minimum alveolar concentration) of volatile gases. Experience indicates that there is more involuntary movement during surgery with TIVA, but it is easy to increase the depth of anaesthesia rapidly. Cases of awareness with TIVA³⁵ often relate to inexperienced use, failure of drug delivery systems, or when unexpectedly high doses are required³⁶. Auditory perception may occur during adequate general anaesthesia³⁷ but so far some studies have found no evidence of recall with propofol^{38,39}. As with any anaesthetic technique, the experience and skill of the anaesthetist is probably the most important factor in avoiding awareness. It is therefore important that all anaesthetists employing TIVA techniques should undergo suitable training.

PONV

There is increasing evidence that TIVA is associated with a decrease in PONV⁴⁰⁻⁴³, although a few studies have found no difference⁴⁴. Patient factors contribute to PONV, with adult females and children being more susceptible, especially in those patients with a past history of PONV or motion sickness. Gynaecological, eye or middle ear surgery are also known to increase the

Table 2. Properties of an 'ideal' total intravenous anaesthetic agent

1. Rapid onset (requires high lipid solubility and un-ionized at blood pH to allow penetration of blood-brain barrier)
2. Rapid recovery (rapid redistribution and metabolism with no accumulation)
3. Analgesia at subanaesthetic concentrations
4. Minimal cardiovascular and respiratory depression
5. No emetic effects
6. No excitatory phenomena (e.g. coughing, hiccough, involuntary movements) on induction
7. No emergence phenomena (e.g. nightmares)
8. No epileptiform activity
9. No interaction with neuromuscular blocking drugs
10. No pain on injection, venous sequelae and safe if injected inadvertently into an artery
11. No toxic effects on other organs with no stimulation of porphyria
12. No hypersensitivity reactions or release of histamine
13. Water-soluble formulation with long shelf-life

incidence of PONV. Finally, pharmacological causes commonly include the use of volatile anaesthetic agents and some intravenous agents, e.g. etomidate and the opioids⁴⁵. The precise role of nitrous oxide in the incidence of PONV remains unclear.

Respiratory advantages

General anaesthesia may cause postoperative hypoxaemia due to atelectasis, alterations in the functional residual capacity and shunting. The use of air/oxygen mixtures provide 'nitrogen splinting' as an aid to avoid atelectasis, and the use of volatile anaesthetic gases abolishes the hypoxic pulmonary vasoconstriction reflex thus increasing the possibility of postoperative hypoxaemia. In addition, TIVA also allows air/oxygen techniques for procedures such as bronchoscopy, without the associated pollution and concerns regarding the accurate delivery of anaesthetic gases.

Cost

One of the advantages of day surgery is the potential for cost savings. When analysing the cost of a procedure, several factors have to be taken into account including the individual costs of agents, equipment and disposables for both surgery and the anaesthetic, together with staff and general running costs. Hidden costs in day surgery may result from admissions caused by poor recovery or uncontrolled PONV and the resultant overnight hospital stay. Significant improvements in early recovery may save on nursing costs and a better overall quality of recovery could save on admission costs. These facts may produce actual overall savings, but it is difficult to cost the 'quality' of recovery. One fact remains clear, propofol is at least four times more expensive in real terms for maintenance, even compared to new agents such as desflurane⁴⁶. However, the drug costs for a procedure are a small percentage of the total overall costs and therefore budgeting should perhaps be patient centred and not drug oriented.

Accumulation

When concentrating on TIVA alone one study, conducted with 14 882 patients, looked at the reasons for

prolonged awakening, defined as >15 min from end of anaesthesia, and found an incidence of 6.8% with a mean wake-up time of 7.2 min. The factors associated with this were males, endotracheal intubation, age >65, abdominal surgery, infusion > bolus, the addition of isoflurane and finally a total dose of propofol >8 mg kg⁻¹⁴⁷.

Epileptiform activity

The true proconvulsant or anticonvulsant activity of propofol remains controversial. Clearly propofol does have anticonvulsant activity⁴⁸ and has been used as an effective treatment for status epilepticus as well as being used on mentally handicapped patients with treated epilepsy, when it produced no epileptiform activity^{49, 50}. Some studies have found no detectable difference in EEG activity in patients with complex partial epilepsy⁵¹ whereas other reports state that propofol is safe to use in patients with epilepsy⁵². Almost all anaesthetic agents have been associated with 'epileptic' EEG changes⁵³ and there are many case reports of 'epileptic' activity with propofol⁵⁴, especially with the rapid reversal of plasma levels after bolus injection as opposed to the slower alterations in plasma concentration associated with the reversal from infusions. The precise nature of the epileptic activity and accompanying tonic-clonic movements are often observer dependent⁵⁵, but it is clear that there is still no definite evidence as to the proconvulsant/anticonvulsant activity of propofol.

The future of TIVA in day case surgery

Propofol TIVA has a pharmacological profile which has advantages when used for neurosurgery, cardiac surgery, some thoracic procedures, but especially in day

Table 3. Advantages of propofol total intravenous anaesthesia

1. No pollution
2. No toxicity after repeated exposure
3. Easy to increase depth of anaesthesia
4. Decreased PONV
5. Safe in malignant hyperpyrexia
6. Respiratory parameters
7. Intracranial pressure/neuroprotection
8. Possible superior recovery profile

Table 4. Disadvantages of propofol total intravenous anaesthesia

1. Cost
2. Accumulation
3. Awareness
4. Allergies
5. Epileptiform activity
6. Not for children <3 yr
7. Adverse publicity
8. Variable and unpredictable dosage
9. Higher incidence of movement during surgery
10. Complex pumps
11. Need for reliable venous access

case anaesthesia where the quality of recovery is vital. The use of short-acting opioids with TIVA, e.g. fentanyl, alfentanil or remifentanil appears to be a cornerstone of the technique. Computerized delivery systems may allow easier administration, and continued research into new short-acting opioids may yield further fine tuning of this technique.

Propofol TIVA offers anaesthetists an opportunity to increase their patients' feelings of wellbeing. In the current medical climate patient satisfaction plays an increasing role, and the use of a TIVA technique may reduce PONV, thereby preventing inpatient hospital admissions from busy day surgical units. In future, anaesthetists will have to consider seriously their day case anaesthetic techniques, and they may discover that TIVA techniques provide a real alternative to the use of the more conventional volatile anaesthetic agents.

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