

Total Intravenous Anaesthesia Using 3-in-1 Mixture of Propofol, Alfentanil and Mivacurium

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Abstract

Introduction: To avoid errors and confusion associated with 3 separate infusions, we conducted a feasibility study of total intravenous anaesthesia (TIVA) using 1 electrically-powered syringe pump to deliver a 3-in-1 mixture containing fixed proportions of propofol, alfentanil and mivacurium. **Materials and Methods:** The 3-in-1 mixture was obtained by mixing 200 mg propofol, 1 mg alfentanil, 20 mg mivacurium, and making up to 40 mL with 5% dextrose solution. Electrical zone sensing sizer and light microscopy were used to compare emulsion instability of the 3-in-1 with control mixtures. In 50 ASA 1 patients, bolus infusions of 0.4 mL of the 3-in-1 mixture per kg body weight were given for induction of anaesthesia. All patients were subsequently intubated and ventilated with air-oxygen mixtures. Anaesthesia was maintained using a continuous infusion of the 3-in-1 mixture with the infusion rate titrated to satisfactory clinical response. Intravenous morphine 0.1 mg/kg was given for intra- and postoperative analgesia. Residual neuromuscular blockade was reversed using glycopyrronium and neostigmine at the end of surgery. **Results:** The 3-in-1 mixtures remained stable for up to 5 hours after preparation. Induction and maintenance of anaesthesia were smooth, intubation conditions satisfactory, and intraoperative haemodynamic changes acceptable. Recovery from anaesthesia and neuromuscular blockade was rapid. There were no major intra- or immediate postoperative complications. **Conclusions:** The 3-in-1 mixtures remained stable for up to 5 hours after preparation. It may be feasible to provide TIVA using the 3-in-1 mixture for induction and maintenance of anaesthesia in ASA 1 patients.

Ann Acad Med Singapore 2000; 29:182-8

Key words: Analgesia, Hypnosis, Muscle relaxation, Single infusion

Introduction

Total intravenous anaesthesia (TIVA) implies achieving the 3 components of anaesthesia (hypnosis, analgesia and muscle relaxation) by the administration of anaesthetics via the intravenous (IV) route without the use of inhalation agents.^{1,2} The main advantages of TIVA are avoidance of both volatile agent and nitrous oxide exposure and reduction of atmospheric pollution. Although TIVA employing separate infusions of hypnotic, analgesic and muscle relaxant drugs administered via 3 separate syringe or multichannel pumps is popular among some anaesthetists,³ the use of 3 syringe pumps in 1 patient has its disadvantages. Firstly, 3 syringe pumps may not always be available; secondly, using 3 syringe pumps with separate infusion rates in 1 patient may be confusing; and finally, more

syringe pumps may lead to greater chances of operator, technical or mechanical errors. To minimise these disadvantages, we therefore conducted a study to investigate the feasibility of providing TIVA using only 1 syringe pump to deliver a 3-in-1 mixture that contained fixed proportions of propofol, alfentanil, and mivacurium. The mixture was delivered at variable rates and titrated to the patient's clinical response. Propofol, alfentanil and mivacurium were selected because of their similar pharmacokinetic profile, with predictable onset time, rapid and good clinical recovery, minimal cumulative effects, and metabolism to inactive metabolites.^{2,4-6} In addition, we also investigated the stability of the propofol-alfentanil-mivacurium mixture *in vitro*, because commercially available propofol is formulated in an oil-in-water emulsion.⁴

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Materials and Methods

This study was approved by the hospital Ethics Committee and written consent was obtained from all patients prior to anaesthesia.

Test of Propofol-alfentanil-mivacurium Mixture Stability

The number of oil globules per mL greater than 2 µm was compared between the 3-in-1 mixture and a control mixture. Under aseptic conditions, the 3-in-1 mixtures were prepared using 1% propofol (Diprivan®, Zeneca Ltd, Macclesfield, Cheshire, UK):500 µg/mL alfentanil (Rapifen®, Janssen Pharmaceutica, Beerse, Belgium):2 mg/mL mivacurium (Mivacron®, GlaxoWellcome Pharmaceutical Ltd, London, UK):5% dextrose solution in a volume ratio of 10:1:5:4. The control mixtures were similarly prepared using 1% propofol and 5% dextrose solution in a volume ratio of 1:1. The size of the oil globules was measured using the electrical zone sensing sizer (Coulter, TA11, UK). A 1 mL sample from each of the 3-in-1 and control mixtures had to be separately diluted with 0.85% sodium chloride solution and mixed thoroughly to give 100 mL. The use of 0.85% sodium chloride solution to dilute these mixtures was necessary because it provided a conductive diluent to enable particle sizing at a relatively low concentration by the electrical zone sensing sizer. From these diluted mixtures, 0.05 mL of each mixture was drawn through a 50 µm aperture tube of sizer and subjected to size analysis repeatedly at 1, 2 and 5 hours after preparation at room temperature. A total of 5 replicates from 5 samples of the 3-in-1 and control mixtures were analysed and the results averaged. The mixtures were also examined under light microscope at various time intervals for up to 5 hours to look for large (>20 µm) oil globules, precipitation and crystal formation. The pH values of each individual anaesthetic solution and the 3-in-1 mixture were also determined (Hanna, HI 8418, Singapore).

Clinical Study

American Society of Anesthesiologists (ASA) class 1 patients who were scheduled for elective upper or lower limb, body surface or body cavity surgery were selected for the study. Pregnant patients, patients aged less than 16 or more than 50 years, and those scheduled for craniotomy or surgical procedures that were likely to be associated with intraoperative red blood cell transfusion were excluded. We also excluded patients with difficult airways and surgeries lasting shorter than 30 minutes. All patients were seen preoperatively and fasted overnight. They were given oral midazolam or diazepam the night before and 1 hour preoperatively as premedication only if they expressed anxiety during the preoperative interview. In the induction room, a vein on the dorsum of the hand or forearm was cannulated with a double-lumen peripheral IV catheter

(Twin-Cath®, Arrow International, Reading, PA, USA) under local anaesthesia. The distal lumen was designated for IV fluid and drug administration, and the proximal lumen for infusion of the 3-in-1 mixture. Each patient was asked to identify himself or herself with his or her National Registration Identity Card (NRIC) number (a 7-digit personal number) before general anaesthesia. Monitoring during anaesthesia included the electrocardiogram, pulse oximetry, capnography, and intermittent non-invasive blood pressure. We also monitored the neuromuscular function by stimulating the ulnar nerve via cutaneous electrodes placed at the wrist with supramaximal stimuli in a train-of-four pattern.

The 3-in-1 mixture was prepared immediately prior to induction by mixing 20 mL 1% propofol (200 mg), 2 mL alfentanil (1.0 mg) and 10 mL mivacurium (20 mg), and making up to 40 mL with 5% dextrose solution. The resulting final concentrations of propofol, alfentanil and mivacurium were thus 5 mg/mL, 25 µg/mL, and 0.5 mg/mL, respectively. An electrically-powered syringe pump (Graseby 3400, Graseby Medical Ltd, Watford, UK) was used to deliver the 3-in-1 mixture for induction and maintenance of anaesthesia. Five minutes before induction, 5 µg/kg glycopyrronium was administered intravenously to attenuate bradycardia and hypotension that might be associated with propofol and alfentanil induction,⁷ and 20 mg lignocaine was also administered intravenously immediately before induction to reduce the pain associated with propofol injection.⁸ Intravenous induction of anaesthesia was achieved using 0.4 mL of the 3-in-1 mixture per kg body weight (equivalent to 2 mg/kg propofol, 10 µg/kg alfentanil and 0.2 mg/kg mivacurium) administered at a rate of 10 mL/kg/h. The induction thus took an average of 2 to 3 minutes to complete, during which time any upper limb pain or excitatory phenomenon were recorded.

All patients were intubated about 1 minute after completing the induction dose. The intubating conditions in each patient were assessed according to 3 criteria:⁹

1) Jaw relaxation:

- 1 = full relaxation, laryngoscopy easy;
- 2 = partial relaxation, laryngoscopy possible;
- 3 = no relaxation, laryngoscopy not possible.

2) Vocal cord position and movement:

- 1 = vocal cords abducted, no movement on laryngoscopy;
- 2 = vocal cords abducted, little movements noted during laryngoscopy, intubation possible;
- 3 = vocal cords adducted or moving during laryngoscopy, intubation impossible.

3) Coughing on intubation:

- 1 = no coughing;
- 2 = minimal coughing;
- 3 = vigorous coughing.

Immediately after induction, the maintenance infusion rate was initially set at 2 mL/kg/h for the first 10 to 15 minutes followed by 1 mL/kg/h. At these rates of 1 to 2 mL/kg/h of the 3-in-1 mixture, the patients received 5 to 10 mg/kg/h propofol, 25 to 50 µg/kg/h alfentanil, and 0.5 to 1 mg/kg/h mivacurium. The aim was to attenuate any stress response associated with surgery while at the same time maintaining adequate neuromuscular block (0-1 twitch response with train-of-four stimulation). If inadequate anaesthetic depth or muscle relaxation was suspected clinically, a 5 mL bolus of the 3-in-1 mixture (rescue solution) was administered followed by a 10% stepwise increase in the infusion rate. However, if the mean blood pressure decreased by more than 30% of the pre-induction value, the patient would be treated with a rapid IV infusion of 250 mL 0.9% sodium chloride solution in addition to a 10% stepwise decrease in the infusion rate. Bradycardia (defined as a heart rate of less than 50 beats per minute) was treated with IV 0.6 mg atropine. All patients were ventilated with air-oxygen mixtures to maintain end-tidal carbon dioxide at 30 to 35 mmHg. Additional intraoperative pain relief was achieved using IV 0.1 mg/kg morphine for all patients. Intravenous crystalloid solutions were given according to the estimated perioperative fluid requirement of each patient, and no regional anaesthetic or antiemetic was employed in this study.

Five minutes before the expected time of completion of surgery (usually during surgical wound closure), the infusion rate of the 3-in-1 mixture was reduced to 0.5 mL/kg/h. The infusion was stopped at the end of surgery and residual neuromuscular block was reversed using 10 µg/kg glycopyrronium and 50 µg/kg neostigmine, both given intravenously. Each patient was extubated when:

- 1) adequate tidal volume and respiratory rate were observed,
- 2) consciousness had recovered (able to obey simple

commands), and

- 3) adequate muscle power had returned with good gag and cough reflexes.

Upon transfer to the recovery area, all patients were monitored with pulse oximeters and non-invasive blood pressure monitoring devices. The ability to recall NRIC number and muscle power (sustained head lift for more than 5 seconds) were assessed, and the incidence of nausea, vomiting or other complications in the recovery room recorded and treated if necessary. Additional pain relief in the recovery room was achieved using further doses of parenteral morphine. When the patients were fully awake and before their discharge to the wards, they were interviewed regarding recall of any intraoperative event during anaesthesia and acceptability of our anaesthetic technique.

All results were expressed as mean $\pm$ standard deviation (range), number or as a percentage. Repeated measures analysis of variance over time was used to compare the particle size number between the 3-in-1 and control mixtures. A *P* value of <0.05 was considered statistically significant.

Results

Tests of Stability of the 3-in-1 Mixture

Table I shows the results of particle size analysis of the 3-in-1 and control mixtures (5 samples each). There was no statistically significant difference in the number of oil globules per mL greater than 2 µm between the 3-in-1 and control mixtures over time (ANOVA, *P* = 0.23). In all the samples studied, there were very few globules larger than 5 µm. Microscopic examination of the 3-in-1 mixture did not reveal any large size (>20 µm) oil globules, or was there any evidence of precipitation or crystal formation. The mean pH values were 4.7 (range 4.66 to 4.79) for mivacurium, 6.3 (range 6.00 to 6.39) for alfentanil, and 7.6 (range 7.50 to 7.70) for propofol, while the 3-in-1 mixture had an intermediate pH of 6.8 (range 6.70 to 7.20).

TABLE I: AVERAGE NUMBER OF GLOBULES PER mL GREATER THAN 2 µm IN THE 3-IN-1 AND CONTROL MIXTURES OVER TIME (see text for details)

Sample	3-in-1 mixture			Control mixture		
	Average number of globules per mL			Average number of globules per mL		
	1 h	2 h	5 h	1 h	2 h	5 h
A (n = 5)	4.7 x 10 ⁷	5.1 x 10 ⁷	4.8 x 10 ⁷	4.2 x 10 ⁷	5.7 x 10 ⁷	4.6 x 10 ⁷
B (n = 5)	6.9 x 10 ⁷	6.7 x 10 ⁷	6.9 x 10 ⁷	4.7 x 10 ⁷	4.1 x 10 ⁷	3.9 x 10 ⁷
C (n = 5)	3.7 x 10 ⁷	4.0 x 10 ⁷	7.0 x 10 ⁷	4.1 x 10 ⁷	4.6 x 10 ⁷	5.7 x 10 ⁷
D (n = 5)	7.2 x 10 ⁷	4.4 x 10 ⁷	6.1 x 10 ⁷	5.0 x 10 ⁷	4.7 x 10 ⁷	4.5 x 10 ⁷
E (n = 5)	5.1 x 10 ⁷	6.2 x 10 ⁷	5.1 x 10 ⁷	4.8 x 10 ⁷	6.1 x 10 ⁷	4.7 x 10 ⁷

n = number of replicates examined in each sample

TABLE II: THE TYPES OF SURGERY PERFORMED USING THE 3-IN-1 MIXTURE OF PROPOFOL, ALFENTANIL AND MIVACURIUM FOR ANAESTHESIA

Operation	No. of patients
Upper or lower limb surgery	10
Laparotomy	8
Laparoscopic surgery	9
Other body surface surgery	20
Thoracoscopic surgery	3
Total	50

Clinical Trial

Fifty consecutive ASA 1 patients were admitted into the study. There were 22 male and 28 female patients. The mean age was 31.1 ± 7.9 years (range 20 to 49 years) and the weight 61.2 ± 11.9 kg (range 41 to 90 kg). The types of surgical procedures performed are shown in Table II.

Anaesthesia

Although only 13 patients (9 males and 4 females) received oral premedication, induction of anaesthesia was smooth in all patients with no excitatory phenomenon noted. Twenty-three patients (46%) complained of pain on injection of the 3-in-1 mixture but all indicated that the pain was tolerable. Intubating conditions were satisfactory: the jaws were fully relaxed (score 1) and the vocal cords abducted without movement (score 1) during laryngoscopy in all patients; only 10 patients (20%) coughed during intubation but the coughing was mild (score 2). Although the time taken from induction to successful intubation was 4.4 ± 1.0 minutes (range 3 to 7 minutes), the delay in intubation was not due to poor intubating conditions but to second intubation attempts because of a difficult airway in some patients. The time taken from induction to surgical incision was 16.9 ± 6.6 minutes (range 5 to 32 minutes), the duration of anaesthesia was 85.5 ± 32.8 minutes (range 39 to 160 minutes) while that of surgery was 68.5 ± 29.7 minutes (range 30 to 140 minutes). The total volume of the 3-in-1 mixture administered for anaesthesia was 115.7 ± 34.8 mL (range 50 to 194 mL). Thirty-two patients (64%) were administered a total of 64 doses of rescue solutions, of which 25 doses were given for inadequate muscle relaxation while the rest were given for signs of light anaesthesia or inadequate analgesia.

Cardiovascular Effects

Figure 1 shows the intraoperative heart rates and Figure 2 the intraoperative systolic, mean and diastolic blood pressures. There was an initial increase in the heart rate peaking at about 108% of the pre-induction value. The systolic, mean and diastolic blood pressures began to decrease immediately after induction, and they reached

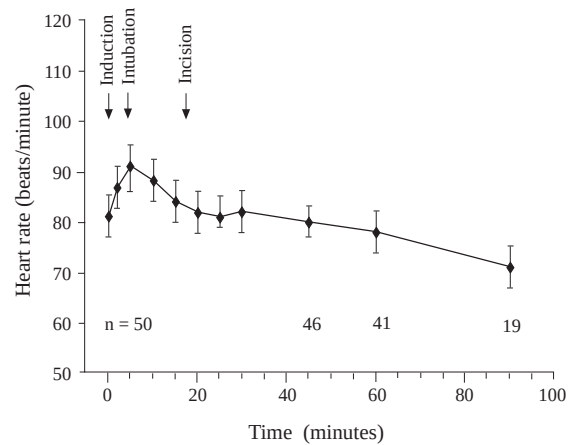


Fig. 1. Intraoperative heart rate changes (mean $\pm$ 2SE).

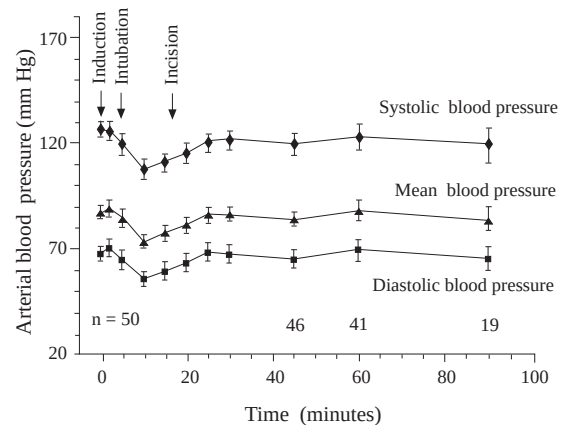


Fig. 2. Intraoperative blood pressure changes (mean $\pm$ 2SE).

their nadir 10 minutes after induction (23%, 12% and 8% reduction of the pre-induction values, respectively). Even with surgical incision and stimulation, the heart rate and blood pressure measurements returned to near pre-induction values 20 to 25 minutes after induction and remained stable thereafter. No patient required any treatment for systemic hypotension or for severe bradycardia.

Recovery

The time taken from cessation of infusion and reversal of neuromuscular blockade to extubation was 5.3 ± 1.8 minutes (range 2 to 11 minutes). Within 15 minutes of recovery room admission, all patients were awake, able to recall their NRIC numbers, and exhibited good muscle power by being able to sustain head lift for 5 seconds. Only 1 patient complained of nausea in the recovery room while none vomited. No other complication was observed in the recovery room. None of the patients had recall of any intraoperative event upon review in the recovery room and all said that they would be happy to have the same anaesthetic again.

Discussion

The idea of mixing different intravenous anaesthetics into a single solution is not new, the main aim being to make TIVA simple and thus avoiding errors and confusion associated with the use of 2 or more separate syringe pumps. Restall et al successfully demonstrated a simple TIVA technique using a mixture containing fixed proportions of ketamine, midazolam and vecuronium, while other investigators have also employed alfentanil-propofol mixtures.¹⁰⁻¹² In the present study, 50 ASA 1 patients undergoing various types of surgical procedures (Table II) were anaesthetised with TIVA using a mixture of propofol, alfentanil and mivacurium. These drugs were selected for the 3-in-1 mixture because of the following reasons:^{2,4-6}

1. Their onset of action are predictable, duration of action short, quality of recovery good, and the speed of clinical recovery rapid. In addition, their onset time, duration of action, and the speed of recovery are similar to each other.
2. There is little risk of cumulative effects after prolonged infusion of any of these drugs.
3. They are broken down in the body to inactive metabolites.

Although sufentanil has a shorter context-sensitive half-time and is therefore a more appropriate opioid to combine with propofol in TIVA lasting less than 6 to 8 hours,¹³ alfentanil was used in our study because of its short blood-biophase equilibration time (1 to 1.5 minutes) which allowed the anaesthetist to alter the blood (and brain) concentrations rapidly in response to different surgical or other noxious stimuli.^{1,4}

Commercially-available 1% propofol is formulated in an oil-in-water emulsion. The vehicle contains 10% soya bean oil, 1.2% purified egg phosphatide as emulsifier, 2.25% glycerol to adjust tonicity, and sodium hydroxide to adjust pH. Propofol emulsions can be further diluted using 5% dextrose solution before use if necessary.¹⁴ The phospholipid emulsifiers that are used in currently-available fat emulsions carry a negative surface charge that stabilises the emulsion. Factors that reduce the surface potential of the lipid phase destabilise the emulsion with the production of larger oil globules, which if greater than 6 µm in size may lead to embolisation and undesirable cardiorespiratory effects.^{15,16} Mixing 1 or more drugs with propofol may destabilize the emulsion in this way. Important factors to consider include the type and quantity of added monovalent or divalent cations (such as alfentanil and mivacurium) and changes in pH of the emulsion.^{15,16} We employed Coulter counter to provide an absolute count of particles of different sizes (0.8 to 20 µm).¹⁵ However, for concentrated solutions, errors could occur if 2 small particles passed through the pinhole together because the machine cannot distinguish them from a single large particle, or if dilution of emulsions with normal saline led to slow flocculation of the samples

in the instrument.^{15,16} Nevertheless comparison of the number of oil globules greater than 2 µm per mL in the 3-in-1 and control mixtures did not indicate emulsion destabilisation for up to 5 hours after mixing at room temperature (Table I), and there were very few globules larger than 5 µm. In addition, light microscopy could not detect any large oil globules (>20 µm) in our concentrated samples.¹⁵ Furthermore, alfentanil and mivacurium dissolved in the mixture without precipitation or crystal formation, and the pH values of the 3-in-1 mixtures (mean 6.8, range 6.7 to 7.2) were well within the range for maximal fat emulsion stability (pH 6.0 to 8.9).¹⁵

Preparation and administration of the 3-in-1 mixture were easy and simple. The IV induction dose and maintenance infusion rates for anaesthesia were calculated according to the patient's body weight and were adapted from previous studies using combined infusions of propofol and alfentanil, as well as from studies on mivacurium which highlighted the average maintenance dose required to achieve >90% suppression of the control twitch.^{2,17-20} In our study, using 0.4 mL/kg of the 3-in-1 mixture (equivalent to 2 mg/kg propofol, 10 µg/kg alfentanil and 0.2 mg/kg mivacurium) administered intravenously over 2 to 3 minutes, induction of anaesthesia was smooth and intubation conditions satisfactory. By adjusting the 3-in-1 mixture infusion rates between 1 and 2 mL/kg/h (i.e. 5 to 10 mg/kg/h propofol, 25 to 50 µg/kg/h alfentanil, and 0.5 to 1 mg/kg/h mivacurium) with additional 5 mL bolus doses given when required, adequate depth of anaesthesia for surgery was readily achieved according to standard clinical criteria.

One major concern with our technique is the effectiveness in providing adequate anaesthesia or analgesia when fixed proportions of an anaesthetic mixture is administered. Although inadequate depth of anaesthesia or analgesia could lead to signs of light anaesthesia (tachycardia, hypertension, sweating, or lacrimation), it was difficult to determine whether pain or awakening was the cause of light anaesthesia.¹⁷ Monk et al¹⁷ showed that supplementary doses of either alfentanil or propofol were equally effective in controlling signs of light anaesthesia during TIVA. We therefore administered rescue solutions containing propofol, alfentanil and mivacurium in the presence of light anaesthesia or inadequate muscle relaxation, followed by an increase in the infusion rate titrated to satisfactory clinical response. Although a high percentage of patients (64%) required rescue solutions, the number of rescue solutions needed per patient was not frequent.

Another major concern is the cardiovascular effects induced by propofol, alfentanil and mivacurium during induction. Propofol and alfentanil are vagotonic in nature when infused together,⁷ while mivacurium is histamine-releasing.⁶ Together they may lead to bradycardia and

hypotension during induction and it is therefore appropriate to employ a single IV dose of 5 µg/kg glycopyrronium 5 minutes before induction to attenuate these effects.^{2,7} In this study, the haemodynamic effects of the 3 anaesthetics were within acceptable limits. Although the initial tachycardia associated with glycopyrronium could make assessment of anaesthetic depth and analgesic requirements difficult, by 20 to 25 minutes after induction, most cardiovascular parameters had returned to pre-induction levels and remained stable for the duration of the surgery.

Many investigators consider administration of neostigmine for antagonism of residual mivacurium-induced neuromuscular block (or acceleration of spontaneous recovery) to be superfluous in the majority of clinical practice.²¹ In addition, neostigmine depresses the activity of plasma cholinesterase which metabolises mivacurium into inactive metabolites.^{22,23} It therefore may not accelerate the reversal of deep (1% to 2% of control twitch height) mivacurium-induced neuromuscular block.²³ On the contrary, other studies have demonstrated faster recovery with neostigmine reversal at moderate (10% to 25% of control twitch height) mivacurium-induced neuromuscular block.²³⁻²⁵ Although it was not our original aim to study neostigmine reversal in mivacurium-induced neuromuscular block, the experience in our institution favoured neostigmine reversal.²⁶ Furthermore, reduction in the infusion rate of the 3-in-1 mixture 5 minutes before reversal might have resulted in partial recovery of mivacurium-induced neuromuscular block, making neostigmine reversal appropriate at the end of surgery.

For all patients, recovery of consciousness (as defined by the ability to recall NRIC number) and muscle power (sustained head lift for 5 seconds) was demonstrated within 15 minutes of arrival in the recovery room. Quick recovery from the effects of the 3 anaesthetics was due to the fast termination of actions of propofol, alfentanil and mivacurium by virtue of their non-cumulative pharmacokinetic profile and rapid metabolism into inactive metabolites.⁴⁻⁶ Although over-dosage of any 1 of the 3 anaesthetics is always a theoretical possibility when employing prolonged TIVA using fixed proportions of propofol, alfentanil and mivacurium, we could not demonstrate any such effects in our study population.

Other advantages of TIVA using a 3-in-1 mixture include:

- 1) Low incidence of nausea and vomiting in the immediate postoperative period which was most likely related to propofol infusion.^{4,27}
- 2) Avoidance of both volatile agent and nitrous oxide exposure, thus reducing atmospheric pollution, avoiding the effects of chronic exposure of nitrous oxide on vitamin B 12 metabolism, and eliminating many factors

that can trigger malignant hyperthermia.

- 3) High acceptability among our patients.
- 4) When the infusion of the 3-in-1 mixture was interrupted due to operator, technical or mechanical error, the recovery of muscle movement might warn the anaesthetist about such a complication. However, there would be no such advantage if the infusion of muscle relaxant was administered separately while the infusion of hypnotic was accidentally interrupted; the patient would become awake and aware, yet still be paralysed.
- 5) Our preliminary results also demonstrated the absence of recall of any intraoperative event, although this did not represent the true incidence of awareness using TIVA with the 3-in-1 anaesthetic mixture because of our small study population.

On the other hand, there are some disadvantages associated with the use of this technique. This includes the need for controlled mechanical ventilation because of the neuromuscular block induced by mivacurium, which may aggravate the hypotension during induction. As well, the effective use of such a technique is not established in pregnant, paediatric, asthmatic, and elderly patients, or in patients with debilitating diseases. There is also a possibility of prolonged mivacurium-induced neuromuscular block in patients with congenital or acquired abnormal plasma cholinesterase activity, although this incidence is extremely low in our healthy local population. Furthermore, although we can estimate the partial pressure of volatile agents in the blood by monitoring their end-tidal concentrations, no equivalent real-time measures of intravenous drug blood concentrations exist to guarantee unconsciousness with a TIVA technique.² Finally, the use of this technique may be limited by the high costs of propofol, alfentanil and mivacurium.

In summary, this study demonstrates that the 3-in-1 mixture containing fixed proportions of propofol, alfentanil and mivacurium remains stable for up to 5 hours after preparation. Our TIVA technique of using 3-in-1 mixture for induction and maintenance of anaesthesia is effective in ASA 1 patients undergoing certain types of surgery, and its advantages lie in its simplicity, easy titratability and rapid recovery with no major intraoperative or immediate postoperative complications. It may be useful in day surgical cases and in situations where a conventional anaesthetic technique is undesirable (e.g. anaesthesia in the field or anaesthesia for patients susceptible to malignant hyperthermia). Future studies are needed to compare this technique with established standard conventional anaesthetic technique or TIVA technique employing separate infusions of hypnotic, analgesic and muscle relaxant drugs.

Acknowledgements

This study was funded by the Singapore General Hospital. The authors would like to thank Ms Teoh Whay Leng and Mr Balram Chowbay from the Department of Pharmacy, Singapore General Hospital and Dr Goh Yong Siah and Dr Agnes Ng of Singapore General Hospital for their invaluable assistance and comments.

REFERENCES

1. Sear J W. Total intravenous anaesthesia. In: Healy T E J, Cohen P J, editors. *Wylie and Churchill-Davidson's: A Practice of Anaesthesia*. London: Edward Arnold, 1996:690-707.
2. Fragen R J. Total intravenous anesthesia. In: Fragen R J, editor. *Drug Infusions in Anesthesiology*. New York: Raven Press, 1991:129-45.
3. Glass P S A, Jacobs J R, Quill T J. Intravenous drug delivery systems. In: Fragen R J, editor. *Drug Infusions in Anesthesiology*. New York: Raven Press, 1991:23-61.
4. Sebel P S, Lowdon J D. Propofol: A new intravenous anesthetic. *Anesthesiology* 1989; 71:260-77.
5. Hug Jr C C, Chaffman M. Alfentanil: pharmacology and uses in anaesthesia. Auckland: ADIS Press, 1984.
6. Frampton J E, McTavish D. Mivacurium. A review of its pharmacology and therapeutic potential in general anaesthesia. *Drug* 1993; 45:1066-89.
7. Skues M A, Richards M J, Jarvis A P, Prys-Roberts C. Preinduction atropine or glycopyrrolate and hemodynamic changes associated with induction and maintenance of anesthesia with propofol and alfentanil. *Anesth Analg* 1989; 69:386-90.
8. McCulloch M J, Lees N W. Assessment and modification of pain on induction with propofol (Diprivan). *Anaesthesia* 1985; 40:1117-20.
9. Saarnivaara L, Klemola U-M. Injection pain, intubating conditions and cardiovascular changes following induction of anaesthesia with propofol alone or in combination with alfentanil. *Acta Anaesthesiol Scand* 1991; 35:19-23.
10. Restall J, Tully A M, Ward P J, Kidd A G. Total intravenous anaesthesia for military surgery. A technique using ketamine, midazolam and vecuronium. *Anaesthesia* 1988; 43:46-9.
11. Sandin R, Nordström O. Awareness during total i.v. anaesthesia. *Br J Anaesth* 1993; 71:782-7.
12. Taylor I N, Kenny G N C, Glen J B. Pharmacodynamic stability of a mixture of propofol and alfentanil. *Br J Anaesth* 1992; 69:168-71.
13. Shafer S L, Varvel J R. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology* 1991; 74:53-63.
14. Package literature. Diprivan (propofol 1% injection). Macclesfield, Cheshire, United Kingdom: Zeneca Ltd.
15. Warshawsky K Y. Techniques and procedures: intravenous fat emulsions in clinical practice. *Nutr Clin Pract* 1992; 7:187-96.
16. Mehta R C, Head L F, Hazrati A M, Parr M, Rapp R P, DeLuca P P. Fat emulsion particle-size distribution in total nutrient admixtures. *Am J Hosp Pharm* 1992; 49:2749-55.
17. Monk T G, Ding Y, White P F. Total intravenous anesthesia: Effects of opioid versus hypnotic supplementation on autonomic responses and recovery. *Anesth Analg* 1992; 75:798-804.
18. Richards M J, Skues M A, Jarvis A P, Prys-Roberts C. Total i.v. anaesthesia with propofol and alfentanil: dose requirements for propofol and the effects of premedication with clonidine. *Br J Anaesth* 1990; 65:157-63.
19. Leeuwen L, Zuurmond W W A, Deen L, Helmers H J H J. Total intravenous anaesthesia with propofol, alfentanil, and oxygen-air: three different dosage schemes. *Can J Anaesth* 1990; 37:282-6.
20. Apfelbaum J L. Mivacurium chloride administration by infusion. *Acta Anaesthesiol Scand* 1995; 39(Suppl 106):55-7.
21. Savarese J J, Lien C A, Belmont M R, Rubin L. The clinical and basic pharmacology of mivacurium: a short-acting nondepolarizing benzylisoquinolinium diester neuromuscular blocking drug. *Acta Anaesthesiol Scand* 1995; 39(Suppl 106):18-22.
22. Mirakhor R K, Lavery T D, Briggs L P, Clarke R S J. Effects of neostigmine and pyridostigmine on serum cholinesterase activity. *Can Anaesth Soc J* 1982; 29:55-8.
23. Szenohradszky J, Lau M, Brown R, Sharma M L, Fisher D M. The effect of neostigmine on twitch tension and muscle relaxant concentration during infusion of mivacurium or vecuronium. *Anesthesiology* 1995; 83:83-7.
24. Baurain M J, Dernovoi B S, D'Hollander A A, Hennart D A. Comparison of neostigmine-induced recovery with spontaneous recovery from mivacurium-induced neuromuscular block. *Br J Anaesth* 1994; 73:791-4.
25. Naguib M, Abdulatif M, Al-Ghamdi A, Hamo I, Nouheid R. Dose-response relationships for edrophonium and neostigmine antagonism of mivacurium-induced neuromuscular block. *Br J Anaesth* 1993; 71:709-14.
26. Hwang N C. Local clinical experience on mivacurium in adult patients—recovery of neuromuscular function after bolus and continuous infusion of mivacurium chloride. *Proceedings of the 24th Central European Congress on Anesthesiology*; 1995 Sept 4-8; Vienna, Austria. Austria, 1995:365-9.
27. McCollum J S C, Milligan K R, Dundee J W. The antiemetic action of propofol. *Anaesthesia* 1988; 43:239-40.