CHAPTER I

# INTRODUCTION

## Background and Rationale

Recovery from general anesthesia is, for most patients, a smooth uneventful emergence from an uncomplicated anesthesia and operation. However, for a small but very significant number of patients, recovery from general anesthesia can be a life - threatening process best managed by prompt intervention delivered by skilled nursing and medical personnel . Actually, the recovery process begins in the operating room when the operation and anesthesia are completed and the trachea is extubated and then continues in the postanesthesia care unit (PACU.).

Ideally, in general anesthesia one should be able to regulate the concentration or the partial pressure of the anesthetic agent in the blood from moment to moment, as the central nervous system, the site of action of the anesthetic, tends to equilibrate with the partial pressure of the anesthetic in the blood. If more is needed, the concentration should be amendable to prompt increase, if overdose is evident, one should be able to reduce the concentration just as promptly. And from the standpoint of elimination, the majority of drugs used for intravenous anesthesia undergo metabolic change in the body. The ultimate safety of these substances is therefore related to the totality of their metabolism. Although subject to careful titration, once an injected drugs enter the circulation there are no means for prompt removal. On the other hand, although inhalation anesthetics

are also metabolized in varying degrees, their uptake and elimination are accomplished primarily by alveolar ventilation. This is therefore the most controllable method for conducting general anesthesia. For these reasons, the volatile anesthetic agents form the mainstay of general anesthesia. They have a good safety record for patients of all ages, are easy to administer and provide a convenient means of varying anesthetic depth.

The ideal volatile anesthetic agent remains undiscovered. Hypothetically, it will be the compound devoid of toxicity which provides immediate onset of surgical anesthesia and the desired muscle relaxation without depressing cardiovascular, respiratory, or other vital functions. Furthermore, it should be eliminated rapidly after being discontinued, with the patient awakening without side-effects, yet nevertheless provide postoperative analgesia.

The introduction of halothane in 1956 had an enormous impact upon clinical anesthesia practice. For the first time we had available an inhalation anesthetic whose attributes included lack of pungency , permitting easy inhalation induction, nonflammability, potency sufficient to permit the use of high concentrations of oxygen, sufficient insolubility in the blood to permit rapid induction and emergence, bronchodilatation, uterine relaxation and minimal postoperative nausea and vomiting.

The search for a better inhalation anesthetic has proceeded largely by trial and error. An important advance in the development of inhalation anesthetics occured in 1971 with the description of the clinical pharmacology of isoflurane. Concerning about halothane's potential for hepatotoxicity in part motivated a rapid acceptance of isoflurane by the anesthesia community. Isoflurane also had advantageous pharmacologic properties that, along with a perceived decreased

propensity for hepatotoxicity, resulted in its becoming the most frequently used inhalation anesthetic in the United States.

From the standpoint of recovery, isoflurane is potentially a suitable agent for anesthesia. Its lower blood solubility (1.4 vs 2.3) and lower biodegradation ( one hundredth of that of halothane ) are theoretical properties which should speed its elimination from the body and hence recovery from anesthesia . This feature should make it an attractive agent for general anesthesia practice.

Early and uncomplicated recovery from anesthesia is of particular importance because it will decrease the workload in the postanesthesia care unit (PACU.) and also affect work productivity, such as; increasing turnover rate of beds, number of day case surgery and reducing waiting lists and time. The additional potential advantage of rapid recovery may be reduced patient morbidity in recovery areas. That is, any factors that result in a more rapid elimination of residual anesthetic may lessen the likelihood of complications related to prolonged somnolence, such as intermittent airway obstruction and hypoxemia. In addition, residual muscle paralysis may be more rapidly dissipated by more rapid elimination of volatile anesthetics.

Increasing costs in the face of limited resources make careful budgeting essential in health services. One way of making economies is to increase the use of day surgery. Many operations can be performed at a lower cost if carried out on a day case basis. This policy is only economical if it can be carried out safely.

Today ambulatory surgery is becoming increasingly common and not only involves simple and short surgical procedures but also trends towards lengthier procedures such as herniorrhaphy, arthroscopy, laparoscopy etc. The appropriate anesthesia for ambulatory surgery must

ensure not only optimal operating condition, but also rapid and smooth recovery.

Pelvic laparoscopy, one of the ambulatory surgical procedures, has been increasing in popularity for diagnostic and therapeutic reasons. The surgical demands of Trendelenberg position, pneumo-peritoneum with $CO_2$ gas create untoward effects to respiratory and cardiovascular homeostasis.[1] An early effect of an increased intraabdominal pressure causes a rise in CVP.and cardiac output which may be due to the squeeze of blood from abdominal contents and IVC. into the thoracic cavity and an enhanced sympathetic activity following an increase in arterial $CO_2$ tension[2]. Desmond & Gordon[3] reported cardiac arrhythmia in spontaneous breathing patients anesthesized with halothane and concluded that patients for laparoscopy should be ventilated mechanically. The most widely accepted technique for laparoscopy is general anesthesia with endotracheal intubation and controlled ventilation.

In Siriraj hospital this procedure used to be done under local anesthesia with systemic sedation and analgesia because local analgesia has advantages over general anesthesia in terms of simplicity, low cost, avoidance of untoward effects of general anesthesia and ability to be done on a day case basis. However, local anesthesia has some disadvantages such as a feeling of pain and discomfort, some risk of hypoxia and hypercarbia and lack of prompt treatment of airway problems. Surgeons prefer general anesthesia to local anesthesia because of their comfort. For these reasons, today this procedure is routinely done under general anesthesia in Siriraj hospital, but it is still performed on a day case basis. Consequently, the anesthetic technique and agents should be considered based on safe practice and rapid uneventful recovery.

Since some operations requiring longer duration of anesthesia are being performed on a day case basis, the assessment of recovery from anesthesia is increasingly significant. We must determine how to anesthesize patients to provide rapid recovery with as little postanesthetic cognitive and psychomotor impairment as possible and how to judge when patients can be sent home safely. Patients with cognitive and psychomotor impairment may be prone to accidents during transportation, or after arrival home. Therefore, the patients' psychomotor and cognitive performance must return to normal level (preanesthetic level) before they are considered fully recovered (e.g. fit to drive). The most important consideration is to determine if the patient can be safely discharged from the hospital and when it is safe to allow the patient to drive or do complex work. Unfortunately, we do not have cognitive or psychomotor tests that could be recommended as standard criteria. In practice we use clinical tests to judge the patient's condition.

The evaluation of recovery following general anesthesia is difficult. No single test can demonstrate accurately when patients are free from the influence of an anesthetic drug and therefore safe to leave the hospital. The complex nature of cerebral function makes the possibility of ever finding a single infallible test exceedingly remote. However, it is important that all safety measures should be implemented in the patient's medical record. To protect against a possible challenge of inappropriate discharge, a physician must have evidence that he or she carefully assessed the patient for home readiness.

In conclusion, today the pressure to develop day case surgery ensures continuing interest in delivering a safe, effective general anesthesia with minimal side effects and achieving a rapid recovery and the assessment of recovery. The use of isoflurane may influence future

trends in this context.

This study would like to compare the recovery characteristics of halothane and isoflurane anesthesia.

## Review of related literatures

Isoflurane was initially synthesised in 1965 by R.C. Terrell. Its scheduled release for use 10 years later was delayed by the unfortunate apparent finding of carcinogenicity in mice exposed to the agent. This was later disproven; the untoward effects resulted from a contaminated food supply.

Isoflurane was finally approved for clinical use in the United States by the Food & Drug Administration in 1979. Approval from agencies in other countries worldwide rapidly followed. At present isoflurane is the most widely used potent volatile anesthetic in the United States and Canada.

Physical characteristics of isoflurane : Isoflurane is non-flammable and resistant to decomposition by physical (e.g. ultraviolet light) or chemical (e.g. soda-lime) stresses. Unlike halothane, isoflurane does not require the presence of a stabilizer to prevent its decomposition.

Anesthetic Potency (MAC): The minimum alveolar concentration (MAC) of isoflurane in middle-aged patients is 1.15%; the value for halothane is 0.75%. The addition of nitrous oxide decreases the MAC for both agents in an additive fashion. Seventy percent nitrous oxide decreases isoflurane MAC to 0.50%.

Pharmacokinetics : The blood/gas partition coefficient of isoflurane is 1.4, which is less than that of halothane (2.4). Its lower blood solubility suggests that recovery should be more rapid

than with halothane. Moreover, recovery from halothane anesthesia may be delayed by the production of bromide from its metabolism.[4]

There are many studies comparing the recovery from isoflurane and halothane anesthesia in different techniques.

Pandit, Steude and Leach (1985)[5] studied induction and recovery characteristics of isoflurane and halothane anesthesia for short outpatient operations in 101 children, 8 months to 14 years of age. They found that recovery times (time from discontinuation of anesthesia to the time the child was awake and appropriately rational in response to verbal commands) from halothane plus isoflurane (22.35 ± 12.25 min.) and pure isoflurane (24.36 ± 14.19) anesthesia were not significantly quicker than pure halothane (27.44 ± 12.86) and thiamylal plus isoflurane (33.00 ± 19.27) [ ANOVA, P=0.1541 ]. This study was a clinical trial but the patients in this study were not assigned to the treatment by randomization. Furthermore,the doses of inhalation agents were not equipotent.

Fisher et al. (1985)[6] found that emergence from anesthesia (time from completion of the procedure to spontaneous eye opening) was significantly more rapid with enflurane (4.7 ± 4.4 min) than with halothane (6.2 ± 4.5) or isoflurane(6.2 ± 3.9) in 66 children,8 months to 18 years of age, undergoing diagnostic and therapeutic procedures (ANOVA, $P<0.05$). In this randomized clinical trial, they did not blind the observer to the anesthetic techniques nor attempt to use standard concentrations of the inhalation anesthetics nor measure the inspired or end-tidal concentrations.

Carter, Dye and Cooper (1985)[7] compared the recovery times of halothane, enflurane and isoflurane anesthesia in 60 female patients (aged 20-50 yr) undergoing dilatation and curettage. They found that there was no difference in the time to open eyes ( H = 5.5 ± 0.6,

E = 5.1 ± 0.3, I = 6.2 ±0.6 ) or to regain their preoperative score with the postbox test ( H=34.2 ± 3.2, E=33.8 ± 3.1, I = 40.2 ± 4.2 ) whether they received halothane, enflurane or isoflurane ( multiple unpaired Student's t-test,P<0.05)

Kingston (1986)[8] conducted a randomized clinical trial in 40 pediatric outpatients 1 to 6 years of age. He found that the times taken to respond to pharyngeal suction,to tracheal extubation and the first cry were not significantly different between halothane and isoflurane anesthesia(Student's t-test,P>0.05). In this study, they measured the end-tidal concentrations of inhalation agents(1.5 MAC in both groups) but they used the MAC levels of adults.

Cattermole et al.(1986)[9] compared the recovery times of halothane and isoflurane anesthesia in 100 children (aged between 2 and 14 yr) undergoing outpatient dental surgery. They found that the recovery times(time from the discontinuation of the inhalation agent to the opening of eyes on request) were almost identical in both groups : halothane 8.1 ± 3.8 min; isoflurane 8.1 ± 3.6 min. This study was a randomized clinical trial but the observers were not blinded to the anesthetic techniques and the concentrations of the anesthetic agents were not equipotent.

McAteer et al. (1986)[10] compared recovery from isoflurane and halothane anesthesia in 80 pediatric dental outpatients (aged between 5 and 12 yr). They found that immediate recovery (return of eyelash reflex, swallowing and obey commands) and late recovery(standing and walking) were significantly slower in patients who had received isoflurane ( Unpaired Student's t-test, P<0.01). In this randomized clinical trial, they tried to use equipotent doses of inhalation anesthetics but the MAC values that they used were adult values and they did not measure the

end-tidal concentrations of agents.

Ghaly, Flynn and Moore (1988)[11] conducted a randomized clinical trial in 50 full term pregnancies undergoing elective Caesarean section. They found that recovery from anesthesia (extubation time) was significantly more rapid with isoflurane (2.6 $\pm$ 1.4 min) than halothane (4.4 $\pm$ 2.0 min) [ Student's t test, $P<0.001$ ]. However, they did not blind the observer to the anesthetic techniques and did not measure the end tidal concentrations of the anesthetic agents.

Wren et al.(1988)[12] studied induction and recovery from isoflurane anesthesia in 248 pediatric patients. They also compared the two further groups of nine children, and found that the mean half times of elimination of halothane and isoflurane were 220 seconds and 54 seconds respectively.

Milligan, Howe and Dundee (1988)[13] compared recovery of halothane and isoflurane anesthesia in 60 outpatients. They found that initial clinical recovery (eye opening,giving date of birth and orientation) was significantly faster in the halothane group(Student's t test, $P<0.05$ ) but no differences were found during subsequent psychomotor testing (4-choice reaction time and Treiger tests)

Almost all of the above-mentioned studies focused on the short duration pediatric anesthesia and the measurement methods used were only the initial clinical assessments of the recovery. Also, the concentrations of the inhalation anesthetics used were not equipotent. Of these studies, only 3 were done in adults and only 2 of these 3 studies used psychomotor tests to measure late recovery. However, the concentrations of inhalation anesthetics used in these 2 studies were not properly measured. Furthermore,the overall results of these studies are still controversial. Until now no

definite conclusion has been achieved. To date, there have not been such studies done in adult anesthesia and using the psychomotor tests to measure recovery time.

For our country, isoflurane is currently a new inhalation anesthetic and more expensive compared with halothane which is commonly used. Moreover, there have not been any studies comparing the recovery characteristics of halothane and isoflurane anesthesia in Thailand. Therefore, this study will compare the psychomotor and cognitive recovery characteristics of these two inhalation anesthetics in adult anesthesia.

Table 1.1 Review of clinical trial studies comparing recovery from halothane and isoflurane anesthesia

| Study | Subject | Allocation | Observer | Anesthetic Potency | Assessment | Result |
|---|---|---|---|---|---|---|
| 1. Pandit et al. (1985) | children (8 mo.-14 yr.) | not randomization | blind | not eqipotent | clinical test | not different |
| 2. Fisher et al. (1985) | children (8 mo.-18 yr.) | randomization | not blind | not eqipotent | clinical test | not different |
| 3. Carter et al. (1985) | adults (20 - 50 yr.) | randomization | blind | not measure end tidal | clinical test psychomotor test | not different |
| 4. Kingston (1986) | children (1 - 6 yr.) | randomization | not blind | measure end tidal but using adult's MAC. | clinical test | not different |

Table 1.1 (Continued)

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|---|---|---|---|---|---|---|
| 5. Cattermole et al.(1986) | children (2 - 14 yr.) | randomization | not blind | not equipotent | clinical test | not different |
| 6. McAteer et al. (1986) | children (5 - 12 yr.) | randomization | blind | not measure end tidal & using adult's MAC | clinical test | H faster than I |
| 7. Ghaly et al. (1986) | full term pregnancies | randomization | not blind | not measure end tidal | clinical test | I faster than H |
| 8. Wren et al. (1988) | children | not randomization | not blind | not equipotent | clinical test | I faster than H |
| 9. Milligan et al. (1988) | adults (18 - 55 yr.) | randomization | blind | not measure end tidal | clinical test & psychomotor test | H faster than I & not different |