COMPARISON OF THE DIRECT COSTS, LENGTH OF RECOVERY, AND INCIDENCE OF POST OPERATIVE ANTI-EMETIC USE AFTER ANESTHESIA INDUCTION WITH PROPOFOL OR A 1:1 MIXTURE OF THIOPENTAL AND PROPOFOL

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ABSTRACT

The modern anesthesia provider must consider drug costs as important as benefits and risks when choosing which drug to use in an anesthetic. ***Thiopental*** has been the gold standard for an IV induction drug although ***propofol*** shows a better recovery profile with less post-operative ***nausea*** and vomiting, but at a higher ***cost***. We attempted to determine if a 1:1 volume mixture of ***thiopental*** and ***propofol*** would show a similar recovery profile compared to ***propofol*** alone, but at a lower ***cost***. This study examined the records of 212 surgery patients receiving ***propofol*** (n=82) or a ***1:1 mixture*** (n=130) for demographic, peri-operative, PACU recovery, anti-emetic use, and ***cost*** data. We found that the ***propofol*** group had significantly more females, post-operative anti-emetic use, and induction drug ***costs***, while the ***1:1 mixture*** group had significantly longer surgery and anesthesia times. Mean post-operative anti-emetic drug ***costs*** were statistically significant ($P<0.05$) at $3.15 for the ***propofol*** group and $1.08 for ***the 1:1 mixture*** group. The mean ***cost*** of induction for the ***propofol*** group was $27.31 and $14.31 for the ***1:1 mixture*** group, a statistically significant ($P<0.05$) difference of $13.09. The average recovery time for the ***propofol*** group was 134 minutes and ***cost*** $1205.37, and for the ***1:1 mixture*** group 147 minutes and cost $1320.03. Thus, the difference in PACU charges was $114.66. This research suggests that the ***1:1 mixture*** of ***thiopental*** and ***propofol*** produced a similar recovery profile to ***propofol*** alone, but at a lower direct ***cost***. This study supported previous work, and recommends that further research be done to confirm its findings.

Key Words: **Thiopental, Propofol, Induction of Anesthesia, Cost, Economics, Nausea, 1:1 Mixture, Drug Synergism**

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PREFACE

This study was conducted to examine the direct costs, length of recovery and incidence of post operative anti-emetic use with a relatively unknown anesthesia induction technique using a 1:1 mixture of sodium thiopental and propofol. It also looked for evidence of clinically significant synergism between sodium thiopental and propofol. This IV induction technique using a 1:1 mixture by volume of propofol and thiopental may allow a similar recovery profile compared to propofol alone but at a lower direct cost. It is hoped that the results of this study might assist the anesthesia provider to make choices in anesthesia technique that will provide quality care at a lower cost.

DEDICATION

I dedicate this to my family. Without your support, dedication, tolerance, love, and ability to laugh at the absurdities of life I would never be what I am today. You are the best part of my life.

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My sincere gratitude and appreciation go to Dr. John P. McDonough, CRNA, chairperson; and the members of my thesis advisory committee, Dr. Eugene Levine and Lt. Col. Judy Ikirt, CRNA. Their assistance, guidance, and knowledge have been invaluable to the completion of this thesis. I also thank Dr. Barney Feinstein, Dr. Barbara Goldwick, Mr. Freddy Lee, and Ms. Evelyn Tucker for their assistance in completing this project.

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CHAPTER I : INTRODUCTION

The anesthesia provider has an extensive choice of anesthetic drugs, agents, and techniques that are useful in everyday practice. Providers must choose between these agents by considering the benefits, risks, and costs. This chapter will examine some of the reasons for including costs in the choice mix. It will also discuss the benefits and side effects of two intravenous (IV) drugs, sodium thiopental (thiopental), and propofol, as well as the accepted physiological reason for their effects.

Background

Anesthesia has developed dramatically since Crawford Long and William Morton first used diethyl ether to produce anesthesia (Nagelhout & Zaglaniczny, 1997). Pharmacologists and anesthesia providers are developing new drugs and techniques in a constant effort to provide safe, effective anesthesia with a minimum of adverse side effects. As a result of these efforts anesthesia providers face multiple choices with each choice possessing its own risks, benefits, and costs. Each provider must choose the best combination of drug and technique to provide adequate anesthesia with the fewest adverse effects and lowest costs.

Eddy (1990) gave three considerations that must be a part of any choice. When making a choice, the health care provider must first measure the outcomes of all alternatives. This involves gathering and analyzing data regarding the benefits, risks and costs. Second, the provider must judge the desirability of each outcome by comparing benefits with potential harms, outcomes with costs, and amount gained versus resources used to give priority to practices that provide the highest yield. Third, the anesthesia provider must make the patient's preferences one of the highest considerations. Sperry (1997) states anesthesia providers should equate patient benefits with anesthesia benefits.

In the past, anesthesia providers placed more emphasis on risks and benefits than costs when choosing which agent to use (Shapiro, 1997). Recent changes in the health care climate require that the costs of techniques and drugs be given a higher priority. Knowledge of the past events will give more understanding of the current atmosphere of cost containment and expense

justification.

Provision of health care changed dramatically after World War II. Social engineers suggested that resources spent on consumer goods should be shifted to providing better public services. As a result of Federal Government policies and involvement: a) society expected high quality care at no personal cost, b) hospitals built an overabundance of beds and encouraged admissions because payment was on a "cost plus" basis (documented cost plus five percent) that guaranteed profits, c) "usual and customary" insurance payments virtually guaranteed a profit on every visit and procedure. "Simply put, the practice of medicine and the delivery of health care became a risk free economic enterprise completely independent of marketplace forces. " (Shapiro, 1997, p. 1020).

In 1970 Milton Friedman claimed that the free market, not the government, was the answer to social ills. Businessmen, feeling that medical care was too expensive, heeded Friedman and managed care was born. Profits were no longer guaranteed, costs became more important in the choice mix (Shapiro, 1997), and anesthesia providers soon found themselves restricted by formularies and the need to justify use of expensive drugs (Suver, Arikian, Doyle, Sweeney, & Hagan, 1995). Business principles continue to govern health care requiring that the anesthesia provider seek ways to reduce costs (Shapiro, 1997). Changes in payments to per capita reimbursement became a direct incentive to reduce costs (Watcha & White, 1997).

Purpose of the Study

This study retrospectively examined the direct costs, length of recovery, and incidence of post operative nausea and vomiting when propofol or a 1:1 mixture of thiopental and propofol were used for anesthesia induction. The study attempted to examine any evidence of clinically significant synergism between propofol and thiopental.

Anesthesia providers may be able to use the results to make informed decisions when choosing induction agents.

Problem of Reducing Costs

How can anesthesia costs be reduced? Watcha and White (1997) found that over half of

intraoperative anesthesia costs could be influenced by the choice of agent or technique. Drugs account for 33% of the non-professional anesthesia costs (Horrow & Rosenberg, 1994) but only 2% of total hospital charges (Dexter & Tinker, 1995). Intraoperative anesthesia costs were 5.6% of total hospital charges (Watcha & White, 1997). Despite the relatively small costs of anesthesia in relation to total hospital charges, department managers may focus on anesthesia drugs as the source of savings and restrict providers to use of the least expensive drug. Limiting choice to cheaper drugs with unsuitable or adverse side effects might reduce direct costs but could also increase indirect costs (Suver et al., 1995). According to Phillip (1995), true cost effectiveness equals the value obtained for the price paid. This concept of value is the reason behind using more expensive agents that have fewer side effects or reduce recovery times.

Several researchers claim that propofol lowers costs by reducing the time that a patient spends in the operating or recovery room (Enlund, Kobosko, & Rhodin, 1996; Kain, Gaal, Kain, Jaeger, & Rimar, 1994; Sung, Reiss, & Tillette, 1991; Suver et al., 1995; Tagliente, 1997; Wagner & O'Hara, 1995). However, equating recovery times to cost savings may be incorrect.

Over 33% of total hospital charges come from operating room personnel costs (Watcha & White, 1997). Phillip (1995) states that reduced time in the operating or recovery room does not generate savings unless room utilization increases or staffing decreases. Recovery unit protocols that mandate a specific length of stay in the PACU can negate any potential savings from an induction agent that provides a quick recovery time.

> Although it is important to note what *potential* savings there are in using propofol over sodium thiopental, anesthesiologists will need to sum the effects of these individual studies and come to a programmic solution to the use of anesthetic drugs that truly allows reduction in PACU staff (emphasis added) (Lubarsky, 1995, p. 13).

Lubarsky also stated that use of high cost drugs that provide rapid recovery such as propofol would not reduce but increase costs until enough changes were made to effect full time equivalent staff reductions.

Dexter and Tinker (1995) found that reduced recovery times with drugs such as propofol

would only reduce costs if the operating room was scheduled to run later or the PACU closed when the last patient left. They found that better scheduling of admissions would maximize personnel productivity and reduce charges as personnel costs are directly related to the peak number of patients in the PACU. Kain et al. (1994) found that PACU costs in the Magnetic Resonance Imaging (MRI) suite were reduced with propofol, but that savings came because the recovery room nurse transferred to the main surgical PACU when the patient recovered or was discharged from the MRI PACU. These results may not reflect typical surgical results because the barbiturate group used for comparison received both thiopental and pentobarbital for anesthesia maintenance which may have prolonged recovery. Both Dexter and Tinker (1995) and Watcha and White (1997) found that anesthesia providers have little control over costs.

If highest cost savings come from reduction in payroll and anesthesia providers have little effect on the staffing patterns and recovery room policies, then how can they reduce costs while maintaining quality care? Anesthesia providers have direct control over the agents and techniques used to provide anesthesia. While drug costs are only 2% of total hospital charges, those costs are substantial and can be reduced (Suver et al., 1995). The cost of a drug should receive as much scrutiny as the scientific factors (Johnstone & Martinec, 1993).

For example, claiming that ondansetron provides a 40% reduction in nausea compared to droperidol seems impressive until the direct drug costs are revealed. The cost of ondansetron for 119 patients was $2,058 (assuming no waste or $20,577 if a new vial was used for each patient) versus $40 for droperidol (Johnstone & Martinec, 1993). "The choice of an anesthetic agent for routine use depends not only on its demonstrated efficacy and side effect profile, but also on economic factors" (Watcha & White, 1997, p. 1,191).

An example of the choices that face anesthesia providers is that of which intravenous (IV) induction agent to use. Several IV induction agents are available, each with their own profile. See Table 1. for a list of ideal characteristics.

Table 1.

Properties of Ideal Intravenous Anesthetic Agent

Water soluble
Pain with arterial injection but no sequelae
Stable in solution with a long shelf life
No pain or irritation with IV injection
Small volume required for induction
Minimal cardiac and respiratory depression
Does not cause histamine release or hypersensitivity reaction
Rapid, predictable onset time (in one arm-brain circulation)
Lack of accumulation
Rapid metabolism to inactive metabolites
Rapid awakening and recovery to pre-induction level of activity
Minimal side effects
Body organ effects are limited to the Central Nervous System

Note. Adapted from D. H. Morison, 1993, Canadian Journal of Anaesthesia, 40, p. R9 and J. W. Sear, 1997, Canadian Journal of Anaesthesia, 44, p. R3.

There are no induction agents that possess all the characteristics of an ideal induction agent. Thiopental was one of the first IV drugs used for induction and remains the standard against which other agents are measured. Thiopental rapidly and reliably produces surgical anesthesia. It provides a measure of protection to the brain by lowering both intracranial pressure through reduced cerebral blood flow and the cerebral metabolic oxygen requirements. Thiopental lowers metabolic oxygen requirements more than propofol, offering greater cerebral protection (Stolting, 1991). Thiopental and propofol show similar effects on cerebral blood flow in the normoxic and hypoxic dog (Haberer et al., 1993). It is associated with "...the least hemodynamic perturbation on induction" in Chinese pediatric patients (Aun et al., 1994, p. 555).

Although inexpensive, thiopental's side effects of prolonged recovery (Chittleborough et al., 1992; Kain et al., 1994; Wagner & O'Hara, 1995), anti-analgesic effect with low doses (Morgan & Mikhail, 1996), increased risk for laryngospasm, cumulative effects, pain and tissue necrosis with intra-arterial injection, and histamine release make it a less than ideal agent (Stolting, 1991). It causes the vocal cords to narrow significantly more than propofol (Barker, Langton, Wilson, & Smith, 1992). Insertion of an oral airway caused increased episodes of laryngospasm, coughing, and gagging with thiopental induction although the differences with propofol were not statistically significant (Szneke, 1989). Tracheal intubation induced bronchoconstriction was significantly more prevalent with thiopental than propofol (Wu, Wu, Sum, & Bishop, 1996). Schrum et al. (1994) found that infants age 1-6 months had significantly longer emergence and extubation times as well as higher incidences of perioperative airway complications when anesthesia was induced with thiopental versus propofol. It is associated with increased post-operative anxiety versus propofol (Jakobsson & Rane, 1995; Winwood & Jago, 1993).

Pizov et al. (1995) found that thiopental induction significantly increased wheezing in asthmatic patients, while propofol caused no wheezing. Both agents cause significant decreases in end expiratory residual volume but there was no difference between the two (Rutherford, Logan, & Drummond, 1994).

Other agents have effects similar to thiopental but have equally noxious side effects that

limit their use (Stolting, 1991). Propofol was one of the first agents to directly challenge thiopental as the standard induction agent (Miller, 1996).

Propofol (2,6, di-isoprophylphenol; trade name Diprivan) is a short-acting, rapidly metabolized intravenous anesthetic. It has a pKa of 11, is highly fat soluble, dissolves poorly in water, and binds 99% to proteins. It is dissolved in Intralipid, a 1% emulsion containing 10% soya oil, 2.25% glycerol and 1.2% purified egg phosphatide as a stabilizer (Doyle, 1998; Searle & Sahab, 1993). Propofol is rapidly metabolized with less than 20% recovered unchanged after 30 minutes (Peskin, 1992). It has a distribution half life ($t_{1/2\alpha}$) of two to four minutes and an elimination half life ($t_{1/2\beta}$) of 21 to 69 minutes from redistribution and metabolism to water-soluble sulfate and glucuronide conjugates. Total body clearance of 1.3 - 2.2 L/minute exceeds hepatic flow, suggesting additional sites of metabolism, possibly the kidneys and lung. The total volume of distribution (V_D) is 387-771 liters. There is a minimal change in clearance with cirrhosis and renal disease. (Doyle, 1998; Searle & Sahab, 1993). Suggested induction dose is 2.5 mg/kg, with onset at 22-125 seconds after injection.

Propofol avoids many of the less desirable side effects of thiopental. Propofol rapidly and reliably induces anesthesia (Tagliente, 1997), is believed by some to reduce postoperative nausea and vomiting when used as both an induction and maintenance agent (Borgeat, Wilder-Smith, Saiah, & Rifat, 1992; Gan, Ginsberg, Grant, & Glass, 1996; Hamunen, Vaalamo, & Mauneksela, 1997; Klockgether-Radke, Piorek, Crozier, & Kettler, 1996; Myles, Hendrata, Bennett, Langley, & Buckland, 1996; Sung et al., 1991) but that result is controversial (Zestos et al., 1997). Propofol may interact with droperidol to increase nausea (Wagner, Berman, Devitt, & O'Hara, 1994). It shows no cumulative effects (Katzung, 1998), and provides a rapid recovery (Morison, 1993) although Aun et al. (1994) found that Chinese pediatric patients had significantly longer recovery with propofol induction and maintenance versus propofol induction and maintenance with another agent. This result was not apparent in Caucasian pediatric patients (Runcie, Mackenzie, Arthur, & Morton, 1993). Propofol is associated with a feeling of well being during recovery (Jakobsson & Rane, 1995; Morison, 1993). It shows a reduced

recovery time compared to thiopental (Wagner & O'Hara, 1995) and is considered to be a "safe" agent in malignant hyperthermia susceptible patients (McKenzie, Couchman, & Pollock, 1992).

Propofol induction followed by propofol maintenance showed the least hemodynamic changes in pediatric patients versus induction with thiopental, propofol, or halothane followed by halothane maintenance (Hannallah, Britton, Schafer, Patel, & Norden, 1994). Patients receiving propofol demonstrated significantly less airway resistance versus thiopental or etomidate (Eames, Rooke, Wu, & Bishop, 1996). One patient who received thiopental and propofol on separate days showed half the airway resistance with propofol (5.7 versus. 11.8). Propofol was associated with greater depression of subcortical nocioceptive processing than thiopental (Wilder-Smith, Hagon, & Tassonyl, 1995), as well as significant blunting of increased intraocular pressure during laryngoscopy (Zimmerman, Funk, & Tidwell, 1996). It produces less postoperative shivering versus thiopental even though axillary temperatures were similar (Singh, Harwood, Cartwright, & Crossley, 1994).

Propofol's cost is five to ten times that of thiopental (Tagliente, 1997). Propofol causes burning upon IV injection but that burning is reduced by previous injection of lidocaine (Stolting, 1991). It is associated with a period of apnea when first administered that quickly resolves. Apnea can be blunted by continuous versus bolus injection (Morison, 1993). Propofol blunted the hypercapnea reflex more than thiopental and this effect continued past awakening (Blouin, Conard, & Gross, 1991). Propofol causes a transient vasodilation coupled with a blunting of the baroreceptor reflex that is similar to thiopental. Blood pressure returned to normal with surgical stimulation. In vitro, propofol depressed immunological reactions and chemotaxis (Stolting, 1991). There is a slight risk for anaphylaxis with patients allergic to eggs due to the lecithin used as a stabilizer. This risk is probably minimal as most patients are allergic to egg protein or albumin and not lecithin, but prudence indicates caution until more information is available (Searle & Sahab, 1993). Patients receiving propofol had significantly more dreams versus thiopental, but the content was similar (Brandner, Blagrove, McCallum, & Bromley, 1997). Chinese pediatric patients experienced significantly greater drops in blood pressure with propofol (Aun, Sung,

O'Mear, Short, & Oh, 1993).

Propofol is prone to bacterial contamination due to its formulation with Intralipid, a one percent emulsion containing soya oil. The anesthesia provider must therefore use or dispose of the drawn up drug within six hours to avoid bacterial contamination. Propofol waste is high because of this requirement (Crowther et al., 1996). Despite these limitations and because of its superior characteristics compared to thiopental, propofol remains a popular induction agent (Katzung, 1998; Peskin, 1992).

The challenge to reduce cost while maintaining quality care becomes one of finding an induction agent that shows propofol's beneficial effects but at a lower cost and with fewer side effects. One possibility that shows promise is a 1:1 mixture of thiopental and propofol. Co-administration of similar agents in reduced dosages to give a better ratio of preferred versus unwanted side effects, reduce cost, or improve therapeutic outcome is a common technique (Amrein, Hetzel, & Allen, 1995; Raphael & Bexton, 1994). Preliminary results indicate that the patients receiving the 1:1 mixture had significantly less nausea and recovery times compared to thiopental. No other significant differences were noted, other than an equal percentage of burning on injection with the mixture and propofol compared to thiopental alone (Rashiq, Gallant, Grace, & Jolly, 1994).

Statement of the Problem

There are limited studies exploring the physical compatibility and recovery profile of a 1:1 mixture of thiopental and propofol. There have been no published studies regarding the direct costs of this mixture. There are no studies that examine the incidence of post operative nausea and vomiting after administration of this mixture. There are few studies that examine the clinical effects of the synergism of propofol and thiopental on the $GABA_A$ receptors.

Research Questions

1. What is the recovery time after induction with a 1:1 mixture of thiopental and propofol, and how does this compare to recovery times after induction with unmixed thiopental or propofol?

2. What is the incidence of anti-emetic use during recovery after induction with a 1:1 mixture of thiopental and propofol, and how does this compare to anti-emetic use for unmixed thiopental or propofol?
3. What is the direct cost for a 1:1 mixture of thiopental and propofol, and how does this compare to costs for unmixed thiopental or propofol?
4. Will these results match predicted results based on the $GABA_A$ receptor theory?

Conceptual Framework

This study was based on two separate but important concepts: proposed mechanisms of action for induction agents, and studying outcome data and applying the results will reduce costs and improve care in providing anesthesia. Understanding the underlying pharmacodynamics of induction agents will help the provider to make informed choices when using these agents.

Barbiturates such as thiopental have been shown to affect the neuro transmitter gamma-aminobutyric acid A ($GABA_A$) receptor sites present in the central nervous system. A $GABA_A$ receptor is an ionotropic, transmembrane heteroligomeric (composed of differing units) protein that functions as a gated chloride channel in the cell membrane. It has a pentameric structure (composed of five proteins) with a variety of combinations of sub-units including alpha, beta, and gamma. Each of these sub-units have individual variations, with six alpha, four beta, and three gamma so far identified. Receptors made of pure alpha or beta receptors respond weakly to GABA stimulation, while receptors that have the gamma sub-unit react most strongly to GABA stimulation. The gamma sub-unit seems to be essential for normal physiologic and pharmacologic action of GABA. Over sixteen genes encode the proteins necessary for the $GABA_A$ receptor (Katzung, 1998).

Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, binds to alpha or beta sub-units on the receptor causing the chloride channel to open. Influx of chloride hyperpolarizes the membrane of the neuron, moving the membrane charge away from threshold and inhibiting formation or transmission of an action potential (Katzung, 1998).

Barbiturates bind to sites on the alpha or beta sub-units of the GABA receptor and enhance the action of GABA by prolonging the duration of GABA-gated chloride channel openings without increasing the frequency of openings. At high doses, barbiturates are GABA-mimetic and directly activate the receptors. Barbiturates also inhibit the action of excitatory neurotransmitters and show nonsynaptic membrane effects similar to their effects on GABA transmission. The end result of high dose barbiturates is central nervous system depression leading to loss of consciousness and full surgical anesthesia (Katzung, 1998).

It is believed that propofol acts in a fashion similar to barbiturates on GABA receptors. It shows a synergism when administered with thiopental (Katzung, 1998; Naguib & Sari-Kouzel, 1991). Naguib and Sari-Kouzel (1991) found that co-administration of thiopental and propofol enhanced the action of both agents producing an effect greater than expected with the dosages given. They postulated that when one agent bound itself to the $GABA_A$ receptor it caused a conformational change in the receptor protein that more fully exposed the receptor site of the other agent. The net result was enhanced GABA function. Further experiments need to be done to confirm this. Propofol and midazolam (a benzodiazipine) show similar synergism (Prince & Simmonds, 1992). Researchers have identified benzodiazipine receptor sites on areas of the $GABA_A$ receptor separate from the barbiturate receptor site. Propofol synergism with agents that bind to two separate sites on the $GABA_A$ receptor gives credence to Naguib and Sari-Kouzel's (1991) findings.

Making an intervention, studying the outcome, and modifying practice to improve efficiency and obtain a desired result offer multiple benefits. Following this procedure will provide objective, documented data to support the use of new techniques or retention of older practices. It will eliminate variation and low value results, and help managers write new practice guidelines (Anderson, 1997). These data will also provide proof of value that administrators demand when a change is suggested. Examining outcomes and applying those finding to practice will eliminate inefficient practices based on intuition, tradition, or habit, with an end result of decreased costs and better value (Tuman, 1995).

Tuman developed a model to obtain these goals (Figure 1). The conceptual variable in Tuman's model is the outcome itself. The operational variables for this study will be the direct cost of the induction drugs, the length of recovery time, and the incidence of post operative anti-emetic use. Comparison of these outcome measurements might also either support or discredit the suggestion that propofol has synergistic effects with barbiturates.

Definitions

Anesthesia provider

A registered nurse with specialized education and training in the field of anesthesia who has successfully completed the certification exam administered by the American Association of Nurse Anesthetists or a licensed physician with specialty training in the field of anesthesia.

Direct Cost

The cost paid in US dollars to obtain the administered dose of the drug.

Induction Agent

A drug given intravenously that causes a rapid central nervous system depression leading to a loss of consciousness and surgical anesthesia.

Synergism

A combination of agents with effects greater than expected from its constituents (Naguib & Sari-Kouzel, 1991).

MAC Hours

The minimum alveolar concentration of an anesthetic agent that results in surgical anesthesia (lack of movement to painful stimuli) in 50% of subjects. MAC hours are calculated by summing the MAC of each hour of a procedure.

Limitations

The study had several limitations. It was completed at one hospital on the East Coast. Therefore, the conclusions may be biased because of geographical variations or homogeneity in patient populations. The sample was convenient which limits its predictive value.

Assumptions

It was assumed that combining propofol and thiopental in one syringe will not affect the physical properties of either drug. Also, that the health status of patients in each group was similar and the charts to be reviewed contained data that was accurate and complete.

Summary

Cost must become as important as possible benefits and risks when considering which drug to use. Anesthesia providers can reduce the cost of anesthesia by choosing drugs that are cost efficient and effective.

Thiopental and propofol show synergistic actions and therefore may provide a response similar to propofol alone but at a lower direct cost. This study examined the effects of this mixture.

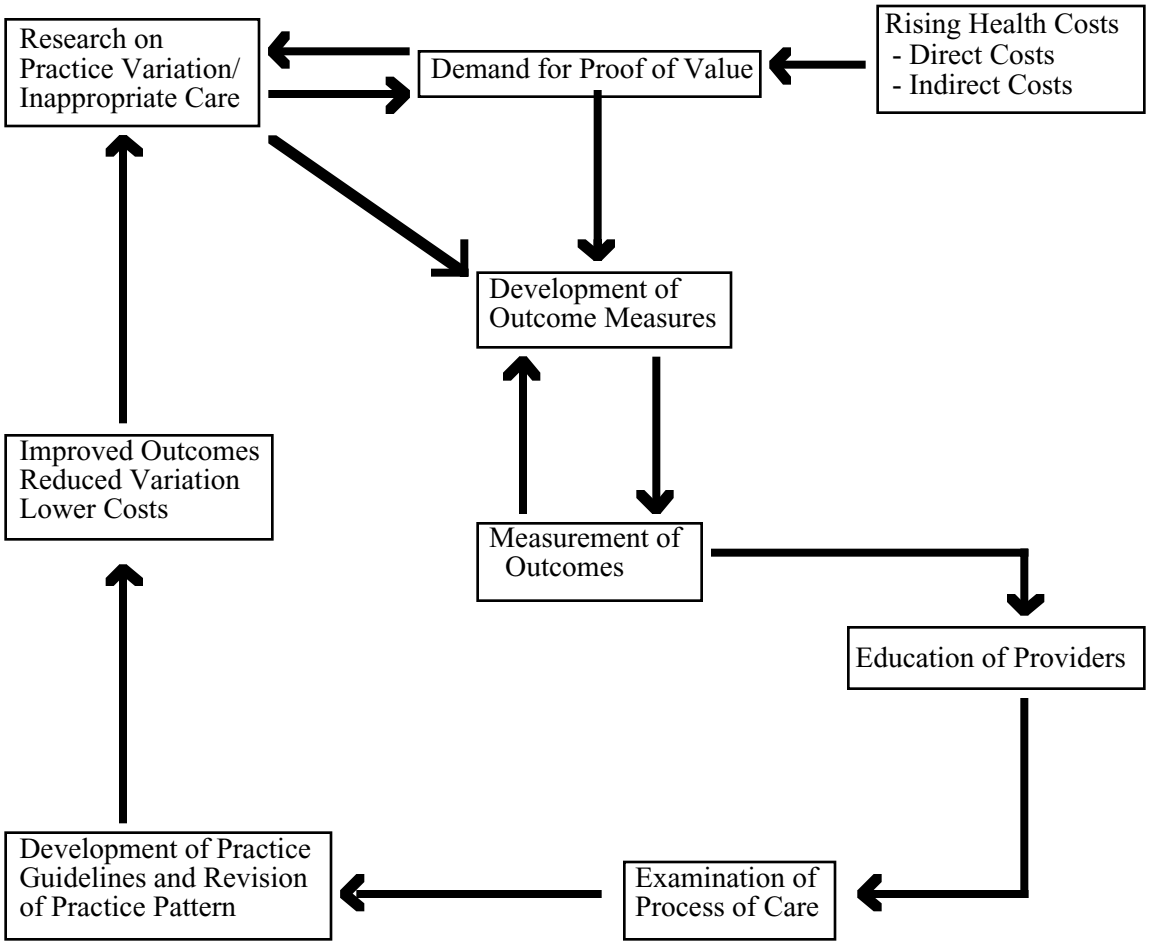

Figure 1.

Algorithm to Use Outcome Data to Improve Efficiency and Reduce Costs.

Note. From Tuman, K. J. (1995). Cost containment and efficiency in perioperative care. In P. G. Barash (Ed.), The American Society of Anesthesiologists, Inc. (Vol. 23, pp. 231-246). Philadelphia: Lippincott-Raven Publishers.

CHAPTER II: REVIEW OF LITERATURE

Introduction

This chapter will report the methods and results of five studies that examined the synergism, recovery characteristics, support or inhibition of bacterial growth, physical and chemical compatibility, and cost of induction with a 1:1 thiopental and propofol mixture. These studies are relevant to the problem.

Synergism of Thiopental and Propofol

Naguib and Sari-Kouzel (1991) administered thiopental (2-6 mg/kg), propofol (1-2.4 mg/kg), and a combination of thiopental and propofol (respectively 0.86 and 0.3-1.1 mg/kg) to 120 surgical outpatients to determine any synergism of the two drugs. The authors used fractional algebraic analysis and isobolographic data to determine the additive line and the interactions between thiopental and propofol.

The fractional analysis equation was based on the component dose of each drug used as a fraction of the doses that gave the same effect when given separately. The sum of fractional doses equals 1.0 as expressed by the equation:

$$Tc/Ts + Pc/Ps = 1.0$$

where Tc and Pc are the amount of thiopental (Tc) and propofol (Pc) used in the combination, and Ts and Ps equals the amount of thiopental (Ts) and propofol (Ps) used separately. A result of less than 1.0 indicates synergism while a result of greater than 1.0 indicates antagonism (Naguib & Sari-Kouzel, 1991).

The isobol graph involves plotting the median effective dose [ED(50)] of each separate drug on the x and y axis of a graph, then drawing a straight line between the points to indicate the additive dose. A combined drug ED(50) dose to the left of the additive line on an isobol graph indicates synergism (see Fig. 2) (Naguib & Sari-Kouzel, 1991).

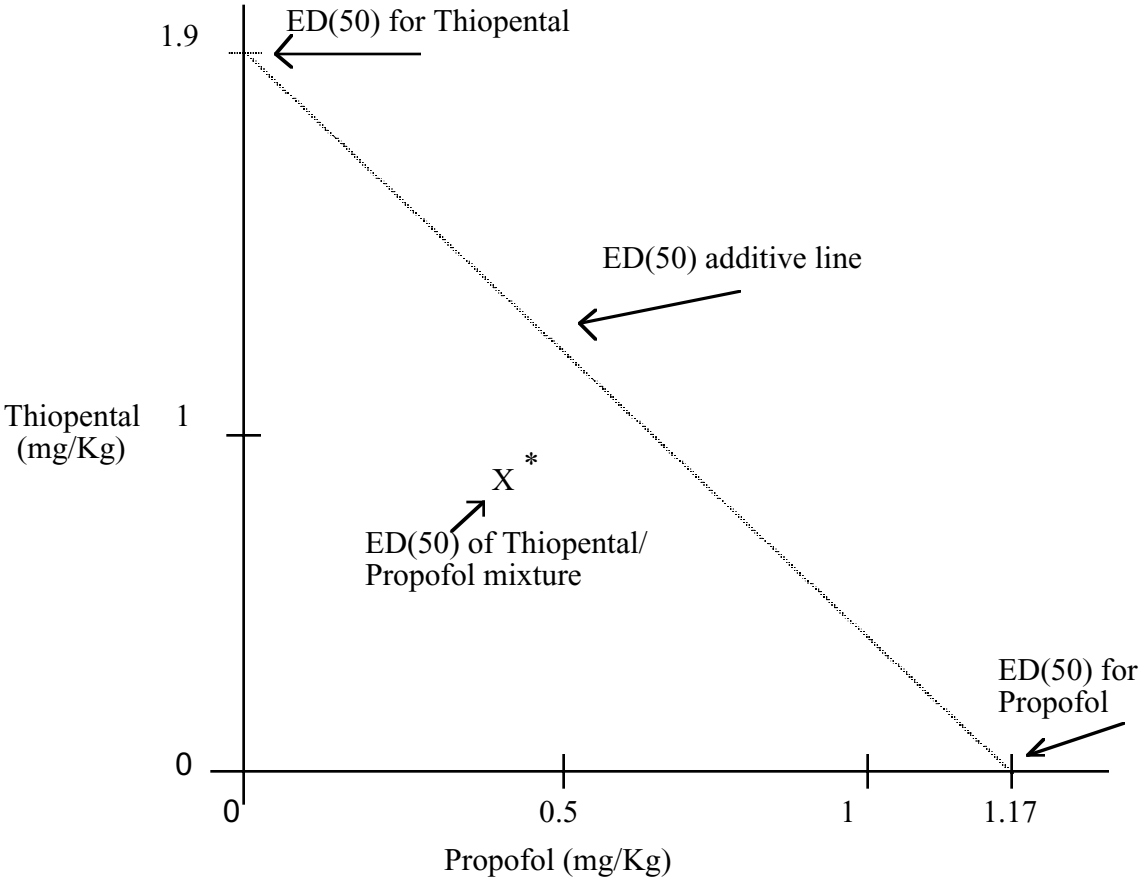

Figure 2.

ED(50) isobologram for the interaction of thiopental and propofol assessed by loss of eye opening to command 60 seconds after injection.

Dotted line is ED(50) additive line. *P<0.05 deviation of combined ED(50) from additive line. Note. Adapted from "Thiopentone-Propofol Hypnotic Synergism in Patients," by M. Naguibe and A. Sari-Kouzel, 1991. British Journal of Anaesthesia, 67, p. 5.

The ED(50) doses for thiopental and propofol were calculated to be 1.9 mg/Kg and 1.17 mg/Kg, respectively. The ED(50) doses for the combination of thiopental and propofol were 0.86 and 0.46 mg/Kg, respectively. The sum of the algebraic equation was 0.84, indicating synergism of the two agents (Naguib & Sari-Kouzel, 1991). The use of the isobolographic technique is a good predictor of relative potencies, but does not predict the dosages that provide maximum synergy. Giving a set dose of thiopental in the mixture may also have skewed the results (Rashiq et al., 1994).

Recovery Characteristics After Induction with a 1:1 Mixture

Rashiq et al. (1994) determined the rate and quality of recovery from general anesthesia in 60 healthy women undergoing laparoscopic surgery after induction with thiopental, propofol, or a 1:1 mixture in a randomized, double blind study. The medications, either thiopental and placebo, propofol and placebo, or thiopental and propofol, were introduced through a dual lumen Y port into a rapidly running intravenous line and bolused until the patient lost the eyelash reflex. Mean doses to produce this end result were: thiopental, 5.2 mg/Kg, propofol, 2.3 mg/Kg, and thiopental-propofol mixture, 3.0 and 1.2 mg/kg, respectively. Fractional algebraic analysis of these results indicated that the drugs were not synergistic at the doses given (sum = 1.1). The dosages reported almost certainly exceeded the ED(50) dose as the anesthesia provider continued dosing until eyelash reflex was lost on all patients. The ED(50) dose is the dose that provided a therapeutic effect in 50% of patients (Katzung, 1998). Rashiq et al. (1994) continued dosing until 100% of the patients became anesthetized. This may account for the differences in dosages and lack of measured synergism compared to Naguib and Sari-Kouzel (1991).

Rashiq et al. (1994) found that the thiopental group recalled significantly less pain on injection versus propofol and the mixture (2 for thiopental vs. 10 for propofol and 10 for the mixture, $P< 0.05$), but the propofol and mixture group received significantly less parentarel anti-emetic (6 for propofol, 9 for the mixture, and 15 for thiopental, $P< 0.05$). There were no significant differences between the two groups regarding other side effects such as nausea not requiring medication, headache, tiredness, hangover, dizziness, sore throat, backache, or myalgia

over 24 hours. Patients receiving thiopental alone had longer discharge times if a strict discharge policy was followed (205 minutes for thiopental, 160 minutes for propofol, and 168 minutes for the mixture). The mixture did allow use of 48% less propofol to obtain results similar to propofol alone. The study concluded that "Induction of anaesthesia with a mixture of propofol and thiopentone provides equally rapid and qualitatively similar recovery to that afforded by propofol alone, in healthy women undergoing outpatient laparoscopy" (p. 1171).

Bacterial Growth in a 1:1 Thiopental and Propofol Mixture

Crowther et al. (1996) injected colonies of *Stapholococcus aureus, Escherichia coli, Pseudomonas aeruginosa,* and *Candida albicans* into vials of thiopental, propofol, a 1:1 mixture, and non-bacteriostatic normal saline, then placed samples of the mixtures on trypticase soy agar culture plate. The plates were stored at 20 degrees Centigrade to represent a realistic clinical scenario of contamination during draw up of agent into a syringe, and storage of the syringe at room temperature until used. The samples were sub-plated at zero, three, six, nine, 12, and 48 hours after inoculation. After sub-plating the plates were cultured at 35 ^{o}C for 24 hours for *S aureus, E Coli,* and *P aeuruginosa*, and 48 hours for *C albicans*.

Thiopental was bactericidal for *P aeruginosa, E coli, and S aureus* at three hours, and bacteriostatic for *C albicans* through 24 hours. Propofol promoted growth of *E coli,* and *C albicans* after 12 hours, and was bacteriostatic for *P aeruginosa* and *S aureus* through 24 hours. The 1:1 mixture was bactericidal at three hours for *P aeruginosa,* and *E coli,* bactericidal for *S aureus* at 12 hours and bacteriostatic for *C albicans* through 24 hours. The measured pH for the mixture was 10.31 versus 10.55 for thiopental and 7.8 for propofol. The high pH of thiopental and the thiopental-propofol mixture may explain the similar effects on bacterial growth (Crowther et al., 1996).

Combining thiopental and propofol may allow a longer margin of safety between drawing up the drug and using it because of reduced risk of perioperative infections from propofol bacterial contamination. Current manufacturer recommendations state that propofol must be discarded six hours after drawing it up into a sterile syringe (Doyle, 1998). The apparent

bactericidal action of the 1:1 mixture may allow safe storage of the mixture for up to 24 hours. This longer window of safety might allow less waste of older agent, thereby reducing costs. However, further study needs to be done to prove or disprove this theory.

Chernin, Smiler, and Buchannan (1998) studied a 1:1 mixture of thiopental and propofol and the effects on bacterial growth and batch mixing of the two agents. *S aureus* inoculated into propofol showed an increase in the number of colonies over 120 hours, while the *S aureus* colonies injected into thiopental and the 1:1 mixture decreased semi-logarithmically over 120 hours. Batch mixing of agents under a laminar flow hood also minimized accidental microbial contamination, eliminated the risk of glass shard contamination from opened ampoules, and provided labeled syringes that were both convenient and easy to use.

Physical and Chemical Stability of a 1:1 Mixture

Prankerd and Jones (1996) mixed propofol and thiopental, stored the mixtures at four or 25 ^{o}C, then examined the physical and chemical changes at various times using microscopy, laser diffraction, and high-performance liquid chromatograpy. They found that droplet size did not appreciably increase over the first 24 hours, and chemical degradation was not significant for the first 6 hours, with a five percent loss of each drug at 30 hours. These findings support the assumption that mixing the two drugs will not cause significant chemical or physical changes for 24 hours.

Chernin, Stewart, and Smiler (1996) examined the chemical stability of a 1:1 mixture stored in polypropylene syringes at four and 23 ^{o}C using high performance liquid chromatography analysis.

The mixture maintained its chemical stability for 13 and five days when stored at four and 23 ^{o}C, respectively.

Drug Costs of a 1:1 Mixture versus Propofol Alone

Chernin, Smiler, and Buchannan (1998) studied a 1:1 mixture of thiopental and propofol and its direct drug costs. They found the average induction cost for a 70 kg. patient using the mixture was $2.83 versus $10.37 for propofol alone. The costs over two months for 811 general

surgical inductions were $2,300 for the mixture and $6,800 for 657 general surgery inductions using propofol alone.

Summary

These studies found that the 1:1 mixture of thiopental and propofol was synergistic, showed similar recovery characteristics compared to propofol alone, was chemically and physically compatible for up to 24 hours, and cost less than propofol alone. These studies did not examine the incidence of nausea requiring rescue anti-emetics and compare that to the total direct costs. These studies do not conclusively demonstrate the superior characteristics of the mixture, but provide support for further study. A literature search did not identify a study that compared the recovery time, incidence of anti-emetic use during recovery, and the direct costs of propofol, thiopental, and a mixture of the two drugs. This study may fill that gap.

CHAPTER III: METHODS

Introduction

This chapter will discuss the method of inquiry of the study, as well as explain the precautions taken to ensure patient and anesthesia provider privacy and safety. It will also explain the plan for data analysis.

Research Design and Procedures

The purpose of this study was to examine and describe the relationship between the use of an induction agent and the resulting length of recovery, amount of nausea medication given, and the direct drug costs. A descriptive correlational research design was appropriate for this study as it examined the relationships that existed in a situation (Burns & Grove, 1993). There was no attempt to manipulate or control the variables.

The setting was a 300 bed metropolitan trauma hospital on the East Coast for a one year retrospective chart review of past surgical patients who received propofol or a 1:1 mixture of the two during IV anesthesia induction.

Sample

The data was collected from the charts of patients who underwent routine outpatient surgery requiring general anesthesia, endotracheal intubation, and induction of anesthesia with either propofol or a 1:1 volume mixture of propofol and thiopental. These records were chosen from a list of patients obtained from pharmacy billing records within the past year. The goal of the study was to examine and record the data from 360 charts. The information collected from the charts was assigned to either a propofol or 1:1 mixture group based on which agent was used for induction.

A power level of 0.80 and an alpha set at 0.05, assuming a 15% difference among the groups, requires a total sample of 345 subjects (Burns & Grove, 1993). Prior studies showed a 20-40% difference in results between propofol, thiopental, and the 1:1 mixture (Chernin et al., 1996, Chernin et al., 1998, Rashiq et al., 1994). A 15% difference was

chosen to avoid errors that might occur if the difference between groups was less than that identified in previous studies.

Measurement

The data gathered from chart reviews was recorded on a data collection tool. A pre-test was performed on the first fifty cases to verify the data collection tool. Demographic, surgical, anesthesia, recovery, and adverse events data of individual surgical patients were recorded by the principal investigator (see Appendix A and B). The patient's American Society of Anesthesiologists classification, and selected pre-existing conditions of hypertension, diabetes mellitus, hepatic disease, renal disease, and chronic pulmonary disease was also recorded. Thiopental and propofol are metabolized by the liver with the metabolites and unchanged drug excreted through the kidneys. Propofol may also be metabolized in the lungs. Hypertension and diabetes mellitus cause renal damage and might therefore affect clearance times. Pulmonary and hepatic disease may also prolong clearance times which may cause longer recovery times (Stolting, 1991).

The diagnosis, surgical procedure, anesthesia provider, amount and type of maintenance anesthesia, and other intraoperative medications were recorded for later classification and examination for trends. Inhalational agents such as Halothane have relatively longer excretion times and may prolong recovery, therefore choice of maintenance agent may affect recovery. Any peri-operative narcotic medication and dose was also recorded. Narcotics cause sedation and may affect recovery times, as well as increase nausea and vomiting (Stolting, 1991). Anti-emetics given post operatively were recorded as anti-emetics increase the cost of surgery as well as represent complications that may prolong recovery times (Morgan & Mikhail, 1996).

Protection of Human Rights

Patient and institutional confidentiality were safeguarded throughout the study. Anesthesia providers were identified only by a code number, and the data was kept in a secured file cabinet when not in use. The master anesthesia provider list and the pharmacy list identifying patients were kept secured during the study, then destroyed after the study was

completed. The hospital was identified only as an East Coast metropolitan medical center. The study was submitted to the Uniformed Services University of the Health Sciences and hospital Institutional Review Board for approval prior to the study.

The institution s anesthesia department director received a letter explaining the purpose of the study, the time involved, a statement of how to obtain the results, and a statement of confidentiality (Appendix C). Hospital administrative and Institutional Review Board approval were necessary before data could be collected.

Plan for Data Analysis

Data collection began March 1999 and proceeded over multiple visits to the hospital until May 1999. The data was analyzed using the Statistical Package for the Social Sciences (SPSS), (5 Dec 1995, version 8.0) program. Mean recovery times, drug costs, and total costs including anti-emetics costs were calculated, plotted, and related to the four research questions. Independent Samples t test and Chi squares were used to determine the statistical significance of mean differences and relationships between the results. These results were correlated with the data on patient demographics, providers, pre-existing conditions, anesthesia maintenance and narcotics administration, and anesthesia time. These results are presented in tables for ease of interpretation.

Summary

We planned to examine the charts of 360 outpatient surgical patients undergoing surgery during the past year in a suburban medical center for data regarding intravenous anesthesia induction and recovery. The data we obtained included patient demographics, length of anesthesia and recovery times, amounts and costs of induction, narcotic, and anti-emetic medication use, and pre-existing conditions that might influence recovery times. This descriptive correlational study was approved by both the university and hospital Institutional Review Boards and maintained patient and institutional confidentiality and human rights. Data collected was analyzed using the SPSS program.

CHAPTER IV: ANALYSIS OF DATA

Introduction

This chapter lists the findings and statistical significance of the data, as well as procedures used to obtain the data. This results are presented in tables for ease of interpretation.

Data Collection Procedures

The pharmacy department at the hospital prepared a list, based on billing records, of surgical patients who received either propofol or the 1:1 mixture between January 1, 1998 and January 1, 1999. This list was further narrowed down to cases that resulted in three or less days hospitalization. There was no attempt to randomize the charts obtained, however the names were in alphabetical and not chronological order. This provided a wide range of dates of drug administration throughout the past twelve months. The pharmacy was unable to identify patients who received thiopental alone. A pharmacy representative reported that thiopental had not been in general use for over 5 years (M. J. Turner, personal communication, February 13, 1999), and it was decided that differences in current techniques and practices would make comparisons with cases from 5 years ago meaningless. For example, the anti-emetic drug Zofran (ondansetron) has only been in common use since 1993 and would likely show different usage compared to current practice (Twersky, 1995). It was elected to proceed with the study examining only the charts of patients receiving propofol or the mixture.

The principal investigator excluded the charts of any patients who were not extubated at the end of the case or who did not recover in the PACU. Comparison of mean recovery times between the two groups in a 50 chart test sample of the propofol and 1:1 mixture group showed a difference of only two percent, not the 20% difference seen in previous studies (Chernin et al., 1996, Chernin et al., 1998, Rashiq et al., 1994). A statistically significant difference of two percent with a power level of 80 and alpha set at 0.05 would require 19,618 subjects (Burns & Grove, 1993). Obtaining such a large sample was beyond the scope of this study, and it was elected to conduct a pilot study with a total of 212 charts.

The average wholesale price (AWP) of each drug was used rather than actual cost to the

hospital. Because a representative from the hospital anesthesia department was unavailable to serve as an advisor, a member of the University Nurse Anesthesia Department faculty served in this capacity. Both the University and facility Institutional Review Boards reviewed the study protocol, and both classified it as exempt. Independent Samples t test and Chi square tests were used to determine the statistical significance of the data.

Patient Characteristics

Two hundred and twelve patients were included in the record review with ages ranging from 17 to 90 years. The mean age for the propofol group was 48.3 years, and the mean age for the thiopental group was 47.8 years, a statistically non-significant difference. Eighty-two patients received propofol, and 130 received the mixture. Ninety five men and 117 women were included. The 1:1 mixture group had almost equal representation between men and women at 55% and 45% respectively, while the propofol group included more women than men, at 72% and 28% respectively (see Table 2). The difference in gender was significant using Chi square analysis. There were no statistically significant differences between the propofol and 1:1 mixture group regarding ASA class (see Table 3).

Surgeries were divided into eleven groups: Abdominal, Cranial, Extrathoracic, Extremity, Genito/Urinary, Head/Neck, Intrathoracic, Neuoroaxial, Oropharynx, Renal, and Vascular. The differences in surgeries of the two groups were not statistically significant.(see Table 4).

Table 2.

Gender of Patients in Propofol and 1:1 Mixture Group

		Induction Drug Used					
		Propofol		***1:1 Mixture***		***Total***	
		#	***%***	***#***	***%***	***#***	***%***
Patient Gender	Male	23	28	72	55	95	45
	Female	59	72	58	45	117	55
Total		82	100	130	100	212	100

Table 3.

ASA* Classifications in Propofol and 1:1 Mixture Group

	Induction Drug Used					
	Propofol		***1:1 Mixture***		***Total***	
ASA Class	***#***	***%***	***#***	***%***	***#***	***%***
ASA I	11	13	19	15	30	14
ASA II	53	65	73	56	126	59
ASA III	17	21	38	29	55	26
ASA IV	1	1	0	N/A	1	0
Total	82	100	130	100	212	100

* ASA = American Society of Anesthesiologists

Table 4.

Comparison of Types of Surgery in Propofol and 1:1 Mixture Groups

	Induction Drug Used					
	Propofol		*1:1 Mixture*		*Total*	
Type of Surgery	*#*	*%*	*#*	*%*	*#*	*%*
Abdominal	24	29	40	31	64	30
Cranial	2	2	0	0	2	1
Extrathoracic	2	2	3	3	5	2
Extremity	14	17	24	18	38	18
Genito-Urinary	9	11	7	5	16	8
Head/Neck	10	12	22	17	32	15
Intrathoracic	0	0	2	2	2	1
Neuroaxial	14	17	21	16	35	7
Oropharynx	1	1	2	2	3	1
Renal	2	4	4	3	6	3
Vascular	4	5	5	4	9	2
Total	82	100	130	100	212	100

Seventy two anesthesia providers supplied anesthesia to the 212 patients. One anesthesia provider used the 1:1 mixture in 10 of the cases, and another provider gave propofol in seven cases. Twenty nine providers used only the 1:1 mixture in 48 of the cases, and 15 providers gave only propofol in 30 of the cases. Twenty eight providers gave propofol in 52 of the cases and the 1:1 mixture in 82 of the cases (see Appendix D). There is a significant correlation between the anesthesia providers and induction drug used ($P< 0.05$). Analysis of the PACU recovery times for the four providers with the largest numbers of cases showed averages of 123, 107, 138, and 146 minutes. These averages are less than or equal to the average recovery times. It is unlikely that these providers abnormally affected the sample.

Patients weights ranged from 43 to 203 kilograms, with a mean weight of 81.9 kg in the propofol group and 86.6 kg in the 1:1 mixture group. The difference of 4.7 kg was not statistically significant. Length of surgery was 22 minutes longer in the 1:1 mixture group (130 minutes) than the propofol group (108 minutes). Length of anesthesia was 25 minutes longer in the 1:1 mixture group (194 minutes) compared to the propofol group (169 minutes). Both the surgery and anesthesia time differences were significant ($P< 0.05$). Recovery time was 13 minutes longer in the 1:1 mixture group (147 minutes) compared to the propofol group (134 minutes), but the difference was not statistically significant.

The mean MAC hours for the propofol group was 1.6, while the 1:1 mixture group was 1.7, with a difference of 0.1 hours. The mean narcotic administration in morphine equivalents was 30 mg for the propofol group and 32 mg for the 1:1 mixture group, with a difference of 2 mg. These differences in MAC hours and narcotic administration were not statistically significant (see Table 5).

Table 5.

Significance of Differences Between Propofol and 1:1 Mixture Groups for Study Variables

	Induction Drug Used	*N*	*Mean*	*Std. Deviation*	*Std. Error Mean*	*Significance*	*Mean Difference*
Weight (kg)	Propofol	82	81.98	22.7	2.51	0.26	-4.59
	1:1 Mixture	130	86.57	28.2	2.47		
Age (years)	Propofol	82	48.28	17.9	1.97	0.39	0.53
	1:1 Mixture	130	47.75	16.5	1.45		
Surgery * Length (minutes)	Propofol	82	107.5	64.5	7.12	0.01	-22.45
	1:1 Mixture	130	130	87.7	7.69		
Anesthesia * Length (minutes)	Propofol	82	168.8	74.6	8.24	0.01	-25.3
	1:1 Mixture	130	194.1	97.5	8.55		
PACU Time (minutes)	Propofol	82	133.9	103	11.3	0.99	-12.74
	1:1 Mixture	130	146.7	87.9	7.71		
Anes. in MAC hours	Propofol	82	1.573	1.2	0.13	0.09	-0.10
	1:1 Mixture	130	1.677	1.19	0.1		
Narcotic (MSO4 equivalent) in mg	Propofol	82	29.89	38.4	4.24	0.90	-2.28
	1:1 Mixture	130	32.17	23.4	2.06		

* Significant at P <0.05

PACU = Post Anesthesia Care Unit

MAC = Minimum Alveolar Concentration

MSO4 = Morphine

Thirteen percent of patients receiving propofol received anti-emetics compared to 6% of patients in the 1:1 mixture group. This difference was not statistically significant. However, this included anti-emetics frequently given as a prophylaxis with narcotics. The drugs phenerghan and vistaril were given with Demerol in both groups post-operatively and may not have been given for true nausea. With these cases excluded, post-operative anti-emetic use was 10% for the propofol group compared to 5% for the 1:1 mixture group (see Table 6).

Mean recovery times for the 1:1 mixture group receiving anti-emetics excluding vistaril and phenerghan was 226 minutes. This included an abdominal case that was in the PACU for 560 minutes for fluid management. Without this case, the average was 159 minutes. Mean recovery times for the propofol group, excluding the patients receiving vistaril or phenerghan, was 182 minutes. With one vascular case with a recovery time of 654 minutes excluded, the mean recovery time was 116 minutes.

Mean anti-emetic drug costs for the propofol group excluding vistaril and phenerghan was $2.83, or $3.15 for all medications. The mean cost of anti-emetic use for the 1:1 mixture group excluding vistaril and phenerghan was $0.96, or $1.08 for all drugs. The differences between the two groups was $1.87 for Droperidol, Reglan, and Zofran alone and $2.07 for all drugs. The difference was statistically significant ($P<0.05$). The principal investigator used a reference book (Medical Economics Company, Inc., 1998) obtained from the hospital pharmacy to calculate the Average Wholesale Price (AWP) per milligram of drug (see Table 7).

Table 6.

Post Operative Anti-Emetic Use

		Induction Drug Used					
Total Post Op Anti-emetic Use		***Propofol***		***1:1 Mixture***		***Total***	
		#	*%*	*#*	*%*	*#*	*%*
	Yes	11	13	8	6	19	9
	No	71	87	122	94	193	91
Total		82	100	130	100	212	100
Zofran, Reglan or Droperidol Only							
	Yes	8	10	6	5	14	7
	No	74	90	124	95	198	93
Total		82	100	130	100	212	100

Table 7.

Calculated Average Wholesale Price (AWP) per Milligram of Each Measured Drug

*****

Drug	***Calculated AWP in U.S. Dollars per Milligram***
Diprivan	0.18
Droperidol	1.55
Phenerghan	0.07
Reglan	0.21
Sodium Thiopental	0.02
Vistaril	0.46
Zofran	6.11

* Cost obtained by dividing AWP by milligrams to obtain cost per milligram of drug

A larger percentage of the 1:1 mixture group received droperidol. The percentage of the propofol group receiving Zofran was twice as much as the 1:1 mixture group (see Table 8). Pre-operative administration of anti-emetics was significant at $P<0.05$.

Table 8.

Intra/Pre-operative Anti-emetic Use in the Propofol and 1:1 Mixture Group

		Induction Drug Used					
		Propofol		***1:1 Mixture***		***Total***	
		#	**%**	**#**	**%**	**#**	**%**
Type of Pre/Intra	No anti-emetic	55	67	75	58	130	61
Operative Anti-emetic	Droperidol	1	1	25	19	26	12
Given	Reglan	10	12	12	9	22	10
	Zofran	7	9	5	4	12	6
	Reglan + Droperidol	5	6	9	7	14	7
	Reglan + Zofran	2	2	1	1	3	1
	Droperidol + Zofran	1	1	2	2	3	1
	Reg + Drop + Zofran	1	1	1	1	2	1
Total		82	100	130	100	212	100

The propofol group showed a higher percentage of cases using Sevoflurane and Isoflurane for anesthesia maintenance. Both groups showed similar numbers of cases with Desflurane (see Table 9). The difference was not statistically significant.

Table 9.

Anesthetic Agent Used in Propofol and 1:1 Mixture Groups

		Induction Drug Used					
		Propofol		***1:1 Mixture***		***Total***	
		#	**%**	**#**	**%**	**#**	**%**
Inhalational Agent	Isoflurane	21	26	47	36	68	32
Used	Sevoflurane	34	16	38	29	72	34
	Desflurane	27	33	45	35	72	34
Total		82	100	130	100	212	100

Both groups had similar rates of pre-existing conditions, with the 1:1 mixture group showing slightly higher percentages of Chronic Renal Failure, Hypertension, Diabetes Mellitus, and decreased hepatic function. The 1:1 mixture group also had more patients with both Hypertension and Chronic Renal Failure (see Table 10). There was no statistically significant difference between the two groups.

Table10.

Pre-existing Conditions Among Patients in the Propofol and 1:1 Mixture Group

		Induction Drug Used					
		Propofol		***1:1 Mixture***		***Total***	
		#	*%*	*#*	*%*	*#*	*%*
Pre-existing	No Pre-existing	55	67	79	61	134	61
Conditions	CRF	-	-	1	1	1	0
	HTN	14	17	23	18	37	18
	DM	4	5	6	5	10	5
	COPD	2	2	1	1	3	1
	Hepatic	1	1	4	3	5	2
Multiple	CRF/HTN	1	1	4	3	5	2
Pre-existing	CRF/HTN/DM	1	1	1	1	2	1
Conditions	CRF/DM	-	-	1	1	1	0
	CRF/HEP	-	-	1	1	1	0
	HTN/DM	2	2	7	5	9	4
	HTN/DM/COPD	1	1	1	1	2	1
	HTN/DM/HEP	-	-	1	1	1	0
	HTN/HEP	1	1	-	-	1	0
		82	100	130	100	212	100

The mean cost of induction for the propofol group was $27.31 compared to $14.21 for the 1:1 mixture group. The difference of $13.09, or almost double the 1:1 mixture cost, is statistically significant at $P< 0.05$ (see Figure 3). The average dose to induce anesthesia for the propofol group was 151.72 mg, while the average dose to induce anesthesia in the 1:1 mixture group was 16.52 ml of the 5 mg propofol/12.5 mg thiopental

mixture, or 77.6 mg of propofol and 206.5 mg of thiopental. Average induction doses were 1.85 mg/kg for propofol and 0.89 mg/kg of propofol and 2.38 mg/kg of thiopental in the 1:1 mixture (see Table 11).

Table 11.

Average and Suggested Induction Drug Doses in Mg/Kg

	Propofol	*1:1 Mixture (prop/STP)*
Dose (mg)	151.7	77.6, 206.5
Weight (kg)	81.98	86.57
Dose in Mg/Kg	1.85	0.89, 2.38
Suggested Dose in Mg/Kg	2-2.5	4.0-5.0

Note. Suggested dose from Stolting, R. K. (1991). Pharmacology and physiology in anesthetic practice (2nd ed.). Philadelphia: J. B. Lippincott Company.

PACU charges were $9.00/ minute (Latoya Turner, personal communication, June 23, 1999). The average recovery time for the propofol group was 134 minutes and cost $1205.37. The average recovery time for the 1:1 mixture group was 147 minutes and $1320.03, with a difference of $114.66 (see Figure 4).

Summary

This study found statistically significant differences between the propofol and 1:1 mixture groups in gender, anesthesia provider, anesthesia and surgery lengths, post-operative anti-emetic costs, and cost of the induction drug. There were no significant

differences between the two groups in ASA classifications, type of surgery, weight, age, length of recovery, MAC hours, narcotic use, anesthesia maintenance drug used, or pre-existing conditions. The propofol drug cost was $13.09 more than the 1:1 mixture cost. The 1:1 mixture group recovery costs were $114.66 more than the propofol group.

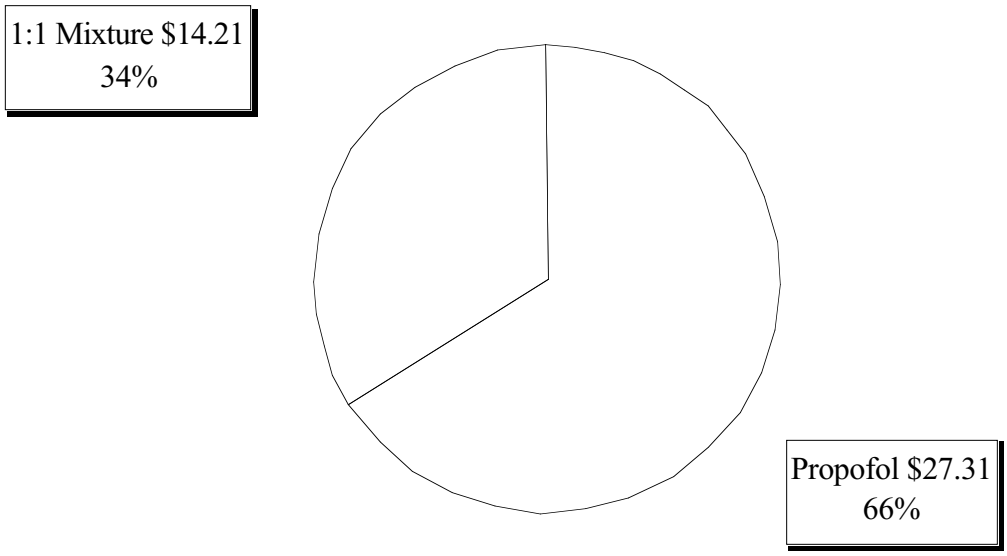

Figure 3.

Mean Cost of Induction Drug

Percentages are of total cost

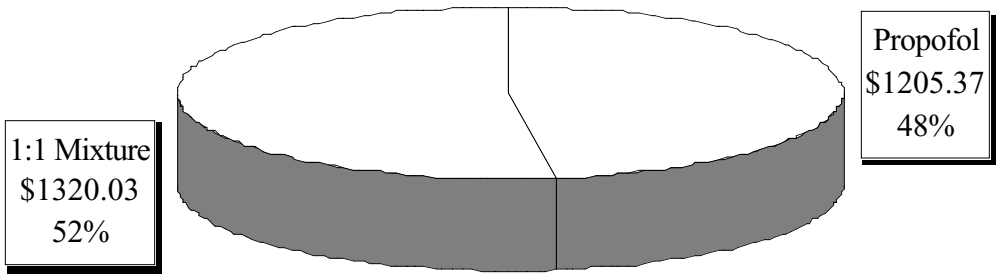

Figure 4.

Mean Cost of PACU* Recovery

Percentages are of total cost
*PACU = Post Anesthesia Care Unit

CHAPTER V: SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Introduction

Data analysis showed that the 1:1 mixture group had lower direct drug costs, but higher PACU recovery times. This chapter will examine the significance of these and other findings, and make recommendations for future study.

Changes in health care require that anesthesia providers make direct drug costs, length of recovery, and side effects that might prolong recovery a greater priority when choosing which agents to use. This study s purpose was to examine the direct drugs costs, recovery length and cost, and post-operative nausea and vomiting after anesthesia induction with a 1:1 mixture of propofol and sodium thiopental. Tuman s (1995) model of gathering outcome data was used to support the use of current anesthesia practices in this study. We collected data on patient demographics, anti-emetic use, pre and intra-operative confounding variables, induction drug use and cost, and PACU recovery costs. We analyzed this data using Independent Samples t Tests and Chi square tests to determine significance.

Demographic Differences

This study found no significant difference in the demographics of the propofol and 1:1 mixture groups other than a difference in gender assigned to the propofol group. We also noted an increased average surgery and anesthesia time in the 1:1 mixture group. This increased surgery length in the 1:1 mixture group may reflect a bias by the anesthesia providers to use propofol only for cases with expected shorter surgical times. For instance, propofol was frequently used to induce anesthesia for lumbar discectomies, a

surgical procedure with a relatively short surgical time. In contrast, anesthesia providers frequently used the 1:1 mixture to induce anesthesia for spinal fusion cases, a procedure with longer surgical times. There was no attempt to quantify this possible discrepancy. Increased surgical times will, of necessity, increase the anesthesia time since anesthetic time is measured from the moment the anesthesia provider assumes care for the patient until the patient is in the PACU/ ICU and others assume that care (Greg Dudley, personal communication, November 17, 1998). Surgery ends before anesthesia care ends.

MAC Hours and Narcotic Use

Mean MAC hours and average narcotic usage were similar between the two groups, but the slight difference may have prolonged the 1:1 mixture recovery time. It was expected that increased MAC hours and narcotic usage would lead to increased recovery times, as higher anesthetic doses over a longer time would lead to increased absorption of anesthetic agent, causing a prolonged recovery as the anesthetic agents were metabolized to non-active metabolites or excreted (Stolting, 1991). A similar effect was expected with higher narcotic administration. The slightly higher MAC hours and mean narcotic use in the 1:1 mixture group, while not achieving statistical significance, may have prolonged recovery.

Synergism of Thiopental and Propofol

In order to use the fractional analysis equation used in Naguib and Sari-Kouzel (1991) to determine synergism between the two drugs, we would need a group of patients that received thiopental alone. This group was not available to the study. If we assumed an average thiopental induction dose to be 5.2 mg/kg as found in Rashiq et al. (1994) with

the average weight of all patients to be 84.8 kg, the average thiopental dose would be 441 mg. Using these numbers, the fractional analysis equation is:

$$Tc/Ts + Pc/Ps = 1.0, \text{ or}$$

$$\frac{207}{441} + \frac{78}{152} = 0.98$$

The result of less than one indicates that the drugs were synergistic. However, this conclusion is probably flawed as the anesthesia induction in these patients was affected by confounding factors. These factors included concurrent administration of narcotics and/or benzodiazapines which will lower the dose necessary to induce anesthesia (Stolting, 1991) and the assumption that the induction dose of thiopental alone would be as high as that as found in other studies. Rashiq et al. (1994) found that the average induction dose for propofol alone was 2.3 mg/kg, while this study found the average induction to be 1.85 mg/kg. The average dose of the 1:1 mixture in the Rashiq et al. (1994) study was 1.2 mg/kg of propofol and 3.0 mg/kg of thiopental, compared to 0.89 mg/kg of propofol and 2.38 mg/kg of thiopental in this study. A 5.2mg/kg dose of thiopental as found in the Rashiq et al (1994) study is probably higher than would have been found if the patients in this study had received thiopental alone, and therefore lowered the algebraic sum, falsely indicting that the mixture was synergistic.

A literature search done after data analysis was complete found a study that indicated thiopental and propofol were additive, not synergistic (Ronald, Bradley, & Kissin, 1999). The authors of this study repeated the work of Naguib and Sari-Kouzel, but found the ED(50) of the two drugs to be additive. They hypothesized the Naguib and

Sari-Kouzel (1991) study had a small difference from the additive line that made it unable to determine significance. They did find that combinations of midazolam and thiopental or propofol were synergistic, and suggested that benzodiazepines affected a different site on the $GABA_A$ receptor than the propofol or thiopental. These contradictory findings suggest that further studies are needed to definitively determine if the drugs are synergistic.

PACU Recovery Times

The longer PACU recovery time for the 1:1 mixture group of 13 minutes is not statistically significant. This difference in mean recovery times is similar to the previous study (Rashiq et al., 1994). The difference in cost of recovery time was $114.66. Recovery times are dependent on many factors, not just the type of agent used to induce anesthesia. A limitation of this study was not being able to identify the reason for abnormally long PACU stays. Some of the patients charts explained the delay such as waiting for an inpatient room, blood pressure control, or electrolyte control. There were many cases of recovery room stays over three hours with no reason for the delay, and only one that showed a prolonged recovery time because of nausea. Because there was little consistent information on the cause for the prolonged recovery room stay, no patients were excluded from consideration which may have affected the results.

Post-Operative Nausea and Vomiting

The propofol group showed an increased use of post-operative anti-emetics. This was not found in prior studies (Rashiq et al., 1994). A higher percentage of patients in the propofol group were either female, underwent Genito-Urinary surgery, or both. Young female patients undergoing gynecological surgery are more prone to nausea (Twersky,

1995). In Rashiq et al. s (1994) study all patients underwent gynecological surgery which may explain the similarity in incidence of nausea requiring intervention between the propofol group and the 1:1 mixture group in that study. One 71 year old female patient who received 2.9 mg/kg of propofol for a mandible reconstruction was admitted overnight due to nausea and vomiting. This was the only patient that was identified to have significant problems with nausea and vomiting requiring an unplanned admission.

Induction Drug Costs

The mean difference in induction drug costs of $13.09 (almost 100% of the 1:1 mixture cost) between the propofol and 1:1 mixture group is an important consideration. This clearly supports the findings of Rashiq et al. (1994) and Chernin et al. (1998) that induction with a 1:1 mixture is more cost efficient than propofol alone. These costs must be individualized for each hospital as the AWP of a drug may not be the actual cost to the hospital, and did not take into consideration the cost of the narcotics or benzodiazapines used during anesthesia induction. Narcotics and benzodiazepines will reduce the dose necessary to induce anesthesia (Stolting, 1991).

Limitations

The study was limited by the number of cases that were possible to evaluate given the resources available to conduct it. Finding statistical significance of differences between the two groups was limited by the sample size. There was no data collected to differentiate the causes of prolonged PACU recoveries. Because we did not record any anesthesia inductions using thiopental, we were unable to determine synergism accurately. We were unable to accurately determine the bias of anesthesia providers to use propofol

for procedures that demonstrate shorter surgical times. We were unable to accurately measure the effect on PACU recovery times of slightly increased MAC hours and narcotic use in the 1:1 mixture group.

Considerations for Future Study

This study was limited by the small number of charts available for review, lack of information on or recognition of confounding factors that prolonged recovery room stay, confounding of anesthesia induction doses by concurrent administration of narcotics and benzodiazipines, and reliance on recorded anti-emetic use to quantify post-operative nausea and vomiting (PONV). Future studies should record other complications that prolong PACU recovery and attempt to control for narcotic use during anesthesia induction. These studies should have a system in place to document PONV not requiring anti-emetic administration but that might prolong recovery length. A prospective, random, double blind design would be more appropriate to control differences between the two groups.

Summary

The study found that the recovery time and profile of the 1:1 mixture were similar to the recovery time and profile of propofol alone. The 1:1 mixture showed a lower cost for anesthesia induction, but a higher cost for PACU recovery. This longer recovery and higher cost may be related to factors other than the induction drug used. The incidence of anti-emetic administration was higher with propofol alone, but this may be due to the higher percentage of factors promoting post-operative nausea and vomiting in the propofol

group. This findings of this study support the suggestion that mixing thiopental and propofol in a 1:1 ratio by volume for anesthesia induction will provide a recovery profile similar to propofol alone, but at a reduced direct drug cost. It did not support the suggestion that using the 1:1 mixture would have the same PACU costs as propofol. Because there was no thiopental group for comparison, the study could not reliably determine if thiopental and propofol were synergistic and cannot conclude that the results matched predictions based on $GABA_A$ theory. Further study needs to be done to verify these results

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APPENDICES

A. IV Induction Agent Recovery Profile Data Collection Instrument

B. Data Dictionary for IV Induction Agent Recovery Profile Data Collection Instrument

C. Agency Cover Letter

D. Anesthesia Provider Frequency Table

APPENDIX A

IV Induction Agent Recovery Profile Data Collection Instrument

APPENDIX A- IV Induction Agent Recovery Profile Data Collection Instrument

ID # _____ Anesthesia Provider _____

Weight _____ Sex _____ M-1, F-2 Age _____

ASA class _____ I (1), II (2), III (3), IV (4) Other _____

Type of Surgery _____

Surgical time Start _____ End _____ Total Time _____

Anesthesia time Start _____ End _____ Total Time _____

PACU time Start ____ End _____ Total Time _____ Cost $_____

Post Op anti-emetic use ___ Yes (1), No (2) Intervention (drug) ____ Cost $ _____

Drug and Amount Used Thiopental _____ Cost $_____

for Induction Propofol _____ Cost $_____

1:1 Mixture _____ Cost $_____

Pre-existing Conditions (list all that apply) _____ CRF (1), HTN (2), DM (3), COPD (4), Hepatic (6)

Intraoperative Meds Inhalational _____ Isoflurane -1, Halothane -2, Sevoflurane -3, Desflurane -4, Enflurane -5

MAC hrs _____

Narcotic _____ Dose _____

Pre/Intra Op anti-emetic use _____

Other _____

APPENDIX B

Data Dictionary for IV Induction Agent Recovery Profile Data Collection Instrument

APPENDIX B- Data Dictionary for IV Induction Agent Recovery Profile Data Collection Instrument

Variable	Code
Anesthesia Provider	Two digit, Laundry list
Weight	Three digits in kilograms
Sex	Male -1, Female - 2
Age	Number of years at time of surgery
ASA class	I -1, II -2, III -3, IV -4
Type of Surgery	Abdominal 1
	Cranial 2
	Extrathoracic 3
	Extremity 4
	G/U 5
	Head/Neck 6
	Intrathoracic 7
	Neuroaxial 8
	Oropharynx 9
	Renal 10
	Vascular 11
Surgical Total Time	Three digit, time in minutes from beginning to end of surgical procedure

Anesthesia Total Time	Three digit, time in minutes under providers care
PACU Total Time	Three digit, time in minutes from admission to discharge in PACU
Anti-emetic use	Yes - 1, No - 2
PONV Intervention Cost	Cost in dollars to two decimal places
Drug Used	1- Thiopental, 2- Propofol, 3- 1:1 Mixture
Drug Cost	Two digits, in dollars
Pre-existing conditions	CRF -1, HTN -2, DM -3, COPD -4, Hepatic -5
Inhalational agents	Isoflurane -1 Halothane -2 Sevoflurane -3 Desflurane -4 Enflurane -5
Mac Hours	Two digits
Narcotic	Three digits, in morphine equivalents
Other intraoperative medications	1- Droperidol 0.625-1.25 mg 2- Reglan 10 mg 3- Zofran 4 mg 4- Reglan 10 mg + Droperidol 0.625 mg 5- Reglan 10 mg + Zofran 4 mg 6- Droperidol 0.625 mg + Zofran 4 mg 7- Reglan + Droperidol + Zofran

APPENDIX C

Agency Cover Letter

APPENDIX C-Agency Cover Letter

Dear Director of Anesthesia,

Your hospital is being asked to participate in a research study involving recovery characteristics after induction of anesthesia with propofol, thiopental, or a 1:1 mixture of thiopental and propofol. We will be measuring the length of recovery, incidence of anti-emetic use and cost during recovery, and the direct costs of induction with these agents. This will involve a retrospective chart review of 360 surgical outpatients that had anesthesia induced with either thiopental, propofol, or a 1:1 mixture at your hospital during the last year.

Gathering the data will require that the principal investigator have access to the PACU recovery room log to identify the patients, the anesthesia and PACU care record for those patients, and the direct costs to the hospital for the PACU care and any anti-emetic and induction drugs used.

All data specific to your institution will be kept confidential. If we publish the results of the study in a scientific journal or book, your agency will only be identified as an East Coast Urban Medical Center. Individual patient data sheets will be identified by a code # only, and all data will be kept in a secured file cabinet accessible only to the principal investigator. The master list with patients name and medical record number will be destroyed after data collection is complete. All data will be reported in the aggregate.

If you have any questions you may contact Capt John Killpack at (301) 963-1052 (home), 1-800-544-4135 PIN# 378-0058 (pager), or (301) 295-6565 (office). The Uniformed Services University of the Health Sciences committee that reviews research with regards to human rights (Institutional Review Board) is available to answer any questions that you might have. You may contact them at (301) 295-3303.

Study results will be forwarded to your agency upon completion of the study. You will be given a copy of this letter to keep for your records.

Thank you in advance for your assistance with this project. Please contact me if you have any questions or need further information.

Capt. John Killpack, USAF, NC
Student Registered Nurse Anesthetist
Uniformed Services University/ Graduate School of Nursing
4301 Jones Bridge Rd.
Bethesda, MD 20814-4799

APPENDIX D

Anesthesia Provider Frequency Table

APPENDIX D- Anesthesia Provider Frequency Table

Anesthesia Provider	Induction Drug Used		Total
	Propofol	1:1 Mixture	
1	3		3
3		1	1
4	1	10	11
5	1	1	2
6	2	5	7
7	5		5
8	1	4	5
9		4	4
10		2	2
11		1	1
12		5	5
13		1	1
14	3	6	9
16	1	2	3
17	2		2
18		2	2
19		2	2
20		2	2
21		2	2
22	1	4	5
23		1	1
24	1	2	3
25	4		4
26		1	1
27	1	1	2
28	2		2
29		1	1
30	3	1	4
31	2	3	5
32		1	1
33		1	1
34	1	3	4
35	1	4	5

36	3	5	8
37	1	1	2
38		1	1
39	2	3	5
40	1	2	3
41	3	4	7
42	2		2
43	1		1
44		1	1
45	2	1	3
46	2		2
47		1	1
48	1		1
49	1		1
50		1	1
51		2	2
52	1	1	2
53	2		2
54		1	1
55		5	5
56	7	3	10
57	1	1	2
58		1	1
59	2	3	5
60	3	2	5
61		1	1
62	4	3	7
63		1	1
64	2		2
65	3	7	10
66		1	1
67	1		1
68		3	3
69		1	1
70	1		1
71		1	1
72	1		1
Total	82	130	212