

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 22.Dec.03	3. REPORT TYPE AND DATES COVERED THESIS		
4. TITLE AND SUBTITLE "GENDER EFFECT ON RECOVERY TIME FOLLOWING ISOFLURANE ADMINISTRATION WHILE USING A BISPECTRAL MONITOR"			5. FUNDING NUMBERS	
6. AUTHOR(S) CAPT FEVURLY THOMAS G				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) UNIVERSITY OF TEXAS HSC FT SAM HOUSTON			8. PERFORMING ORGANIZATION REPORT NUMBER  CI02-1337	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) THE DEPARTMENT OF THE AIR FORCE AFIT/CIA, BLDG 125 2950 P STREET WPAFB OH 45433			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION AVAILABILITY STATEMENT Unlimited distribution In Accordance With AFI 35-205/AFIT Sup 1			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words)				
<p><b>DISTRIBUTION STATEMENT A</b> Approved for Public Release Distribution Unlimited</p> <p style="font-size: 2em; font-weight: bold;">20040419 059</p>				
14. SUBJECT TERMS			15. NUMBER OF PAGES 67	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT	

GENDER EFFECT ON RECOVERY TIME FOLLOWING ISOFLURANE  
ADMINISTRATION WHILE USING A BISPECTRAL INDEX MONITOR

By

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A Cluster Research Proposal  
submitted in partial fulfillment  
of the requirements for the degree of  
Master of Science in Nursing  
The University of Texas Health Science Center at Houston  
School of Nursing  
December, 2003

## ABSTRACT

Gender has been implicated as affecting outcomes of anesthesia (Gan et al., 1999; Myles, McLeod, Hunt, & Fletcher, 2001). The literature is replete with studies indicating significant gender differences in analgesic requirements. In contrast, literature comparing gender differences in recovery times following general anesthesia is sparse. Review of the literature found little published research considering recovery variations among genders using volatile inhaled agents; in addition, most of the studies referring to this potential were retrospective in nature.

Recovery time differences have been reported between genders during propofol, alfentanil, and nitrous oxide anesthesia (Gan et al., 1999), with women recovering faster than men. Additionally, a prospective cohort study found that women emerged faster than men from general anesthesia but had a slower rate of return to preoperative health status (Myles et al., 2001).

The purpose of this study was to further investigate gender differences in recovery times from general anesthesia using isoflurane and the Bispectral Index monitor (BIS). A convenience sample of 30 men and 22 women (ASA classification: I or II) was enrolled. Subjects received a standardized anesthetic of isoflurane and fentanyl. Depth of anesthesia was assessed using clinical parameters and the bispectral index monitor (BIS) monitor. Wake-up time was measured by the number of minutes it took for subjects to meet both of two endpoints (opening of eyes and hand grasp-and-release to command). An average time of 5.6 minutes for women versus 6.87 minutes for men was found. An analysis of covariance (ANCOVA) was performed to determine if there was any effect of gender on wake-up time. The difference in wake up times was not statistically significant ( $F_{1,46}=0.063$ ;  $p=0.802$ ). The covariates used in our analysis (age, BMI, length of surgery, and total fentanyl dose) were not significantly related to wake-up time ( $p>.05$ ). Thus, no significant gender effects on wake-up time using isoflurane and the BIS were found.

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NOTICE OF APPROVAL TO BEGIN RESEARCH

December 30, 2002

**HSC-SN-02-037** – "Does Gender Affect Recovery Time Following Isoflurane Administration While Using a Bispectral Index (BIS) Monitor?"  
PI: Thomas G. Fevurly, MSN; James Olanda & Gary Pulmano

**PROVISIONS:** Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consent, etc.

**APPROVED:** At a Convened Meeting

**APPROVAL DATE:** December 20, 2002

**EXPIRATION DATE:** November 30, 2003.

**CHAIRPERSON:** Anne Dougherty, MD

Subject to any provisions noted above, you may now begin this research.

**CHANGES:** The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. **ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.**

**INFORMED CONSENT:** Informed consent must be obtained by the PI or designee(s); using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. **Please note that only copies of the stamped approved informed consent form can be used when obtaining consent.**

**UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS:** The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

**RECORDS:** The PI will maintain adequate records, including signed consent documents if required, in a manner that ensures subject confidentiality.

Located in the Texas Medical Center

## ACKNOWLEDGEMENTS

We would like to thank the following people for their dedication and contributions to our educational and research experiences. Their leadership, guidance, support, and generous time commitments throughout this thesis/research process were greatly appreciated: Dr. Mary S. Nelson, LTC, USAF, Associate Director, Clinical Investigation Facility, David Grant Medical Center; Dr. Jennifer A. Thornton, Biostatistician, Clinical Investigation Facility, David Grant Medical Center; and Sylvia Cayetano, LTC, USAF, CRNA, Program Director of Nurse Anesthesia Education, David Grant Medical Center.

We would also like to acknowledge Dona Bovey, Research Protocol Coordinator, Clinical Investigation Facility, David Grant Medical Center, for her assistance and support during this process.

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## CHAPTER I

### Introduction

Gender has been implicated as affecting outcomes of anesthesia. The literature is replete with studies indicating significant gender differences in analgesic requirements (Kest, Sarton, & Dahan, 2000). In contrast, literature comparing gender differences in recovery times following general anesthesia is sparse. Review of the literature found no published research considering recovery time variations between genders using volatile inhaled agents. Recovery times were found to differ between genders during propofol, alfentanil, and nitrous oxide anesthesia (Gan et al., 1999). Additionally, a prospective cohort study found that women emerged faster than men when propofol was used (Myles, McLeod, Hunt, & Fletcher, 2001).

Isoflurane is a commonly used volatile inhaled agent for general anesthesia and is instrumental in fulfilling the U.S. Military's medical readiness mission. The military's newest deployable anesthesia machine, the Narkomed M, is purchased with an isoflurane vaporizer, and any other vaporizer has to be specially ordered. Isoflurane is economical, possesses moderate lipid solubility properties, and requires minimal metabolism (Basak, 1984). With multiple research studies implicating gender-related variations in analgesic requirements and recovery times after intravenous anesthetic agents, it is important to determine if gender affects recovery after volatile anesthetic agents are used. This study will investigate recovery variation between genders following isoflurane and fentanyl administration.

#### Statement of the Problem

The focus of this study is to investigate gender differences in recovery times following a balanced anesthetic plan incorporating the use of isoflurane and fentanyl. Gender has recently been implicated as a contributing factor in post-anesthesia recovery times (Gan et al., 1999; Myles et al., 2001), but literature on gender differences related to anesthesia is limited. Research is needed in this area to increase the anesthesia

community's body of knowledge on this topic.

### Significance of the Problem

To date no published literature has investigated whether gender-related recovery differences exist following the use of volatile inhaled agents for general anesthesia. In the past, women were excluded as research participants mainly due to fluctuations in hormones and the hormones' potential effects on study results (LaRosa & Pinn, 1993). In addition, in the past the Food and Drug Administration's policy excluded women of childbearing years from participating in early phases of clinical trials (Merkatz, Temple, Subel, Feiden, & Kessler, 1993); this policy has since been changed. However, the majority of studies enrolling both genders fail to analyze their findings by gender, thus treating them as homogeneous subjects. This bias in clinical research participants and analysis is a concern among healthcare professionals and government agencies (Levey, 1991).

The incidence of patients experiencing recall or awareness regarding intraoperative events, and thus displaying learning while under anesthesia is disproportionately higher for females than for males (Abernathy, Divoll, Greenblatt, & Ameer, 1982; Dorsh, 1988; Ghoniem & Block, 1997; Kiviniemi, 1994; Ranta, Laurila, Saario, Ali-Melkkila, & Hynynen, 1998). The consequence of intraoperative awareness can range from mild to long-term effects, such as sleep disturbances, flashbacks, panic attacks, development of post-traumatic stress disorder, and preoccupation with death (Ghoniem & Block, 1997; Ouellette & Simpson, 1998). The results of these unexpected occurrences can result in huge economic, psychosocial, and medicolegal sequelae (Ouellette & Simpson, 1998). If gender differences are found to exist following anesthesia, providers could potentially improve patient satisfaction, healthcare costs, and undesired sequelae by delivering gender-specific, evidence-based care. The lack of literature about females and comparing genders further necessitates the need for conducting studies looking at gender differences in pharmacological responses.

### Theoretical Framework

The theoretical framework for this study will be based on a consciousness model (see Figure 1). The concept of *consciousness* represents a continuum of varying states or levels of mental functioning. The extent and duration that a particular anesthetic agent alters an individual's level of consciousness can be influenced by multiple variables. These variables arise from pharmacogenetic factors (Wolf, Smith, & Smith, 2000), brain receptor morphology and neuronal pathway circuitry (LeVay, 1993), biochemical mediator and/or sex-hormone influences (Smith et al., 1999), and learned social, environmental, psychological, and cultural influences (Choleris & Kavaliers, 1999; LeVay, 1993). All of these variables interact with basic pharmacokinetic and pharmacodynamic principles to cause potential gender differences in an individual's level of consciousness, thus affecting recovery from general anesthetic agents.

Pharmacokinetics involves the actions the body has on a drug and entails absorption, distribution, metabolism, and elimination (Ebert & Schmid, 2001). Important fundamental concepts are volume of distribution and clearance. Volume of distribution is the extent that a given dose of a drug disperses within the body's compartments, which directly impacts the drug concentration available to target tissues.

The study of pharmacodynamics encompasses the effects that drugs have on the body. The potency of an inhalational anesthetic agent is related to its lipid solubility. In order to compare relative potencies between agents, the concept of MAC (minimum alveolar concentration) was developed (Koblin, 2000). MAC is the concentration of an inhaled anesthetic vapor that causes immobility in 50% of patients when they are exposed to noxious stimuli (Gold & Finander, 1998).

A drug's physicochemical properties, such as lipid solubility and molecular electrical charge greatly affect its pharmacokinetic properties (Ebert & Schmid, 2001). Clearance involves the elimination of the drug from the body. This process results from

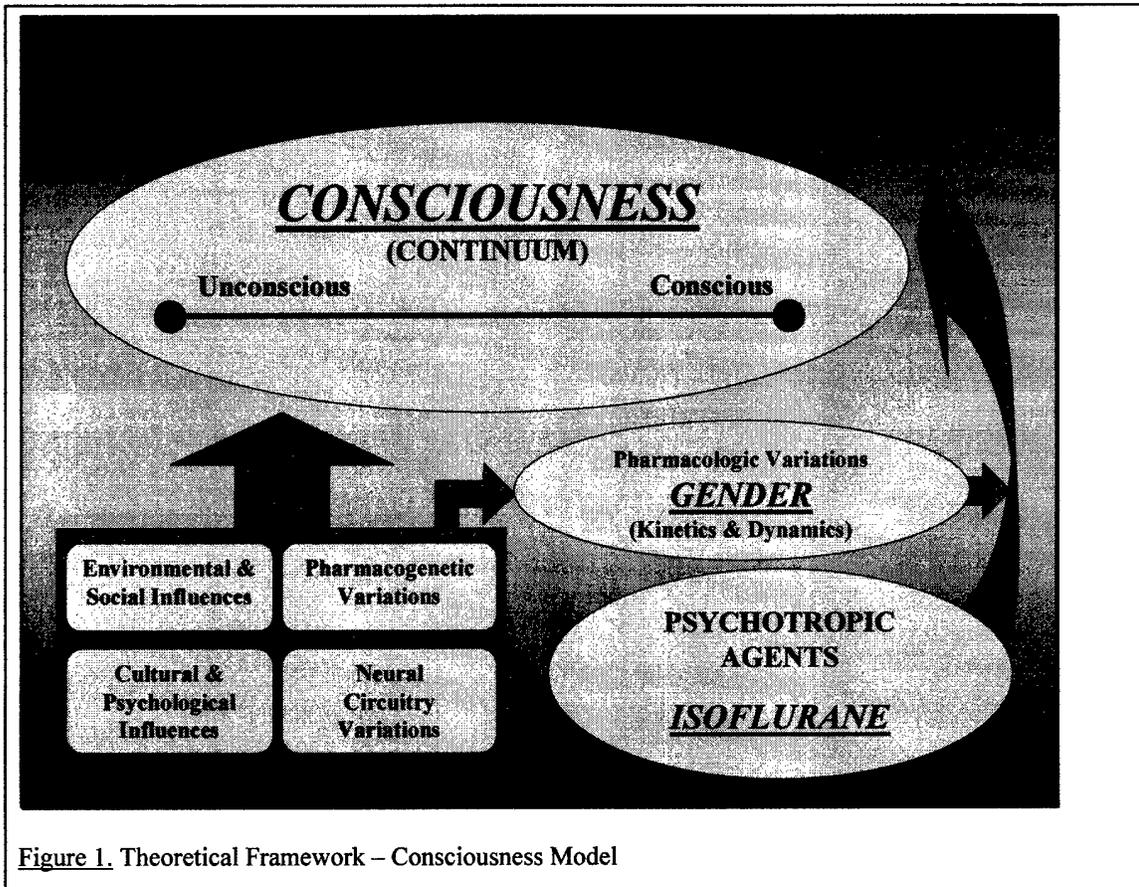


Figure 1. Theoretical Framework – Consciousness Model

enzymatic, hepatic metabolism, renal excretion or by ventilatory washout as with volatile anesthetics (Katzung, 2001). The higher the lipid solubility of a drug the larger its volume of distribution within the body. Women generally are smaller in stature and have a higher fat to muscle ratio (Ciccone & Holdcroft, 1999). This difference in fat composition and body mass between genders can affect target tissue and blood/plasma concentrations by increasing drug deposition into fat stores. Sex-related differences in the pharmacokinetic and pharmacodynamic properties of many drugs is in all likelihood a result of gender variation in body size and composition as well as sex-specific hormone effects (Merkatz et al., 1993).

The anesthetic properties of isoflurane result from increased concentrations of the drug within brain tissue rendering the patient unconscious and free of painful sensation. Recovery results from the clearing of the agent from the brain. The depth of the anesthetic plane is directly related to the concentration of the agent in the central nervous system (Ebert & Schmid, 2001). Whether the effects result from lipid membrane disruptions, changes to the lipid bilayer, or direct receptor-ligand interactions is unknown. However, GABA<sub>A</sub> receptors have recently been implicated as a potential site of action (Koblin, 2000). Ciccone and Holdcroft (1999) reported direct and indirect interactions between sex steroid hormones, such as progesterone metabolites and GABA<sub>A</sub> receptors. They also implicate sex hormone and GABA<sub>A</sub> receptor interactions as having potential effects on anesthetic agents, to include volatile anesthetic agents.

#### Purpose

The purpose of this research study was to investigate whether there were gender differences in recovery time following the use of isoflurane and fentanyl in a balanced anesthesia technique.

#### Definition of Terms

Body Mass Index (BMI). Conceptual definition: the body mass index is a measurement index for estimating obesity. It is obtained by taking a person's weight in

kilograms (kg) divided by their height in meters squared ( $m^2$ ). An important factor in interpreting the BMI value is age; a high value is more likely to indicate obesity in a younger person than an older person (Thomas, 1997). Operational definition: age, height and weight will be obtained during the pre-operative interview. Height and weight will be measured using a hospital balance scale.

General Anesthesia. Conceptual definition: Unconsciousness and loss of ability to perceive pain associated with inhalation and/or intravenous anesthesia. Operational definition: Anesthesia with unconsciousness maintained with isoflurane. Patients may be either spontaneously breathing or assisted with ventilation. A Bispectral Index (BIS) value in the range of 40 to 60 will indicate general anesthesia has been achieved.

Minimum alveolar concentration. Conceptual definition: Minimum alveolar concentration (MAC) is the concentration of an inhaled anesthetic vapor that causes immobility in 50% of patients when they are exposed to noxious stimuli (Gold & Finander, 1998). Operational definition: The MAC required to maintain anesthesia. The concentration of agent will be measured with a respiratory gas monitor (vol %) required to maintain a BIS value of 40 to 60 and correlates with a level consistent with the hallmarks of general anesthesia: unconsciousness, muscle relaxation, and autonomic control (Bard, 2001; Dahan, Olofsen, Frank, & Swen, 1999).

Recovery time. Conceptual definition: period of time from discontinuation of anesthesia delivery to eligibility for discharge to recovery room (Ebert, Robinson, Uhrich, Mackenthun, & Pichotta, 1998). Operational definition: measurement of recovery time will be assessed by the time interval after isoflurane is discontinued until the patient is able to follow verbal commands (hand grasp and release) and open eyes.

#### Research Hypothesis

Because of variations in pharmacologic effects due to differences in body mass composition and hormonal influences, women will have a faster recovery time than men following general anesthesia with isoflurane and fentanyl.

### Assumptions

The assumptions for this study were as follows:

1. The patients were rendered unconscious and remained unconscious during the administration of isoflurane.
2. The patient recovered from general anesthesia following the cessation of isoflurane.
3. The patient did not have significant organ or system dysfunction to decrease respiratory ability or drug elimination.
4. Additional pharmacologic agents given during the operative procedure were controlled for by establishing preset allowable dose ranges and did not create a bias between genders or significantly affect recovery times.
5. Recovery was dependent almost entirely on ventilatory elimination of isoflurane

### Limitations

The limitations of the study were the following:

1. This was a quasi-experimental study using a convenience sample. Therefore, the results cannot be generalized to all patient populations.
2. Only patients in American Society of Anesthesiology (ASA) category I or II were included in this study. (Category I or II patients are generally in a good state of health, with only mild to moderate systemic disturbances or co-existing disease processes). Patients with an American Society of Anesthesiology (ASA) category of III, IV, or V were excluded from the study. (Category III, IV, or V patients are those with severe systemic disturbances and/or co-existing disease processes).
3. The results of this study are limited to isoflurane and cannot be generalized to other inhaled agents without further study.
4. The investigators were not blinded regarding the subjects' gender.
5. This study investigated gender differences in recovery times only, not the causative factors for any differences found.

### Summary

Historically males were typically used in drug studies while females were excluded as research participants. However, the findings were clinically applied to both men and women despite obvious physiological differences between genders. Those studies that enrolled both genders failed to analyze their findings by gender, thus treating them as homogeneous subjects. This bias has led to a concern among healthcare professionals and government agencies since current literature and practices lack gender related dosing requirements.

Review of the literature found no published research evaluating recovery time differences between gender and isoflurane administration. However, there are studies linking gender to variations in recovery times following intravenous agent and nitrous oxide general anesthesia. This study used principles of pharmacokinetics and pharmacodynamics to evaluate potential gender differences in the recovery of patients after general anesthesia using isoflurane. The significance of this research was to increase the anesthesia communities' body of knowledge concerning gender and isoflurane administration. This research used women as research participants in an area that previously displayed bias against female subjects. Additionally, this study provided valuable information on a specific inhalational agent used during general anesthesia that could create a safer patient environment and stimulate further research.

## CHAPTER II

### Review of the Literature

The purpose of this literature review is to examine published research as it relates to the concepts of consciousness and gender. Multiple known differences between genders may influence an individual's level of consciousness and thus, recovery time, following psychotropic or other pharmacologic agents. Major topics covered are gender differences in consciousness, gender differences in pharmacologic principles, isoflurane, and the Bispectral Index (BIS) Monitor. An OVID search engine was used for the literature search. MEDLINE, PsycINFO, CINAHL, and OVID full text, were searched using keywords: general anesthesia, gender differences, sex differences, sex hormones, isoflurane, pharmacology, isoflurane, obesity, age, and bispectral index monitor (BIS).

#### Gender Differences in Consciousness

Consciousness is defined as: "a clear state of awareness of self and the environment in which attention is focused on immediate matters, as distinguished from mental activity of an unconscious or subconscious nature" (Como, 1990). Following general anesthesia, an individual's mental state passes through phases or planes along a continuum known as consciousness. General anesthesia is a state of unconsciousness with concomitant loss of sensation, without changes in vital functions (Ouellette & Simpson, 1998).

Classically, five components compose general anesthesia: anxiolysis, analgesia, muscle relaxation, hypnosis, and suppression of autonomic and somatic responses. Of these, the component of hypnosis most closely relates to consciousness and is the most difficult to assess (Domino, Posner, Caplan, & Cheney, 1999; Dorsh, 1988; Ouellette & Simpson, 1998; Ranta et al., 1998; Tempe, 2001). The incidence of intra-operative recall, awareness, and memory (implicit and explicit) is well documented (Averbuch & Katzper, 2000; Domino et al., 1999; Dorsh, 1988; Ghoniem & Block, 1997; Kiviniemi, 1994). All of these phenomena suggest some level of consciousness or higher brain function; however, by definition they are not supposed to occur during general anesthesia. During a

closed claims analysis, Domino et al. (1999) found that women were three times more likely to experience awareness and/or recall than men, and that the majority of intraoperative awareness occurred during the maintenance phase of anesthesia. Five risk factors have been identified as statistically related to awareness: no volatile anesthetic agent, female gender, obstetric or gynecologic procedures, intraoperative opioids, and muscle relaxant usage (Dahan, Sarton, Teppema, & Olievier, 1998). The reason for this gender difference is not known.

Numerous theories ranging from gender variations in neuronal circuitry, environmental conditioning, and social or cultural influences have been used to explain gender differences in consciousness, moral development, and persona. This study addressed potential gender differences in consciousness, founded more on the science of pharmacology principles than the philosophical or psychological basis of origin.

#### Gender Differences in Pharmacologic Principles

Recovery from general anesthesia is based largely on pharmacokinetic and pharmacodynamic principles. Gan et al. (1999) was the first study to implicate gender as a contributing factor in emergence times from general anesthesia. Volume of distribution, rate of elimination, and drug concentration are critical concepts regarding pharmacokinetic principles. Pharmacodynamics principles involve the effects a drug has upon the body. Gender can have a profound influence on pharmacologic principles because of differences in body mass index and body composition, sex-hormone concentrations, and organ function. Some of these variables will be addressed in the following sections.

#### Pharmacokinetics

##### Gender and Bioavailability/Absorption.

The ability of a drug to cross a lipid bilayer affects its absorption, systemic concentration, and bioavailability. Several studies have shown gender differences in gastric acid secretion and gastric emptying. Women secrete less gastric acid and have

slower gastric emptying times. The delayed gastric emptying can be linked to increased sex-hormone concentrations (i.e., increased hormones related to pregnancy and use of contraceptives) (Kando, Yonkers, & Cole, 1995).

Drug bioavailability is influenced by drug metabolism and elimination. Enzymes and specific isoenzymes (enzyme subtypes) have been shown to vary by gender. Gender differences in digestive enzymes can affect the drug's metabolism and its bioavailability. There is extensive literature investigating the effects of gender on hepatic drug metabolism and elimination. In a study by O'Malley, Crooks, Duke, and Stevenson (1971) age and sex were found to be significant variables in the metabolism of antipyrine (phenazone), with decreased drug metabolism noted in the elderly and the mean half-life being 30% longer in males. When women alone were considered, the antipyrine half-life was 78% longer in the elderly female group compared to the younger females.

The cytochrome P450 isoenzyme subtype (CYP3A) is the major isoenzyme in metabolism of drugs and is responsible for the metabolism of over 50% of therapeutic drugs (Michalets, 1998; Tanaka, 1999). Cytochrome P450 enzymes are present in the gut and liver. In several studies hepatic CYP3A activity was significantly higher in females than males, which could result in faster drug metabolism for women (Harris, Benet, & Schwartz, 1995; Hunt, Westerkam, & Stave, 1992).

In order for a drug to be metabolized it must be in its free, unbound state. Drugs and hormones that are highly bound to plasma proteins have a long half-life. Several studies have investigated the effects of gender on plasma protein binding. Routledge, Stargel, Kitchell, Barchowsky, and Shand (1981) found that the unbound level of lignocaine (lidocaine) was not significantly different between genders if the female was not taking oral contraceptives; however, there was significantly higher unbound drug in the plasma if the female was on oral contraceptives. This emphasizes the impact that sex-hormone level and hormonal environment have on drug interactions and their effects.

### Gender and Drug Distribution/ Drug Plasma Levels

The distribution of a drug is affected by its physical and chemical properties, vascular and tissue volume of distribution, and the ratio of lean body mass to adipose tissue mass. Men and women, on average, have different body compositions. Women generally have a higher percentage of body fat than men (Legato, 1997). Studies have shown that the distribution of lipophilic drugs differs markedly between genders. A drug classification frequently administered in anesthesia and known to alter consciousness is the benzodiazepine agents. Multiple studies regarding this class of agents have shown gender differences in their pharmacologic profiles (Abernathy et al., 1982; Divoll & Greenblatt, 1981; Greenblatt et al., 1984; Greenblatt, Divoll, Harmatz, & Shader, 1980; Ochs et al., 1981). These differences may be partly explained by gender differences in BMI affecting plasma circulating drug levels. In a study investigating diazepam kinetics, age and gender were found to significantly alter the pharmacokinetic drug properties. Young women were found to have significantly higher volumes of distribution (1.87 vs. 1.34 liters/kg) and higher total clearance (0.63 vs. 0.49 ml/min/kg) than males. The elimination half-life among males increased significantly with age, as did the volume of distribution (Ochs et al., 1981). Similar results were obtained in a study on midazolam kinetics (Greenblatt et al., 1984). In a study on oxazepam kinetics (Greenblatt et al., 1980), the effects of age and sex were also investigated, with sex proving more important in drug clearance than age. Men were found to have significantly greater unbound (free) oxazepam levels than females and a shorter half-life (7.4 vs. 9.7 hrs). Also in the study, higher oxazepam clearance was noted in the participants that smoked cigarettes, likely due to the effects of smoking on liver cytochrome P450 concentrations, but this was found not to explain the sex-related difference.

In another study on trazodone kinetics after intravenous administration, the investigators found that volume of distribution was significantly larger in women than men, in older than younger individuals, and in obese patients compared to controls of

ideal body weight (Greenblatt et al., 1987).

All of these studies found gender to be a significant variable in pharmacokinetic actions. However, there are other studies that failed to find significant gender related effects in pharmacokinetic properties. Lorazepam protein binding has been found to positively correlate with the age, but not the sex of the individual (Divoll & Greenblatt, 1981). In another study comparing the effects of age and gender on chlordiazepoxide kinetics, the volume of distribution was related to body weight, but not to gender or age (Greenblatt et al., 1989).

#### Gender and Hormones.

Multiple studies have investigated the effects of sex-steroid hormones on brain membrane receptors and neurotransmitter functions. Sex-steroid hormone and metabolite levels during embryonic development play a vital role in brain formation, differentiation, and lifelong genomic and hormonal influences (Mortaud & Degrelle, 1996). Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain and has recently been implicated as being a major player in the mechanism of anesthetic agents.

Sex-steroid effects have been demonstrated on GABA, as well as NMDA receptors. The sex-hormones progesterone and estrogen, along with their metabolites, have been shown to interact with GABA<sub>A</sub> receptors. Progesterone metabolites increase the receptor's affinity for GABA, thus augmenting the chloride ion influx, reducing neuronal excitability, raising the seizure threshold, and producing anesthetic and/or hypnotic actions (Aveleira, 2001; Etchegoyen & Del Zotto, 1996; Maggi & Perez, 1984; Smith et al., 1999). Estrogen derivatives elicit an opposite response on seizure threshold and neuronal excitability (Smith et al., 1999). Hormonal changes during the female menstrual cycle have been reported as contributing to differences in plasma drug levels and pharmacodynamic responses (Kirkwood, Moore, Hayes, DeVane, & Pelonero, 1991); however, during a study on alprazolam, no significant differences were noted during the phases of the menstrual cycle.

Drug and membrane receptor interactions can be influenced by hormone supplementation therapy; therefore, oral contraceptives can affect a drug's therapeutic and pharmacologic effects. It has been found that estrogen containing oral contraceptives reduces the circulating plasma  $\alpha_1$ -acid glycoprotein (AAG) concentrations by as much as 35% (Gleichmann, Bachmann, Dengler, & Dudeck, 1973). The effects from alterations in AAG by estrogen containing contraceptives were demonstrated in a study looking at plasma protein binding in lignocaine (lidocaine) and diazepam (Routledge et al., 1981). In females taking oral contraceptives, AAG and albumin concentrations were both significantly lower, and the percent of free lignocaine and diazepam levels were significantly higher. These hormonal changes in AAG concentrations can directly affect the concentration of free circulating drug and pharmacologic response.

#### Pharmacodynamics

##### Animal Studies.

In a study by Chiari, Tobin, Pan, Hood, and Eisenach (1999) using Sprague-Dawley rats, females were found to have a higher antinociception response than males. Specifically, females were found to have an antinociceptive response to intrathecal neostigmine that was five times greater than males to a noxious heat stimulus applied to their hind paw. The  $ED_{50}$  for neostigmine for females was  $0.57 \pm 0.15$  mcg versus  $3.3 \pm 0.4$  mcg in males. In another animal study by Bartok and Craft (1997) male and female Sprague-Dawley rats were observed for differences in opioid antinociception after a thermal stimulus was applied to the rats' tails or their hind paws. The results demonstrated a significant difference ( $p = 0.05$ ) in antinociceptor response in two of the three known opioid receptors with female rats exhibiting a quicker response than males to the tail-withdrawal test. These studies show pharmacodynamic differences between genders in the animal model.

##### Human Studies.

In a human study by (Gear et al., 1996) pharmacodynamic differences in

analgesics were found between genders. A total of 48 subjects (28 males and 20 females) participated in the study involving third molar extraction (oral surgery). The surgery was performed by the same oral surgeon and included removal of at least one bone-impacted third molar from the mandible for standardization. The subjects were randomly assigned into two drug groups postoperatively and were administered an intravenous injection of 2-mg of butorphanol or 10-mg of nalbuphine. The butorphanol group consisted of eight females and twelve males. The nalbuphine group consisted of twelve females and sixteen males. The results found that women had significantly greater ( $p < 0.05$ ) analgesic effects than men to both medications.

Gender has also been cited as affecting ventilatory response to carbon dioxide and oxygen after morphine administration. A study by Dahan et al. (1998) was performed to determine the influence of gender on morphine-induced respiratory depression. Assessment of the data revealed that women experienced a 30% decrease in ventilatory response to carbon dioxide levels and a 50% decrease in hypoxic response (sensitivity) after morphine administration.

#### Isoflurane

Isoflurane is a potent inhalational anesthetic with a chemical structure of 1-chloro-2,2,2-trifluoroethyl difluoromethyl. It is a halocarbon and an isomer of enflurane, another volatile inhalational agent. Isoflurane has a minimum alveolar concentration (MAC) of 1.28% in oxygen and a MAC of 0.56% in 70% nitrous oxide. This volatile gas is moderately insoluble with a blood-gas partition coefficient of 1.4 and a brain-blood partition coefficient of 2.6 at 37 degrees Celsius (Cheung & Longnecker, 1998).

Isoflurane is used to induce and maintain unconsciousness in patients. A study conducted by Newton et al. (1990) focused on memory and the alveolar concentration of isoflurane that was needed to produce unconsciousness in the absence of noxious stimuli in non-surgical patients. Eight male subjects between the ages of 25 and 43 were studied.

Each subject was administered 0.1, 0.2, or 0.4 MAC of isoflurane in oxygen, or 100% oxygen in a session. These sessions were conducted at least seven days apart. Levels of consciousness were assessed by when they responded to the command of "open your eyes" and by testing the eyelash reflex. The eyelash reflex is performed by gently stroking the patient's eyelash to test whether there is a reflexive "blink" response. This test is often performed prior to endotracheal intubation of the airway to test if an appropriate level of unconsciousness is present. Memory was evaluated using "shock" word lists (words used to increase arousal) and finger movements. The study concluded that at a MAC of 0.4 in oxygen, all subjects lost recall and recognition, and 62% lost the eyelash reflex. In MAC concentrations of 0.2 and below, memory of shock words was still present in some subjects (Newton et al., 1990).

Munglani, Andrade, Sapsford, Baddeley, and Jones (1993) conducted a study that evaluated the effects of isoflurane on cognitive function. The purpose of their study was to compare the changes in cognitive function and coherent frequency created with increasing isoflurane concentrations. Coherent frequency is derived using auditory clicks transmitted at frequencies in the range of 5-47 Hz and is associated with the auditory evoked response. Seven subjects, all anesthetists, agreed to take part in this study and none reported any auditory deficits. Each of the seven subjects breathed increasing doses of isoflurane from 0% to 0.2%, 0.4% and 0.8% end-tidal concentrations and then the dose was decreased to 0% isoflurane end-tidal concentration. Psychological performance and coherent frequency were measured on each of the subjects while they were inhaling these concentrations. Both psychological performance and coherent frequency declined as the end-tidal concentration of isoflurane was increased from 0% to 0.8%, and at 0.8% no response of cognitive function or awareness was noted from the subjects (Munglani et al., 1993).

Isoflurane is often administered with nitrous oxide for the benefit of the second gas effect. The second gas effect modifies the uptake and pharmacokinetic profile of

volatile agents. It involves the concentration of volatile anesthetic agent exposed to the lung's capillary-alveolar membrane by replacement of the absorbed agent with another inspired gas (nitrous oxide). This results in higher mean alveolar agent concentrations within the lung (alveoli) after uptake of the agent into the bloodstream. This phenomenon allows for use of lower volatile agent percentages with the same pharmacologic effects seen with higher doses (Longnecker, Tinker, & Morgan, 1998).

However, nitrous oxide has the capacity to increase sympathetic nervous system outflow, which could antagonize the effects of isoflurane (Chortkoff, Bennet, & Eger, 1993). Chortkoff et al. (1993) conducted a study to determine whether nitrous oxide anesthesia antagonizes the suppression of learning by isoflurane. A total of 24 subjects were studied; all were male between the ages of 22 to 30 years of age. All participants initially breathed 100% oxygen via facemask; following that, nitrous oxide and isoflurane were entrained to maintain 40% nitrous oxide and 0.06% isoflurane (test concentration #1). The concentration of isoflurane was increased to 0.22% (concentration #2) for 15 minutes, and 0.38% (concentration #3) for 15 minutes with nitrous oxide remaining at 40%. End-tidal concentrations were measured by mass spectroscopy. Learning assessment was evaluated by questions, category-example tasks, and behavioral tasks at each of the three concentration levels. Chortkoff et al. concluded that nitrous oxide antagonized isoflurane's ability to suppress learning only at the 0.06% (first test) concentration.

#### Bispectral Index (BIS) Monitor

Gender has recently been implicated as having an influence on recovery times from general anesthesia. Gan et al. (1999) conducted a study to determine whether the bispectral index (BIS) monitor would improve titration of anesthetic drugs and lead to improved recovery. Ninety-six men and 178 women from 18 to 80 years of age completed the study. They encompassed relatively healthy patients (ASA categories I-III) who underwent various surgical procedures (e.g., general surgery, gynecologic, urologic,

ear-nose-throat, and orthopedic) that lasted at least one hour. The BIS is derived from the electro-encephalogram of cortical regions and displays a dimensionless value of 0 to 100 (see table 1, (Ouellette & Simpson, 1998)). Readings of 90 to 100 represent values of an awake individual. Values less than 60 represent a low probability of mental responsiveness.

Table 1

Bispectral Analysis Range Guidelines

<b>BIS Value</b>	<b>Clinical endpoints/ sedation ranges</b>	<b>Clinical situation</b>
100	Awake Sedated	Awake or resting state. Sedated for special procedures; conscious sedation. Response to vigorous stimulation during surgery. Emergence from general anesthesia.
70	Light hypnotic effects Very low probability of recall	Short surgical procedures requiring deep sedation or light anesthesia.
60	Moderate hypnotic effects Unconscious	Maintenance range during general surgical procedures
40	Deep hypnotic effects	High dose opioid anesthesia. Surgical procedures in which deep anesthesia is required. Barbituate coma or profound hypothermia.
0	Electroencephalogram (EEG) Suppression	

All patients were administered similar pre-medications and infusions of propofol based on dose/kg body weight. Maintenance of anesthesia with alfentanil and 50% nitrous oxide was standardized. Paralytic agents were also used as needed for endotracheal tube placement and surgical relaxation. Fifteen minutes before the end of the procedure, anesthesia was decreased in both groups (BIS and control). Recovery time was then evaluated by response times to eye opening and response to verbal command. As it became apparent that recovery times were different between men and women, gender effect was evaluated by post hoc analysis. BIS values were reported to highly correlate ( $r = 0.911$ ) with levels of drug-induced hypnosis and sedation. After analysis of the data, Gan et al. (1999) concluded that BIS monitoring resulted in significant ( $p = 0.02$ ) reductions in propofol dose and recovery time. They also concluded that gender significantly ( $p = 0.001$ ) influenced recovery time. Women's response to eye opening was 7.05 minutes compared to 11.22 minutes for men after discontinuation of anesthesia.

#### Summary

As demonstrated by previous research studies, gender can influence the pharmacologic response of drugs. Therefore, gender may influence a person's level of consciousness following exposure to volatile anesthetic agents. Critical variables (age, BMI, other drug interactions, sex hormone levels) may influence the pharmacokinetic and pharmacodynamic properties of psychotropic or anesthetic agents. These variables can potentially alter an individual's level of consciousness. However, some studies have shown conflicting results when gender is studied. Additionally, there is lack of research specifically on gender related differences with general anesthetics necessitating more research in this area.

## CHAPTER III

### Methodology

The purpose of this study was to investigate gender differences in recovery times following a balanced general anesthetic technique using isoflurane and fentanyl. Since gender is the independent variable, the investigators used a quasi-experimental, non-randomized study design.

#### Population, Sample, and Setting

This study was conducted using a convenience sample of adult patients that presented to a large medical center on the West coast. The sample consisted of Department of Defense, TRICARE (military healthcare) eligible patients that presented for elective surgery.

The sample consisted of male and female patients between 18 and 55 years of age who had surgical procedures of 45 to 180 minutes in duration. They were assessed as having an American Society of Anesthesiologists (ASA) classification of I or II (patients assessed as ASA classification I or II generally represent patients in a good general state of health, without physical limitations due to disease state). Patients of higher classifications (ASA III-V) have uncontrolled systemic disease and were excluded because of the influence their disease state and co-morbidities may have on recovery time. The age selection was based on the available population. Other exclusion criteria included: body mass index (BMI) greater than 30; general anesthesia in the past two weeks; and pregnant females. Also excluded were patients with recent history of alcohol or drug abuse, and severe psychiatric disorders.

Recovery time data (mean and standard deviation values for eye opening and responses to verbal command) from the Gan et al. (1999) study using non-volatile general anesthetic agents were analyzed using an effect size calculator (Becker, 1998) to determine the effect size of the study. The results showed a medium effect size (0.27).

The current investigators felt that the mean time difference of 3 - 4 minutes found between genders in the Gan et al. study was not clinically significant, although it was statistically significant. Thus, clinical significance for the current study was considered as a difference in recovery times greater than or equal to 10 minutes. Based on the standard deviation results from the Gan et al. study and the desired time difference (10 minutes) a large effect size was used in our sample size calculations.

A required sample size,  $N = 60$  was calculated using the statistical program G\*Power (Buchner, Erdfelder, & Faul, 1997). This was based on using analysis of covariance (ANCOVA), a medium-large effect size of 0.35, an alpha ( $\alpha$ ) of 0.05 and a power ( $1 - \beta$ ) of greater than or equal to 0.80. In addition to the independent variable gender, our covariates were: BMI, total opioid dose, patient age, and total surgical time. The final sample size for this study consisted of 30 males and 22 females.

#### Instrumentation

In this study, recovery time was measured with the use of an electronic stopwatch. The time interval(s) required for the patient to meet the study recovery variables were recorded on the data collection tool (see Appendix). The readings on the Respiratory Gas monitor (RGM) and Bispectral Index monitor (BIS) that correlate with each data collection point (recovery time criteria) were also collected. These values were statistically analyzed for the presence of a significant gender difference. The criteria used in this study have been used in multiple studies to assess or measure recovery time (e.g., Gan et al., 1999; Myles et al., 2001).

Data Collection Tool. All pertinent information of the study was recorded on a data collection tool created by the study investigators. Recorded data included: patient demographic data (gender, age, height and weight (to calculate BMI)); ASA physical status as classified by the anesthesia provider; medical history and current medications; baseline BIS value; medication doses and types; time to each recovery criteria endpoint;

length and type of surgical procedure; and BIS and RGM values corresponding with above recovery criteria times.

Recovery was measured using several criteria endpoints. The point at which the isoflurane vaporizer was turned off represented time zero. The elapsed time required to achieve each of the two recovery criteria points was also recorded. The recovery criteria was time required to eye opening, and time to hand grasp and release on command. A hand grasp *and* release response to command was required because this complex response represents higher cortical functioning (cognition), not a simple reflex response. The information collected was obtained and recorded by the anesthesia provider on the data collection tool. Each provider was given guidance on how to properly collect and record study data points. This was done to improve reliability of data collection procedures and to decrease inter-rater variance.

Bispectral Index Monitor (BIS). The BIS is relatively new technology used to correlate the level of hypnosis during general anesthesia. Multiple studies have shown that the BIS can be useful for cost containment measures allowing for less anesthetic agent usage, assessment of hypnosis, and to assist in titration of anesthetic dose for earlier recovery times (Bard, 2001; Gan et al., 1999). The BIS monitor uses a complex algorithmic computational program to interpret electrical signal frequency, phase angle, and amplitude to provide the anesthetist with a dimensionless number from 0 – 100, with lower numbers corresponding to increasing hypnotic depths (Bard, 2001). For this study, patients were maintained at a BIS value of 40 – 60. This value represents a hypnotic level appropriate for surgical anesthesia (Bard, 2001). Using the BIS as a tool for titration of anesthetic depth should have improved validity and decreased marked variations in anesthetic doses between patients. Multiple studies have illustrated the reliability and validity of the BIS monitor for use in anesthesia. In a study by (Dahan et al., 1999) it was found that sex differences did not exist in the pharmacodynamics of isoflurane with

respect to their effects on the EEG in general and the BIS in particular.

End-tidal gas concentration analyzer. The Datex-Ohmeda 5250 RGM provided data on inspired and expired O<sub>2</sub>, CO<sub>2</sub>, and NO<sub>2</sub>, minute and tidal volume, airway pressure, SpO<sub>2</sub>, pulse rate, circuit CO<sub>2</sub> concentration and quantification of isoflurane. The monitor range for isoflurane used in this study is 0-15%, with an accuracy in the 0-5% range of  $\pm$  0.2% (Datex-Ohmeda, 1998). The RGM value correlating with each recovery criteria endpoint was recorded for statistical comparison between genders. The end-tidal concentration was titrated, as necessary, to maintain a BIS value between 40 and 60.

#### Procedure for Data Collection

Institutional Review Board approvals from the university and institution were obtained. The investigator(s) evaluated patients presenting for surgery as potential study participants. Potential participants were informed of the purpose, risk, and benefits of the study. If they were interested, informed consent was obtained. Data collection began preoperatively and continued until both recovery criteria were met.

Demographic data, including gender, height, weight, age, medical history, and current medications were obtained from the patient's chart and during the anesthesia pre-operative interview. On the day of the scheduled surgery, while in the pre-operation holding area, all patients received pre-medication of midazolam (0.03 - 0.1 mg/kg) for anxiolysis. Baseline vital signs to include heart rate (HR), blood pressure (BP), respirations, temperature, and a baseline BIS value were obtained in the operating room. Monitors were attached after the patient was transferred to the surgical table. Prior to induction of general anesthesia, the patient inhaled 100% oxygen for three to five minutes to remove all the nitrogen gas from the lungs (alveoli).

Induction of general anesthesia consisted of fentanyl (2 mcg/kg) and propofol (1.5-2 mg/kg) intravenously (IV). Muscle relaxation for intubation was achieved by using vecuronium (0.1 mg/kg) IV. If rapid sequence induction was required, succinylcholine

(1.0 mg/kg) IV was given instead of vecuronium. The patient was intubated using an appropriate size endotracheal tube. Once intubated, placement was verified by auscultation of breath sounds over the epigastrium and lung fields. After an appropriate end-tidal carbon dioxide (EtCO<sub>2</sub>) value and waveform were obtained, the isoflurane vaporizer was turned on with a fresh gas flow of two liters/minute. Vital signs, BIS value, and EtCO<sub>2</sub> were obtained every five minutes until isoflurane administration was discontinued and every minute until the study's end point.

General anesthesia was maintained with the volatile anesthetic isoflurane and titrated to maintain a BIS value between 40 and 60. Fresh gas flow during the maintenance phase was no less than two liters. If additional neuromuscular blockage was required for the surgical procedure vecuronium was used to achieve a train-of-four count, of one or two. Upon completion of surgery, glycopyrolate 0.01 mg/kg and neostigmine 0.05 mg/kg were used for reversal of neuromuscular blockade.

Emergence from general anesthesia began five minutes prior to the end of surgery. The isoflurane was discontinued and fresh gas flow was increased to ten liters/min. This point represented time zero for the study. Data collection (recovery criteria) was assessed every minute after time zero until the patient opened their eyes and followed a hand grasp and release command. The anesthesia provider provided verbal and tactile stimulation every minute. The time interval required for each criterion was recorded. Data collection was completed when the patient accomplished both criteria.

Subjects requiring a fentanyl dose of greater than or equal to 3 mcg/kg/hr, in addition to their induction dose, were dropped from the study due to the potential interference with recovery time.

#### Protection of Human Subjects

Those patients that met the eligibility requirements of the study were asked to participate in the study during the pre-operative anesthesia. A thorough explanation of the

study was given to each patient by one of the study investigators and included the purpose of the study, inclusion and exclusion criteria, and risks and benefits as outlined in the informed consent form. Each patient that agreed to be included in the study signed an informed consent document and was given a copy of the consent. To maintain confidentiality, each patient in the study was assigned a study number that was used on all forms associated with the study. Only the primary investigators had access to the patient's name assigned to each number to maintain anonymity. All records of the study were kept in a secure location that would be maintained for two years after completion of the study. The results of the study (not including subject names) were included in the thesis submitted by the principal investigators to the University of Texas Health Science Center at Houston and disseminated per university policy.

#### Study Design

The purpose of this study was to determine if there was a difference in recovery times between males and females following a general anesthetic using isoflurane and fentanyl. The study design was quasi-experimental. A power analysis determined the required sample size to be 60 subjects. A total of 60 subjects were initially enrolled in the study, which consisted of 30 males and 30 females. However, eight of the females were dropped from the study. Seven of the eight females were dropped due to surgical times greater than 180 minutes. One was dropped due to surgical time less than 45 minutes. Both groups (males and females) received the same treatment protocol.

A potential threat to internal validity stemmed from instrumentation. This might have occurred because data was obtained from monitors in different operating rooms. Ensuring that the monitors were identical and were calibrated to standards set by the manufacturer helped to control for this. Another threat is loss of subjects from the study for multiple reasons to include: withdrawal from the study; intraoperative complications that may necessitate the use of additional medications known to markedly alter

consciousness; exceedingly high opioid requirements; or death. The eight females that were dropped from the study was due to the surgical times that was either over or under the allowable time limit as mentioned previously. A potential threat to the external validity of our study is generalizability. Our study limited our sample population to active duty military personnel and dependents/retirees between 18 and 55 years of age that approximated our target population of war fighters. The accessible population for our study included active duty military personnel and their dependents of active duty military personnel, retired active duty military personnel and their dependents, and other Department of Defense employees. Characteristics of this population might differ from those of the general population. Differences in individual researchers in measuring the dependent variable could also have affected the external validity of the study (Polit, Beck, & Hungler, 2001).

#### Data Analysis

The variable of interest in this study was recovery time following isoflurane anesthesia. The data points included the time interval values from time zero (turning off the agent) to the time of eye opening (while being verbally prompted at one minute intervals), and the time interval to follow commands (evaluated by patient being able to squeeze and release the anesthetist's hand on request). These time intervals are interval/ratio data so a parametric test was used for the statistical analysis. Two additional values were recorded at each time interval point: the BIS score and the RGM value (end-tidal concentration). Descriptive statistics (i.e., mean and standard deviation) were calculated for BIS scores, RGM values, total opioid dose/kg, and study demographic data.

For this study an ANCOVA (*F* test) was used to analyze the data and adjust for extraneous variables that have been shown to influence the dependent variable of interest (recovery time). The independent variable for this study was gender and the four

covariates were: age, length of surgery, BMI, and opioid dose. Using the G\*power program (Buchner et al., 1997) prior to the study, we calculated that we would need 30 subjects per group to obtain a desired effect size of 0.35 with at least 80% power and an alpha level of 0.05.

### Summary

In conclusion, this study used a convenience sample consisting of surgical patients presenting to a large medical center. The subjects received a general anesthesia designed to limit agents that affect recovery time. Study participants received BIS monitoring which allowed the anesthesia provider to objectively maintain a consistent hypnotic (anesthetic) depth intraoperatively, as well as between patients. ANCOVA was used to determine if a gender difference exists in recovery times following isoflurane anesthesia while adjusting for age, length of surgery, BMI, and total opioid dose.

## CHAPTER IV

### Analysis of Data

#### Description of the Sample

A convenience sample of 30 females and 30 male patients was enrolled. Eight of the females were dropped from the study leaving a final sample of 22 females and 30 males. Seven of the eight females were dropped due to surgical times greater than 180 minutes. One was dropped due to surgical time less than 45 minutes. Demographic data including height, weight, age and Body Mass Index (BMI) are listed in the table below.

Table 2

#### Demographics of study subjects

	Arithmetic Means	
	Male (n=30)	Female (n=22)
Height (in)	70.60	64.91
Weight (kg)	86.95	65.43
Age (years)	31.27	33.77
BMI (kg/m <sup>2</sup> )	26.91	23.97

Data on the type of surgery of each participant was obtained and categorized into the different surgical specialties. This included orthopedics (ortho), gynecological (GYN), general, plastics, urology, occillo-maxillo-facial (OMF), ears-nose-throat (ENT), and neurology (neuro) surgery. In the table on the following page is a listing of surgical specialties with the distribution of the number of males and females in each.

Table 3

Surgical Services Breakdown

Specialty	Ortho	GYN	General	Plastics	Urology	OMF	ENT	Neuro	Total
Males	8	0	5	1	5	1	6	4	30
Females	0	8	7	3	0	0	2	2	22
Totals	8	8	12	4	5	1	8	6	52

It is interesting to note that there were no females in the study that had orthopedic or urology surgeries while for obvious reasons there were no males that had gynecological procedures.

During the intra-operative period, data were collected and analyzed to determine if there were differences between the groups that could affect the findings of the study. Results are listed in the table on the next page. This included the total propofol dose required for induction; the average of the BIS value (BIS intraop) recorded every 5 minute intervals during surgery; the average end-tidal isoflurane (ET iso intraop) recorded every 5 minute intervals during surgery; the BIS value (BIS time zero) and end-tidal isoflurane (ET iso time zero) at time zero when the surgical dressing was placed and the isoflurane vaporizer was turned off; and the fentanyl dose required for induction.

Table 4

Analysis of data using t test

	N	Propofol Dose (mg)	BIS value Intraop	ET Iso level Intraop	BIS Time Zero	ET Iso Time Zero	Fentanyl Dose Induction (mcg)
Females	22	132.5	51.1	0.69 %	57.4	0.6 %	122
Males	30	170.2	47.8	0.67 %	55.8	0.5 %	156.3
Student's t test		t= -6.2 p=0.00*	t= 2.81 p=0.01	t= 0.62 p=0.54	t= 0.84 p=0.41	t= 1.74 p=0.09	t= -4.55 p=0.00*

Note. \* Statistically significant ( $p < 0.05$ ).

A Student's t test was used to analyze the data. The results showed that the propofol dose and the fentanyl dose were significantly ( $p < 0.05$ ) higher in men than in women. This can be attributed to the fact that the required dose of both propofol and fentanyl was based on weight. The average weight of the males was 87 kg while the average weight of the females was 65 kg. As a result of this, males received a larger dose of both drugs. The average BIS value was also significantly different between both groups. However, the average BIS for females of 51.1 and males of 47.8 were both within the criteria for the study (between 40 and 60). The BIS values at time zero and at eye opening were not significant between the groups ( $p > 0.05$ ).

Findings

The sample of 22 females took 5.60 minutes to meet both recovery time criteria while the sample of 30 males took 6.87 minutes. On average, it took 1.27 minutes longer for males to wake up than females. To determine if this was statistically significant an analysis of covariance (ANCOVA) was performed with the covariates of age, BMI, length of surgery, and total fentanyl dose.

The hypothesis of the study was that because of variations in pharmacologic effects due to differences in body mass composition and hormonal influences, women will have a faster recovery time than men following general anesthesia with isoflurane and fentanyl. Recovery times were measured by the time it took for subjects to meet both of two endpoints (opening of eyes and hand grasp-and-release to command). The results showed that there was no significant effect of gender on wake-up time ( $F_{1,46} = 0.063$ ;  $p = 0.802$ ).

Therefore the hypothesis that women will have a faster recovery time than men following general anesthesia with isoflurane and fentanyl is rejected and the null hypothesis is not rejected. The results are listed in the table below.

Table 5

Recovery times when criteria was met

Gender	Eye opening (min)		Hand Grasp-and-Release (min)		Both Criteria Met (min)	
	Mean	SD	Mean	SD	Mean	SD
Females	5.09	2.29	5.60	2.31	5.60	2.31
Males	6.17	4.68	6.87	4.88	6.87	4.88

## CHAPTER V

### Discussion, Conclusions, Implications, and Recommendations

The purpose of this study was to determine if there was a significant difference in recovery times between males and females when using isoflurane and fentanyl for general anesthesia. This chapter will focus on a discussion on the results of the study, conclusions based on the findings, implications of the research to current practice, and recommendations for future research.

#### Discussion

The hypothesis of the study was that because of variations in pharmacologic effects due to differences in body mass composition and hormonal influences, women will have a faster recovery time than men following general anesthesia with isoflurane and fentanyl. However, this was not supported by the findings of the study.

The theoretical framework of the study was based on a consciousness model. It outlined how a person's level of consciousness changes along a continuum following the administration of psychotropic agents. A person's place on the continuum is governed principally by pharmacodynamic and pharmacokinetic factors. However, multiple factors unique to an individual to include social, cultural, and environmental factors can also influence a person's place on the continuum. With known pharmacodynamic and pharmacokinetic differences between males and females along with social, cultural, and environmental differences it was hypothesized that women will have a faster recovery time than men following general anesthesia with isoflurane and fentanyl. The results showed that although on average females recovered faster than males, this difference was

not statistically ( $p < 0.05$ ) or clinically (time difference  $> 10$  minutes) significant. This may have been due to extraneous variables that were not controlled for and may have obscured a difference. Additionally, of the 30 males and 30 females originally enrolled in our study, eight participants were dropped. All of these participants were female, which could have underpowered our study.

### Conclusions

While other studies have implicated gender as a contributing factor in post-anesthesia recovery times, (Gan et al., 1999; Myles et al., 2001), the results of this study showed that when using an inhalational agent, specifically isoflurane, to maintain general anesthesia, gender does not affect recovery times. Gan et al. found a significant difference in recovery times with gender ( $p = 0.001$ ) while using a propofol, nitrous oxide, and alfentanil general anesthetic technique. They found that on average females woke up 3.55 min sooner than males. Although a 3.55 minutes difference was statistically significant, this was not clinically significant. Our study looked for both a statistical and clinical significance (difference of greater than 10 minutes) in recovery times between genders. The results of this study found that although women recovered sooner than males, the 1.27 minutes difference was not statistically significant.

### Implications for Nursing

Although the literature is replete with studies demonstrating gender influences on pharmacologic response to drugs, this study does not support gender variations while using an isoflurane and fentanyl anesthetic. It also does not support the previous studies (Gan et al., 1999; Myles et al., 2001) that reported that women emerge faster than men from general anesthesia. It should be noted that our study used drugs that were different

pharmacokinetically from the drugs used in those studies. We used isoflurane and fentanyl for maintenance of general anesthesia while Gan et al., 1999, used a propofol/nitrous oxide/alfentanil technique and Myles et al., 2001, used propofol as part of maintenance for general anesthesia. These drugs have shorter elimination half-lives than the drugs we used. However, based on our findings, when using an isoflurane and fentanyl technique for general anesthesia, no gender specific concerns need be addressed until further studies can investigate this issue further.

#### Recommendations for Further Research

Although the difference between genders was not significant women on average woke up about one minute sooner than men. The focus of the study was to look for a clinically significant difference of greater than ten minutes. This raises the need for further research in this area. Enrolling a larger study population may help in identifying possible gender differences by accounting for possible attrition. This study included subjects having different types of surgical procedures with varying degrees of surgical stimuli. There were some surgical procedures where only males had that specific type of surgery (i.e. orthopedics and urology) while other surgical procedure had only females (i.e., GYN). Limiting participants to identical and/or more uniform surgical procedures would help to limit the varying degrees of surgical stimuli among the study population. The varying degree of surgical stimuli may have affected the amount of anesthetics required under general anesthesia and thus obscured a possible gender difference. Additionally, our study did not consider the effects of temperature on recovery times. Hypothermia delays drug metabolism whereas hyperthermia enhances drug metabolism. Thus, temperature differences should be considered in future research.

APPENDIX A  
Data Collection Worksheet

## DATA COLLECTION WORKSHEET

DATA COLLECTION TOOL Gender Differences in Recovery Times -- Isoflurane Study				
<b>Demographic data:</b>				
Random number assignment:				
Age:	Height:	in.	Weight:	kg
			BMI:	kg/m <sup>2</sup>
Sex: M F				
ASA Classification I II		Surgical Procedure:		
<b>Preoperative information:</b>				
Medical History:				
Current Medications:				
Baseline BIS Value:		Midazolam:		mg total/ mg/kg dose
Adjunctive medication and doses:				
<b>Intraoperative information:</b>				
Propofol induction dose: Range (1.5-2 mg/kg)		Fentanyl total induction dose: Dose (2 mcg/kg)		Fentanyl supplemental doses: (50-100 mcg increments)
mg given		mcg given (A)		mcg supp'd (B)
				mcg total (A+B)
Vecuronium total dose: (0.1 mg/kg) mg given		RSI: yes no Succinylcholine Dose (1.0 mg/kg) Total dose:		
Average end-tidal isoflurane concentration (%):				
Average BIS Value (Intraoperative):				
Adjunctive medication and doses:				
<b>Outcome Criteria Data:</b>				
Time zero: isoflurane off			BIS value:	End tidal isoflurane concentration (%):
Time to opening of eyes: min. secs.			BIS value:	End tidal isoflurane concentration (%):
Time to hand grip & release: min. secs.			BIS value:	End tidal isoflurane concentration (%):
Elapsed time to achieve both recovery criteria:			min.	secs.
Total Anesthetic Duration:			hrs.	min.
Investigator:			Data collector:	

Intraoperative Readings

1 <sup>st</sup> Hr	00	05	10	15	20	25	30	35	40	45	50	55
BIS value (0-100)												
E/T (%) Isoflurane												

2 <sup>nd</sup> Hr	00	05	10	15	20	25	30	35	40	45	50	55
BIS value (0-100)												
E/T (%) Isoflurane												

3 <sup>rd</sup> Hr	00	05	10	15	20	25	30	35	40	45	50	55
BIS value (0-100)												
E/T (%) Isoflurane												

Outcome Criteria - Measurement Readings

Patient Response	Time Zero	1min	2min	3min	4min	5min	6min	7min	8min	9min	10min
Eye Opening											
Grasp & Release											
BIS value (0-100)											
E/T (%) Isoflurane											

Patient Response	11min	12min	13min	14min	15min	16min	17min	18min	19min	20min
Eye Opening										
Grasp & Release										
BIS value (0-100)										
E/T (%) Isoflurane										

Patient Response	21min	22min	23min	24min	25min	26min	27min	28min	29min	30min
Eye Opening										
Grasp & Release										
BIS value (0-100)										
E/T (%) Isoflurane										

Patient Response	31min	32min	33min	34min	35min	36min	37min	38min	39min	40min
Eye Opening										
Grasp & Release										
BIS value (0-100)										
E/T (%) Isoflurane										

**\*\*Legend:**

BIS = Bispectral Index monitor  
 kg/m<sup>2</sup> = kilogram per meter (squared)  
 min. = minutes  
 kg = kilograms  
 E/T = End-tidal Concentration (% fraction) on respiratory gas monitor (RGM)  
 Eye opening and Handgrip Response:

RSI = rapid sequence intubation  
 supp'd = supplemented  
 hrs. = hours  
 mg = milligrams

Iso = Isoflurane  
 secs. = seconds  
 in. = inches  
 mcg = micrograms

✓ = stimulated with no response, ✗ = stimulated and met criteria

**APPENDIX B**  
**Sample Consent Form**

## INFORMED CONSENT DOCUMENT

60TH MEDICAL GROUP  
David Grant Medical Center  
101 Bodin Circle  
Travis AFB, CA 94535-1800

Privacy Act of 1974 applies. DD Form 2005 filed in Clinical/ Medical Records.

*PRIVACY ISSUES: Records of your participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 USC 552a, and its implementing regulations. DD Form 2005 contains the Privacy Act Statement for the records. You understand that records of this study may be inspected by the U.S. Food and Drug Administration (FDA), the sponsoring agency and/or their designee, if applicable.*

### TITLE OF STUDY

**DOES GENDER AFFECT RECOVERY TIME FOLLOWING ISOFLURANE  
ADMINISTRATION WHILE USING A BISPECTRAL INDEX MONITOR?**

### INVESTIGATORS' NAMES, DEPARTMENTS, PHONE NUMBERS

Thomas G. Fevurly, 60<sup>th</sup> MSGS / SGCSA, 423-3590, Beeper 420-6323  
James G. Olanda, 60<sup>th</sup> MSGS / SGCSA, 423-3590, Beeper 420-6259  
Gary A. Pulmano, 60<sup>th</sup> MSGS / SGCSA, 423-3590, Beeper 420-6246

### INTRODUCTION

It is important that you read and understand several general principles that apply to all who take part in research studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. If you have personal, religious or ethical beliefs, which you think, might limit the types of medical treatment (for example, blood transfusions) that you would agree to receive; you should discuss them fully with your physician(s) before entering this study. You are urged to discuss any questions you have about this study with your doctor(s) and/or the clinic staff members.

### PURPOSE OF STUDY

(This section will explain the nature, purpose(s), approximate number of subjects, and the duration of participants' involvement.)

You, \_\_\_\_\_ (SSN: \_\_\_\_\_), understand that you are being asked to participate in a research study. The purpose of the research study is to determine if there are differences between men and women in recovery times following general anesthesia with an inhaled gas. There will be 60 patients in the study: 30 males and 30 females. Your participation will start from the time you meet your anesthesia provider the day of your surgery until you are admitted to the post-operative recovery room following your surgery.

### PROCEDURES

(This section will explain all procedures and the purpose of the procedures to be undergone as part of this study. Any experimental procedures will be explained as such.)

INFORMED CONSENT DOCUMENT FOR PROTOCOL # \_\_\_\_\_

Page 1 of 4

Informed Consent Final (date here) [updated 11/01]

\_\_\_\_\_  
(Volunteer's Initials)

On the day of your surgery, while in the holding room, a catheter will be started in your vein. The anesthesia provider and operating room nurse will greet you, check your ID band and your chart. You will then be given medications to help you relax prior to being taken to the operating room. Once in the operating room equipment will be placed to evaluate your how fast your is beating, how well you are breathing and to check your blood pressure. In this study, a "sticky" strip will be place on your forehead to measure how "asleep" you are. A mask will be place on your face, you will be asked to place your chin up and to take deep breaths. Medications will be given through your vein catheter to make you pain free and fall asleep. You may feel "stinging" where the medication is entering your vein; this is normal and will soon go away. After you are asleep, a breathing tube will be placed into your throat for the rest of your surgery. A common anesthetic gas (isoflurane) used for this study will then be turned on. During your surgery information will be collected every five minutes until the surgery is complete. After your surgery is complete and all bandages have been placed, the anesthetic gas will be turned off and information will be collected every minute until you can open your eyes and grab and release the anesthesia provider's hand when asked. Once you are able to complete these tasks your participation requirements for this study are complete. The remainder of your care will be routine.

#### BENEFITS

You understand that no benefits can be guaranteed. By participating in this study an additional monitor, the Bispectral Index Monitor, will be used. This monitor fastens to the forehead by a "sticky" strip and provides the anesthesia provider an additional means of evaluating your level of sleep. It also has the potential benefit of requiring the use of less anesthetic drugs and/or faster recovery times.

#### ALTERNATIVES

(This section will explain your alternative treatment possibilities)

The alternative is for you not to participate in the study. In which case, routine monitors and procedures will be used during your anesthesia. Your care will not be influenced in any way, should you choose not to participate.

#### RISKS/INCONVENIENCES

(Any discomfort, risks, inconveniences caused from procedures or drugs used that may be expected from participation in this study.)

In addition to the risks associated with general anesthesia, which were explained during your consent for general anesthesia. A risk associated from participating in this study includes a potential for a skin reaction to the "sticky" strip that will be attached to your forehead. This skin reaction may cause redness, itching, hives, blisters, and/or other local skin irritations. Although extremely unlikely, a more serious reaction; such as, an anaphylactic reaction to the "sticky" strip is possible.

#### EVENT OF INJURY

You understand that your entitlement to medical and dental care and/or compensation in the event of injury is governed by federal laws and regulations, and if you have questions about your rights or if you believe you have received a research-related injury, you may contact the 60th Medical Group (DGMC) Patient Advocate, at (707) 423-2388, the Director of the Clinical Investigation Facility at (707) 423-7400, and/or the investigator Capt Thomas G. Fevurly at (707) 423-3590 or Beeper # (707) 420-6323.

#### OCCURRENCE OF UNANTICIPATED EVENT

If an unanticipated event (clinical or medical misadventure) occurs during your participation in this study, you will be informed. If you are not competent at the time to understand the nature of the event, such information will be brought to the attention of your guardian or next of kin.

#### AUTHORIZATION FOR RELEASE (If Applicable- Please Complete All Blanks)

(The following statement is to be included and applies ONLY if it is known that commercial or outside use of donated samples is anticipated.)

INFORMED CONSENT DOCUMENT FOR PROTOCOL # \_\_\_\_\_

Page 2 of 4

Informed Consent Final (date here) [updated 11/01]

(Volunteer's Initials)

"Records from your participation/treatment while in the study will be kept confidential at David Grant Medical Center and will only be released in accordance with Federal Law. "Every effort will be made to keep records of your treatment confidential while on the study at David Grant Medical Center. Surveys are anonymous and your information will only be identifiable to the study investigator through an assigned code. Your records will only be released in accordance with Federal Law. Your confidentiality and research study records are carefully guarded; however, those monitoring the study may view records. Qualified groups or organizations that have a role in this study may have access to medical records that contain your identity. However, no information by which you can be identified will be released or published."

#### DECISION TO PARTICIPATE

The decision to participate in this study is completely voluntary on your part. No one has coerced or intimidated you into participating in this program. You are participating because you want to. Your investigator(s) has adequately answered any and all questions you have about this study, your participation, and the procedures involved. You understand that the investigator will be available to answer any questions concerning procedures throughout this study. You understand that if significant new findings develop during the course of this study that may relate to your decision to continue participation, you will be informed. You further understand that you may withdraw this consent at any time and discontinue further participation in this study without prejudice to your entitlement to care. You also understand that the investigator of this study may terminate your participation in this study at any time if you feel this to be in your best interest. You have been provided a copy of this consent form.

**Your signature below indicates your willingness to participate in this research study.**

_____ (Subject's Printed Name)	_____ (Subject's SSN)	
_____ (Subject's Signature)	_____ (FMP* & Sponsor's SSN)	_____ (Date)
_____ (Advising Investigator's Signature)	_____ (Investigator's SSN)	_____ (Date)
_____ (Witness's Signature)	_____ (Witness's SSN)	_____ (Date)

**Distribution:**

(1) Clinical Investigation Facility (60MDSS/SGSE) [original]  
 (2) Research Volunteer  
 (3) Volunteer's Outpatient Medical Record (permanently maintained)  
 (4) Principal Investigator

\* FMP (Family Member Prefix) such as 20 - sponsor, 30 - dependent spouse, 01 - first child, etc.

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## VITAE

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**PERSONAL**

Thomas Guy Fevurly was born in Leavenworth, Kansas on [REDACTED], [REDACTED], the son of [REDACTED] and [REDACTED]. After completing his work at Leavenworth High School, Leavenworth, Kansas, in 1984, he attended Kansas City Kansas Community College for several years prior to receiving an Associates of Science in Pre-Engineering in 1990. In the fall of 1990, he attended the University of Kansas to pursue a degree in mechanical engineering prior to changing his major to nursing. In 1994, he was awarded the degree of Bachelor's of Science in Nursing. Prior to his graduation, in April of 1994, he was commissioned as a Second Lieutenant in the U.S. Army. Upon graduation he attended the U.S. Army's Officer Basic Course at Ft. Sam Houston, San Antonio, Texas. His first duty station was Ft. Lewis, Washington, working as a medical-surgical nurse at Madigan Army Medical Center. One year later he attended the U.S. Army's sixteen-week long critical care nursing program and was the program's honor graduate. He worked the next three years in the adult/pediatric critical care unit caring for patients, teaching sections of the critical care program and playing a critical role as a primary preceptor for critical care nursing students.

In February of 2002 he switched services to the U.S. Air Force and was assigned to Wilford Hall Medical Center in San Antonio, Lackland AFB, Texas,

where he worked in the pediatric critical care unit. In June of 2002 he attended a two-week training course to become an ECMO (extracorporeal membrane oxygenator) specialist. After completion of the course, he was hand-selected to take over the Pediatric ECMO Coordinator role. During the next three and a half years, he participated in over eighty aeromedical/ambulance transports of critically ill children and adults, as an active member of the ECMO, Pediatric and adult Critical Care Aeromedical Transport Teams. He also participated as co-investigator for clinical research protocols involving ECMO and an artificial blood substitute (H-BOC 201) manufactured by Biopure Industries. In 2000, he was awarded the distinguished honor of "The Jaunita Redmond Award" the Air Force Association's (AFA) highest honor in nursing. In 2001, he was selected for an AFIT position in graduate education in nursing and sent to Ft. Sam Houston, Texas to attend the U.S. Army's Graduate Program in Anesthesia Nursing which is affiliated with the University of Texas-Houston Health Science Center, where he completed the first year of training (Phase I - didactic portion) as an Honor Graduate. For Phase II (clinical residency portion) he was assigned to David Grant Medical Center, Travis AFB, California.

#### **MILITARY EDUCATION**

1994	Officer Basic Course / OBC (U.S. Army)	Residence
1996	Army Critical Care Specialty Course	Residence
1996	Intra-aortic Balloon Pump Training (IABP)	Residence
1998	ECMO Specialist Training Program	Residence
1999	Pediatric Critical Care Transport Course	Residence
2001	Squadron Officer School / SOS	Correspondence

#### **CIVILIAN EDUCATION**

#### **DEGREE**

1984-1985; 1988-1990	Associates of Science - Pre-Engineering Kansas City Kansas Community College
----------------------	---

1990-94	Bachelor's of Science - Nursing University of Kansas
2000-01	Undergraduate Non-Degree Seeking St. Philip's College
Jun 2001-Jun 2002	Phase I (Didactic) nurse anesthesia training U.S. Army Graduate Program in Anesthesia Nursing, Ft. Sam Houston, TX  *(Affiliated with The University of Texas-Houston Health Science Center)
Jun 2002-Present	Phase II (Clinical) nurse anesthesia training U.S. Army Graduate Program in Anesthesia Nursing, Travis AFB, CA  *(Affiliated with The University of Texas-Houston Health Science Center)

#### **EMPLOYMENT HISTORY**

1994-1998	Staff Nurse, U.S. Army, Madigan Army Medical Center, Ft. Lewis, WA  Worked on a 42-bed adult medical/surgical unit. Provided patient care, patient and staff education, and charge nurse duties. Researched and established SOP guidelines for care of ENT patients (radical necks, etc.). Attended the 16 weeks Army Critical Care Course - Honor Graduate. Then worked on a ten-bed Pediatric/Adult ICU unit. Provided float to CCU/CT surgery and IABP specialist duties.
1998-2001	Staff Nurse, U.S. Air Force, Wilford Hall Medical Center, San Antonio, TX

Worked in a 6-10 bed Pediatric ICU. Provided patient care, patient and staff education, and charge nurse duties. Performed the duties of ECMO coordinator, training, managing and supervising 43 ECMO specialists in quarterly proficiency labs. Instructed physicians and nurses in the annual training course. Performed ECMO and blood substitute clinical research. Provided cross-coverage for the SICU/MICU/CCU/CT surgery units. Member of Pediatric and Adult Critical Care Aeromedical Transport Teams (PCCATT / CCATT teams) as well as. ran the only worldwide ECMO transport team. Duties included supervising, ordering, inventorying, and designing aspect of the transport team and equipment.

2001-Present

Full-Time Student, U.S. Army Graduate Program in Anesthesia Nursing

### **AWARDS, HONORS & MEMBERSHIPS**

AANA Member (student - status)

AACN Member (CCRN - certification holder)

U.S. Army / NSNA "Sprit of Nursing Award" recipient - 1994

U.S. Air Force "Juanita Redmond Award" recipient - 2000 (Air Force Association's (AFA) highest nursing honor)

Air Force Achievement Medals 1998 and 2000 - for ECMO transports

U.S. Army Critical Care Course "Outstanding Clinical Preceptor Award" - 9 time recipient

U.S. Army Graduate Program in Anesthesia Nursing (Phase I)

"Honor Graduate" \*(Ranked 2nd in class of 43 students)

Captain James G. Olanda  
 117 Randolph St.  
 Travis AFB, CA, 94535  
 Phone: (707) 439-9424  
 Email: [row1vin@hotmail.com](mailto:row1vin@hotmail.com)

#### MILITARY EDUCATION

#### DEGREE

2000	Combat Casualty Care Course/C4	Residence
2000	Squadron Officer School/SOS	Residence
1999	Nursing Service Fundamentals/NSF	Correspondence
1998	Battlefield Nursing Course/BFN	Residence
1995	Military Indoctrination for Medical Service Officer/MIMSO	Residence

#### CIVILIAN EDUCATION

2000	University of South Florida	Undergraduate courses
1993	University of Cincinnati	BSN
1989	Ohio State University	Undergraduate general courses

#### EMPLOYMENT

Jun 02-Present	Phase II training Nurse Anesthesia Program, David Grant Medical Center, Travis Air Force Base
Jun 01-Jun 02	Phase I training Nurse Anesthesia Program in United States Army Graduate Program in Anesthesia Nursing, Fort Sam Houston Texas.
Jun 99- Jun 01	Staff Nurse, Emergency Department, MacDill AFB, Tampa, Florida.  Responsible for triaging patients, providing appropriate care as needed in a 10-bed Emergency department. Facility has 25 inpatient beds.
Apr 98- Apr 99	Staff Nurse, Urgent Care Clinic, Kunsan AFB, South Korea

Responsible for triaging patients, providing appropriate care as needed in a two bed urgent Care Clinic. Facility had no inpatient beds.

Feb 97- Apr 99

Staff Nurse, Extended Outpatient Clinic/23 Hour Observation Unit  
Keesler AFB, Biloxi, Mississippi

Provide intravenous antibiotics and dressing changes to outpatient. Pre-op minor procedure patients and monitored them post-op in a 15-bed unit. Facility had 100 inpatient beds.

Jun 95- Feb 97

Staff Nurse, Cardiac Telemetry Unit, Keesler AFB, Biloxi,  
Mississippi

Assess, monitor and provide necessary care to cardiac patients requiring telemetry in a 23-bed telemetry unit. Provide pre-procedure and post procedure care to cardiac catheterization patients. Facility had 100 inpatient beds.

Jun 93- Jan 95

Staff Nurse, Operating Room, Trident Regional Medic Center,  
Charleston, South Carolina

Circulated and scrubbed in General, Orthopedic, Neurological, Plastic and Cardiac surgeries in an eight bed Operating Room. Facility had 250 inpatient beds.

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## MILITARY EDUCATION

## DEGREE

2000	Combat Casualty Care Course/C4	Residence
1999	Infection Control & Epidemiology	Residence
1998	Commissioned Officer Training School	Residence

## CIVILIAN EDUCATION

2000	South Dakota School of Mines & Technology	Undergraduate studies
1997	University of Alabama	BSN
1989	Shelton State University	Undergraduate studies

## EMPLOYMENT

Jun 02-Present	Phase II training Nurse Anesthesia Program, David Grant Medical Center, Travis Air Force Base
Jun 01-Jun 02	Phase I training Nurse Anesthesia Program in United States Army Graduate Program in Anesthesia Nursing, Fort Sam Texas.
Oct 98- May 01	Nurse Manager of Internal Medicine Clinic, Coumadin Clinic, Endoscopy Clinic, Infection Control Officer, Staff Nurse on Multi-Service Unit  Responsible for assessing outpatient internal medicine patients and providing telephone triage for acute/routine appointments.  Managed a 30 patient weekly coumadin clinic; responsible for tracking & notifying patients of laboratory results/prescription changes.

Managed biweekly endoscopy clinic; responsible for providing conscious sedation for screening/diagnostic colonoscopies/EGD's. Infection Control Officer responsible for ensuring multiple clinics meet national OSHA/JACHO standards and preparing for JACHO inspection for Jun 00.

Staff nurse on MSU responsible for providing nursing assessment and care of pediatric patients, medical patients, ambulatory surgical patients and postpartum patients.

Aug 97- Aug 98

Staff Nurse, Trauma/Surgical Intensive Care Unit, DCH Regional Medical Center, Tuscaloosa, AL (500-bed facility)

Responsible for providing assessment and care as needed in a twenty-bed unit to trauma/surgical intensive care patients.