

Sufentanil and its Application in the Clinical Setting

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Abstract

The purpose of this research study was to assess the level of understanding within the Adventist University (ADU) student registered nurse anesthesia (SRNA) population regarding sufentanil and its application in the clinical setting. As future anesthesia providers, SRNAs, need to be not only knowledgeable and familiar with the variety of modalities available, but also be proficient in utilizing them. Therefore, having a strong theoretical knowledge about sufentanil and familiarizing oneself with its practical applications can promote its safe utilization in the clinical setting. A literature review of sufentanil and its application in the clinical setting was conducted in preparation for this study. After the literature review was completed, a PowerPoint presentation was assembled and presented to 37 SRNAs graduating cohorts of 2017 and 2018. Pre-tests were administered prior to the PowerPoint presentation to evaluate the SRNAs baseline knowledge on sufentanil. After completion of the lecture, each student filled out post-test in order to assess the effectiveness of the lecture. Data was then analyzed using the paired sample t-test, which yielded statistical significance with a P value <0.05 . In conclusion, the improvement of the posttests when compared to the pre-tests suggested that the SRNAs developed a better understanding of sufentanil and its application in the clinical setting.

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Problem

Opioids play a vital part in anesthesia during the entire perioperative period. They can be grouped by their potency, duration of action and onset, chemical class, and pharmacodynamic and pharmacokinetic profiles. Anesthesia providers have a variety of choices when it comes to selection of opioids. It is imperative that the nurse anesthetist not only be familiar with all types of treatment modalities available, but also proficient in utilizing them.

One of the opioids available for use by anesthesia providers is sufentanil. Sufentanil is a piperidine-derived mu agonist opioid (Lundeberg & Roelofse, 2011). It is five to ten times more potent than fentanyl, has faster onset of action and shorter duration (Scholz, Steinfath, & Schulz, 2012). Sufentanil is a powerful and safe, with very limited side effects, synthetic opioid analgesic that can be used as supplementation to general anesthesia or as primary anesthetic that can be used for the induction and maintenance of anesthesia (Scholz et al., 2012). Sufentanil can be administered by intravenous, epidural, intrathecal injections, also by transdermal, sublingual and intranasal application. Sufentanil has a wide range of applications in pediatrics, geriatrics, plastics, neuro, obstetrics, and general surgery (Lundeberg & Roelofse, 2010).

Anesthesia providers can choose from multitudes of opioids available to deliver effective anesthesia intraoperatively, as well as safe analgesia during preoperative and postoperative periods. As future anesthesia providers, student registered nurse anesthetists (SRNAs), need to be knowledgeable and familiar with the variety of modalities available. Therefore, having a strong theoretical knowledge about sufentanil and familiarizing oneself with its practical applications can promote safe utilization in the clinical setting.

Fentanyl continues to be the most popular opioid used for anesthetic management and being utilized majority of the time for surgical anesthesia and procedural analgesia (Maciejewski, 2012). Sufentanil is not as widely utilized, but is one of the strongest and safest

clinical opioids available. Sufentanil exhibits remarkable characteristics such as fast onset and strength of analgesic action with a remarkably high margin of safety (Vardanyan & Hruby, 2014). These characteristics are mainly associated with its high lipid solubility that allows ease of penetration through the blood brain barrier (Vardanyan & Hruby, 2014). Sufentanil is usually supplied in ampoules with 50 mcg/ ml concentration which requires reconstitution prior to its use in order to get final concentration of 5mcg/ml (Vardanyan & Hruby, 2014).

Sufentanil is proven to be safe, and is an effective analgesic/anesthetic that is underutilized in the clinical practice (Maciejewski, 2012). The purpose of this study was to educate SRNAs about pharmacodynamics and pharmacokinetics of sufentanil, and its appropriate clinical applications. This study also discussed the potential side effects associated with sufentanil, so it can be utilized efficiently and safely. This study was intended to evaluate the effectiveness of a class lecture (PowerPoint presentation), combined with a pre and posttest to educate SRNAs and enhance their knowledge about pharmacodynamics, pharmacokinetics, and clinical application of sufentanil. The class interaction included classroom lecture and explanation of pharmacodynamics and pharmacokinetics of sufentanil, a literature review, and provision of a post-lecture test to evaluate the effectiveness of the educational program.

Review of Literature

The “magnificent four” opioid compounds of the 4-anilidopiperidine series were introduced into clinical practice of medicine within last 50 years, and they are fentanyl (1968), sufentanil (1984), alfentanil (1986), and remifentanyl (1996), with sufentanil, selective μ -1 opioid receptor agonist, being the most powerful one (Vardanyan & Hruby, 2014). Chemical adjustments at the fourth position of the piperidine ring in fentanyl led to development of potent compounds of fentanyl series (Vardanyan & Hruby, 2014). Sufentanil has been registered for intravenous, transdermal, sublingual, epidural and subarachnoid administration (Maciejewski, 2012). It is being used off-label for intra-articular and intranasal administration; moreover, it has been utilized as an adjunct in peripheral blocks (Maciejewski, 2012).

Sufentanil has a rapid onset of action, about 1000 -times more potent than morphine, and approximately 10-times that of fentanyl at the time of peak effect when administered intravenously; moreover, it has a rather short duration of action when compared to fentanyl and an extraordinarily high safety margin (Vardanyan & Hruby, 2014). Sufentanil has a context sensitive half-time of approximately 30 minutes after 4-hour intravenous infusion. These properties make sufentanil the most potent and one of the safest analgesic among clinical opioids available for use today (Maciejewski, 2012). Due to its fast acting properties and high potency, sufentanil is a great choice for total intravenous anesthesia (Radke, Sippel, Radke, Hilgers, & Saur, 2014). Preservative free solution of sufentanil is highly lipid soluble, consequently, when given intravenously, it has fast onset of action (Lundeberg & Roelofse, 2010).

Enzymes P450 CYP3A4 are accountable for the main metabolic N-dealkylation pathway and clearance of sufentanil in the liver (Lundeberg & Roelofse, 2010). In adult population, the terminal half-life is approximately 2.5 hours. Majority of sufentanil excreted as inactive

metabolites in the urine and feces within 24 hours with only 2% of sufentanil eliminating as unchanged compound. Cautions need to be exercised when sufentanil is used because it crosses the placenta and is excreted into breast milk. Pharmacokinetic characteristics of sufentanil are mainly unchanged in patients with renal impairment. Its clearance, terminal half-life, and volume of distribution is largely unaffected in the presence of renal disease (Lundeberg & Roelofse, 2010). According to Maciejewski (2012), the rate of sufentanil metabolism can be affected and may be inhibited by the drugs that use the same or similar metabolic pathways for their metabolism and elimination. This is essentially true when metabolism is facilitated by cytochrome P450 CYP3A4 enzymes. Many medications that are part of home or inpatient treatment regimens such as cimetidine, ranitidine, ketoconazole, and erythromycin to name a few, may inhibit the metabolism of sufentanil.

Sufentanil is a highly protein bound medication. Approximately 90% of it is bound to alpha 1-acid glycoproteins (AAG) in plasma. The free fraction of the unbound 10% of the medication is mainly responsible for the analgesic and respiratory effects with protein binding significantly varying by patients' age (Lundeberg & Roelofse, 2010). The pharmacokinetics of sufentanil also can be significantly affected by several factors such as plasma protein content, acid-base status and cardiopulmonary bypass (Qi, Yao, Zhang, & Du, 2016). However, its metabolism is not significantly affected by renal insufficiency or compensated hepatic dysfunction (Scholz, Steinfath, & Schulz, 2012). Furthermore, the pharmacokinetics of sufentanil appear to be unaffected in hepatic disease (Bosilkovska, Walder, Besson, Daali, & Desmeules, 2012). Moreover, the clinicians need to take into consideration that pharmacokinetic properties can be influenced by changes in hepatic blood flow and administration of drug combinations which compete for the same plasma protein carrier or metabolizing pathways

(Scholz et al., 2012). Using pharmacokinetic-pharmacodynamic models, computer simulations based on changes in the effect site opioid concentration, or context-sensitive half-times seem to be extremely useful for selecting an opioid on a more rational basis (Scholz et al., 2012).

When sufentanil is administered intravenously at the doses of up to 8 mcg/kg it exhibits strong analgesic characteristics and can be used as a component of general anesthesia. Deep level of anesthesia and hypnosis demonstrated by EEG can be attained when sufentanil is administered intravenously at the doses greater than 8 mcg/kg without addition of other anesthetic agents (Vardanyan & Hruby, 2014). Sufentanil attenuates sympathetic response to surgical stress by diminishing the catecholamine release, especially norepinephrine, in the dose related fashion (Vardanyan & Hruby, 2014). When sufentanil is administered intravenously at the dosages of up to 30 mcg/kg it further attenuates the sympathetic response to surgical stress with remarkable hemodynamic stability and preservation of favorable myocardial oxygen balance (Yeganeh, Roshani, Latifi, & Almasi, 2013).

According to Gerlach et al. (2003), when sufentanil is administered intravenously at the dosages of 20 mcg/kg it was associated with more adequate reduction in intracranial volume when compared with the equivalent doses of fentanyl. Furthermore, sufentanil requires less furosemide administration and anesthesia supplementation in patients undergoing craniotomy than fentanyl. Sufentanil administered during cardiovascular surgery produced EEG patterns that represent adequate general anesthesia (Bhavsar, Sloth, Folkersen, Greisen, & Jakobsen, 2011). Sufentanil intraoperative administration at the anesthetic dosages maintains cardiac output, with a very negligible reduction in systemic vascular resistance during the immediate postoperative period (Bhavsar et al., 2011). The need for postoperative analgesics, the prevalence of postoperative hypertension, and the requirements for vasoactive medications are largely reduced

in patient population who received sufentanil at the moderate to high doses. Sufentanil's analgesic effect occurs within 10 minutes when it is administered by the epidural route with the ropivacaine (Chen, Qian, Fu, Lu, & Bein, 2010). Median effective dose of the ropivacaine is greatly reduced when sufentanil administered intrathecally in conjunction for the cesarean delivery (Chen et al., 2010).

The most common side effects of opioids, including sufentanil, are respiratory depression and skeletal muscle rigidity. Truncal muscle rigidity as well as the stiffness of the muscles of the neck and the extremities are primarily associated with sufentanil administration (Maciejewski, 2012). Dose dependent decrease in the respiratory drive and increased airway resistance occur with sufentanil administration as well (Liao et al., 2009). When sufentanil administered at the high doses, a prolonged pronounced diminution in pulmonary exchange and significant apnea may be observed. Furthermore, pruritus is another common side effects that may be associated with the sufentanil administration and may occur in up to 25% of the cases. However, pruritus is more commonly associated with epidural administration of sufentanil (Maciejewski, 2012). Gastrointestinal (GI) side effects such as nausea and vomiting are not as common and account for about 3% to 9% of the cases. However, when compared to fentanyl, sufentanil has markedly lower GI side effects. Intravenous administration of sufentanil demonstrates no elevation of histamine levels in blood of the patients that received it (Maciejewski, 2012). Additionally, euphoric symptoms are also less prevalent and less bothersome with sufentanil administration when compared to fentanyl due to limited effects on dopaminergic structures of the nucleus accumbens and lateral tegmental field (Maciejewski, 2012).

Due to its pharmacodynamic and pharmacokinetic profiles, sufentanil is safe for cardiovascular compromised patients and responsible for hemodynamic stability during various

phases of anesthesia, faster recovery and less demand for post-operative analgesics when compared with fentanyl, alfentanil, and remifentanyl (Bhavsar et al., 2011). Moreover, hemodynamic parameters and left ventricular systolic and diastolic function were preserved after sufentanil bolus doses (Bhavsar et al., 2011). Limited side effects of sufentanil, together with its attractive pharmacokinetic and pharmacodynamic profiles, should promote its wider use in clinical practice. However, fentanyl, precursor of sufentanil, is still being used a majority of the time during surgical anesthesia and procedural analgesia due to low cost and provider familiarity with this medication.

Project Description

Literature review was performed on Ovid, Medline, EBSCO, Google Scholar, PubMed, Up to Date, Science Direct, and ProQuest databases with the following key words: “sufentanil clinical application”, “sufentanil and anesthesiology”, and “sufentanil pharmacodynamics and pharmacokinetics”. The literature review yielded several case studies and original research articles about clinical application of sufentanil, its side effects, and pharmacodynamic and pharmacokinetic profiles. A majority of research articles were referenced within the last 5 years.

PowerPoint presentation and lecture was presented to Adventist University of Health Sciences SRNAs graduating cohorts of 2017 and 2018. This presentation discussed sufentanil and its clinical application, pharmacokinetics, and pharmacodynamics, as well as its side effects. Prior to administering the pre-test, a voluntary consent was administered informing the subjects that they were not obligated to take the test. Anonymity was attained by using a number system for both the pre-test and post-test. Pre-test was administered prior to the presentation in order to assess subjects' base knowledge about sufentanil and its application. Presentation, pre and post-test were conducted in the classroom of ADU during clinical conference. After the lecture, a post-test was administered to determine if the subjects' understanding on the topic increased, decreased, or remained the same. The convenience sample consisted of 37 SRNAs who study at ADU Nurse Anesthesia Program. The results of the pre-test and post-test were analyzed and organized into a chart. The data obtained was statistically analyzed and included within the scholarly paper and poster presentation. A poster presentation was completed and will be displayed in the annual Capstone Project Poster Presentation day at ADU. To ensure this study was within ethical bounds, the project was submitted to the Institutional Review Board (IRB) and Scientific Review Committee (SRC) at ADU for approval.

Evaluation Plan

In order to evaluate the effectiveness of this quantitative research study, a convenience sample of 37 SRNAs at ADU participated in the Sufentanil PowerPoint presentation, and took a pre and post-test in the Fall semester 2016. The pre-tests were administered to evaluate students' baseline knowledge. After the lecture and PowerPoint presentation, post-tests were administered to determine if the subjects' understanding on the topic increased, decreased, or remained the same. Both the pre and post-tests included the same questions. Prior to the start of the presentation, each student received a consent form. The pre and post-tests were analyzed using SPSS at the University Research office in order to measure the outcomes of this project. A sample paired t-test was used to analyze the data. As expected, the average percentage between the pre and post scores showed statistical significance. After implementing the capstone presentation, the increase in test score between the pre and post-test was 34.59%. Such a high score indicated that the students were able to increase their knowledge base after the Sufentanil PowerPoint presentation and could answer questions in relation to that subject.

Results and Conclusions

The results of the pre-test scores showed that teaching was needed in regards to the purpose of sufentanil and its application in the clinical setting. Though the pre-test average score was 56.49%, there was still need for knowledge-based improvement over this subject. The results of the pre-test showed a standard deviation of 0.13787 as well as a standard error mean of 0.02267. As shown by the standard deviation and standard error mean, students taking the pre-test scored around the same. After the PowerPoint presentation was completed, SRNAs were instructed to complete the post-test. The post-test results showed that there was an increase in average in regards to pre and post-test scores. Whereas in the pre-test, the students had an

average score of 56.49%, the post-test showed an average of 91.08%. This dramatic increase concluded that the students increased their knowledge base from the presentation and were able to answer questions regarding sufentanil, whereas, prior to the PowerPoint presentation, there was a knowledge base deficit. The post-test standard deviation was 0.08427 along with a standard error mean of 0.01385. The standard deviation from the post-test showed that once again, students scored similarly when taking the test. The higher score on the post-test after the sufentanil presentation indicated the effectiveness of the presentation as it relates to the students ability to identify benefits, side effects, as well as pharmacokinetics and pharmacodynamics of sufentanil and its clinical application. The obtained t-value of -16.696 was associated with a P value of less than the conventional .05 level of confidence. Therefore, it can be concluded that the average scores increased significantly between pre-test and post-test administrations. The statistical analysis of this data was completed by Dr. Roy Lukman at Adventist University of Health Sciences in the research office.

Capstone Data Analysis:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-Test	.5649	37	.13787	.02267
	Post-Test	.9108	37	.08427	.01385

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1 Pre-Test – Post-Test	-.34595	.12604	.02072	-.38797	-.30392	-16.696	36	.000

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Appendix A

Pre-Test/Post-Test

1. Sufentanil belongs to which chemical class of medications
 - a. Phenanthrenes
 - b. Phenylheptylamines
 - c. Phenylpiperidines
 - d. Morphinans
2. Sufentanil can be classified based on its effect on G-protein coupled opioid receptor
 - a. Pure Agonists
 - b. Partial agonists
 - c. Antagonists
3. Due to high affinity to this receptor , Sufentanil produces its effects mainly at
 - a. Mu
 - b. Delta
 - c. Kappa
4. Sufentanil can be delivered by which route of administration
 - a. Epidural
 - b. Intrathecal
 - c. Intranasal
 - d. Intravenous
 - e. Intraarticular
 - f. Transdermal
 - g. All of the above
5. Sufentanil main site of biotransformation is
 - a. Kidney
 - b. Liver
 - c. Lungs
6. Sufentanil common side effects are
 - a. Chest wall rigidity /Truncal rigidity
 - b. Bradycardia
 - c. Pruritus
 - d. Nausea and vomiting
 - e. Respiratory depression
 - f. All of the above

7. Sufentanil is about ____ bound to plasma proteins.
 - a. 0%
 - b. 25%
 - c. 50%
 - d. 90%

8. Sufentanil has a context sensitive half-time of _____ after 4- hour infusion.
 - a. 30 min
 - b. 1.5 hours
 - c. 2 hours

9. Sufentanil can be used for
 - a. Induction of anesthesia
 - b. Analgesic supplementation to general anesthesia
 - c. Primary anesthetic
 - d. All of the above

10. Sufentanil, pure opioid agonist that is (choose correct statement)
 - a. Highly potent due to its low lipid solubility.
 - b. Highly potent due to its high lipid solubility
 - c. Not highly potent due to low lipid solubility.

Appendix B

ADU NAP CAPSTONE PROJECT – INFORMED CONSENT

My name is Sviatlana Zizemskaya, RN, BSN, MSNA student in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU). I am doing a Capstone Project called *Sufentanil and its Application in the Clinical Setting*. This project is being supervised by Steve Fowler, DNP, CRNA, NAP, ADU. I would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to Educate Student Registered Nurse Anesthetists (SRNAs) about Sufentanil and its application in the clinical setting.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment (pre-test), attend a classroom presentation, and then complete an anonymous post-assessment (post-test). The assessment will address pharmacokinetics, pharmacodynamics of sufentanil, and its clinical application. Your participation by attendance at the presentation and completion of the pre and post-test is anticipated to take approximately 1 hour.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the ADU NAP graduating cohorts of 2017 and 2018. Participation in this project is voluntary. If you choose not to participate or to withdraw from the project, you may do so at any time.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we do not anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We do not expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional knowledge about Sufentanil and its application in the clinical setting.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigators will conduct this project in such a way to ensure that information is submitted without participants' identification. The project will consist of anonymous pretest, followed by lecture presentation, and posttest at the end of the lecture. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately 1 hour of your time, but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigator will be happy to answer any questions you have about the project. If you have any questions, please feel free to contact Sviatlana Zizemskaya at sviatlana.zizemskaya@adu.edu. If you have

concerns about the project process or the investigator, please contact the Nurse Anesthesia Program at (407) 303-9331.

Participant Signature

Date

Participant Name (PRINTED LEGIBLY)

Appendix C

Sufentanil and its Application PowerPoint Presentation

**Sufentanil and its Application
in the Clinical Setting**

Sviatlana Zizemskaya, RN, BSN, SRNA
Project Mentor: Cheryl Dryer, MSNA, CRNA, JLR Medical Group
Committee Chair: Steve Fowler, DNP, CRNA
Nurse Anesthesia Program, Adventist University of Health Sciences

Learning Objectives


- Increase knowledge and comfort of Sufentanil use for student registered nurse anesthetist population at Adventist University of Health Sciences
- Discuss clinical use
- Current literature review

Ideal Analgesic

- Pain-relieving activity for wide range of pain states
- Minimal negative adverse effects
- Cost effective
- Does not facilitate hyperalgesia
- Anesthesia providers have a variety of choices when it comes to selection of opioids
- Vital part in anesthesia during the entire perioperative period
- It is imperative that the nurse anesthetist not only be familiar with all types of treatment modalities available, but also proficient in utilizing them (Scholz, Steinfath, & Schulz, 2012).

History of Sufentanil

- The "magnificent four" opioid compounds of the 4-anilidopiperidine series
- Fentanyl (1968)
- Sufentanil (1984) (synthesized 1974)
- Alfentanil (1986)
- Remifentanyl (1996)
- Sufentanil, selective mu opioid receptor agonist being the most powerful one (Lundeberg & Roelofse, 2011).



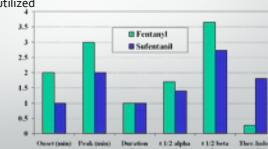
Characteristics of Sufentanil

- Synthetic opioid analgesic: addition of a methoxy group on the fourth position of the piperidine ring and the replacement of the phenyl ring by thiophene in fentanyl
- Phenylpiperidine class
- Pure opioid receptor agonists / very strong affinity to Mu Receptor (Opioids μ -Receptor Binding Affinity Sufentanil 0.1, Fentanyl 1.6)
- Highly lipid soluble, preservative free, pH of 4.5-7.0
- Supplied in ampoules with 50 mcg/ml concentration, which requires reconstitution prior to its use in order to get final concentration of 5mcg/ml (Scholz, Steinfath, & Schulz, 2012).



Characteristics of Sufentanil

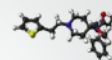
- Sufentanil ten times more potent than fentanyl with faster onset of action and shorter duration
- Fentanyl continues to be the most popular opioid used for anesthetic management and being utilized 70-80% of the time for surgical anesthesia and procedural analgesia
- Sufentanil is not as widely utilized (Maciejewski, 2012).



Routes of Administration of Sufentanil

- Intravenous
 - Intramuscular
 - Epidural
 - Intrathecal
 - Subcutaneous
 - Off-label intra-articular
 - Intranasal
 - Adjunct in peripheral blocks
 - Transdermal
 - Sublingual
- (Vardanyan & Hruby, 2014).

Clinical Application of Sufentanil



- Pediatrics, geriatrics, plastics, neuro, obstetrics, ENT, general surgery
- When given via intrathecal injection sufentanil decreases the median effective dose (ED₅₀) of intrathecal hyperbaric ropivacaine for caesarean delivery (Bhavsar et al, 2011).
- High safety margin (LD₅₀/lowest ED₅₀ = 25,000, ED₅₀ = 0.00071 mg/kg, LD₅₀ = 17.9 mg/kg)
- Most potent and one of the safest analgesic among clinical opioids used today
- Fast acting properties and high potency- total intravenous anesthesia
- Supplementation to general anesthesia
- Primary anesthetic that can be used for the induction and maintenance of anesthesia (Vardanyan & Hruby, 2014).

Metabolism of Sufentanil

- P₄₅₀ CYP3A₄ metabolic N-dealkylation pathway and clearance
- Metabolized in the liver and to some degree in the small intestine by N-dealkylation and O-demethylation and the inactive metabolites are excreted in the urine and feces
- Pharmacokinetics appear to be unaffected in hepatic disease
- Renal function impairment has negligible effect and does not alter its clearance, volume of distribution, or terminal half-life (Bosilkovska, Walder, Besson, Daali, & Desmeules, 2012).

Pharmacokinetics of Sufentanil

- The rate of metabolism is affected and may be inhibited by the drugs of a similar metabolic pathway (cimetidine, ranitidine, ketoconazole, itraconazole and erythromycin)
- Context sensitive half-time of approximately 30 min after 4-hour infusion
- In adults, the terminal half-life is about 2.5 hours (Maciejewski, 2012).

Pharmacokinetics of Sufentanil

- 90% bound to proteins as α_1 -acid glycoprotein (AAG) in plasma
- The unbound 10% of fraction of the drug is accountable for the analgesic and respiratory effects; whereas, protein binding varies significantly with age
- Pharmacokinetics of sufentanil can be affected by age, plasma protein content, acid-base status and cardiopulmonary bypass, but not significantly by renal insufficiency or compensated hepatic dysfunction (Bosilkovska, Walder, Besson, Daali, & Desmeules, 2012).

Sufentanil Use in Pediatrics

- Sufentanil is highly protein bound, and the active free fraction could increase especially in neonates and infants.
- The free active fraction is affected by age because of the reduced α_1 -acid glycoprotein plasma concentrations in neonates.
- 2- 8 years, the clearance of sufentanil twice as rapid as in adults and adolescence. (Lundeberg & Roelofse, 2011).

Side Effects of Sufentanil

- No elevation in plasma histamine levels and no indication of histamine release
- Gastrointestinal (nausea and vomiting)- 3% to 9% of the time, compared to fentanyl, with markedly lower tendency
- Euphoric symptoms - less common and less severe - limited effects on dopaminergic structures of the nucleus accumbens and lateral tegmental field (Maciejewski, 2012).

Adverse Reactions of Sufentanil

- The most common adverse reactions - respiratory depression, decreased respiratory drive, increased airway resistance (duration and degree - dose related)
- Skeletal muscle rigidity, particularly of the truncal muscles, skeletal muscles of the neck and extremities
- Other common side effects are pruritus that may occur in up to 25% of the cases and associated more with epidural administration (Liao et al., 2009).

Pharmacodynamics of Sufentanil

- Sufentanil -intravenous doses of up to 8 mcg/kg - analgesic component of general anesthesia
- ≥ 8 mcg/kg - deep level of anesthesia (Dose related attenuation of catecholamine release, particularly norepinephrine)
- The intraoperative use at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period
- At intravenous dosages of ≥ 8 mcg/kg - hypnosis and anesthesia without the use of additional anesthetic agents
- Catecholamine response, particularly norepinephrine, is further attenuated at doses of sufentanil of 25-30 mcg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance (Yeganeh, Roshani, Latifi, & Almasi, 2013).

Pharmacodynamics of Sufentanil

- Sufentanil is safe for cardiovascular compromised patients, hemodynamic stability during various phases of anesthesia, faster recovery and less demand for post-operative analgesics when compared with fentanyl, alfentanil, and remifentanyl
- Hemodynamic parameters and left ventricular systolic and diastolic function preserved after bolus doses
- Limited side effects, together with its attractive pharmacokinetic and pharmacodynamic profiles, should promote its wider use in clinical practice
- However, fentanyl, precursor of sufentanil, is still being used a majority of the time during surgical anesthesia and procedural analgesia due to low cost and provider familiarity (Bhavsar et al., 2011).

Literature Review

Bhavsar, R., Sloth, E., Folkersen, L., Greisen, J. R., & Jakobsen, C. (2011). Sufentanil preserves hemodynamics and left ventricular function in patients with ischemic heart disease. *Acta Anaesthesiologica Scandinavica*, 55(8), 1002-1009. doi:10.1111/j.1399-6576.2011.02479.x

Methods:

- 30 patients with ischemic heart disease between 45 and 80 years old scheduled for an elective coronary by-pass
- Prospective observational study
- Own control undergoing echocardiographic imaging before and after bolus Sufentanil 2.5-2.0 mcg/kg.
- Full invasive hemodynamic monitoring was established before Sufentanil administration (central venous pressure and pulmonary artery pressure. Continuous cardiac index (CI) and mixed venous saturation (SvO₂) were measured using a thermistor-tipped, flow-directed pulmonary artery catheter)
- Global LV systolic function was evaluated with a global longitudinal peak systolic strain (GLPSS) by speckle tracking ultrasound; systolic displacement by tissue tracking (TT) and diastolic function was evaluated using Doppler tissue imaging and pulse wave Doppler.

Bhavsar, R., Sloth, E., Folkersen, L., Greisen, J. R., & Jakobsen, C. (2011). Sufentanil preserves hemodynamics and left ventricular function in patients with ischemic heart disease. *Acta Anaesthesiologica Scandinavica*, 55(8), 1002-1009. doi:10.1111/j.1399-6576.2011.02479.x

Results:

- Hemodynamic monitoring showed a minor decline in systolic blood pressure from 159 to 154 mmHg
- No changes were observed in the cardiac index, stroke volume index and heart rate. An unchanged tissue tracking (TT) score index and global longitudinal peak systolic strain (GLPSS) indicated preserved Left Ventricular (LV) global systolic and diastolic function
- Sufentanil preserves hemodynamic parameters as well as echocardiographic indices of LV systolic and diastolic function in patients with IHD

Son, I., Oh, C., Choi, J. W., & Kim, S. (2014). The effect of sufentanil administration on remifentanyl-based anesthesia during laparoscopic gynecological surgery: A double-blind randomized controlled trial. *Anesthesiology*, 74(1), 53-63. doi:10.1155/2014/701329

Methods

- Prospective, double-blind, randomized study 78 patients undergoing laparoscopic gynecological surgery with postoperative intravenous patient controlled analgesia (PCA)
- The patients were randomly allocated to a sufentanil administration group (S group) or a normal saline administration group (C group)
- Anesthesia was induced and maintained with controlled administration of remifentanyl at 10 ng·mL⁻¹ and propofol under bispectral index guidance using two target controlled infusion (TCI) devices
- Once the surgical specimen was obtained, sufentanil or normal saline was administered at 0.15 ng·mL⁻¹ (target controlled infusion) and maintained until extubation
- Mean blood pressure (MBP), heart rate (HR), bispectral index during emergence, visual analogue pain scale (VAS), postoperative nausea and vomiting were measured and assessed

Son, I., Oh, C., Choi, J. W., & Kim, S. (2014). The effect of sufentanil administration on remifentanyl-based anesthesia during laparoscopic gynecological surgery: A double-blind randomized controlled trial. *Anesthesiology*, 74(1), 53-63. doi:10.1155/2014/701329

Results:

- MBP and HR after extubation in the S group were significantly lower ($P < 0.001$)
- The S group had a significantly lower PONV scale ($P < 0.001$)
- The VAS significantly lower in the S group ($P < 0.001$)
- Sufentanil remains metabolically active longer than remifentanyl but sufentanil administration for a short duration results in early recovery
- Sufentanil administration before concluding remifentanyl anesthesia improved postoperative hyperalgesia and achieved hemodynamic stability at extubation without delaying recovery or increasing PONV

Lee, J.Y., Lim, B.G., Park, H.Y., Kim, N.S. (2012). Sufentanil infusion before extubation suppresses coughing on emergence without delaying extubation time and reduces postoperative analgesic requirement without increasing nausea and vomiting after desflurane anesthesia. *Korean Journal of Anesthesiology*, 62(6), 512-517. doi.org/10.4097/kjae.2012.62.6.512

Methods:

- 84 patients laparoscopic hysterectomy
- Randomly divided into two sufentanil groups and a control group.
- During emergence, sufentanil was administered in the sufentanil groups at a rate of 0.2 µg/kg/hr (Group S1) or 0.3 µg/kg/hr (Group S2), and saline was administered to the control group.
- Cough score, hemodynamic changes, and recovery profiles (duration from skin closure to a bispectral index of 80, to eye opening at verbal command, to tracheal extubation and the total duration of study solution infusion, were recorded.
- The pain score, the total volume of administered patient-controlled analgesia (PCA), and the postoperative nausea and vomiting (PONV) score were evaluated 1, 6, and 24 hours after surgery.

Lee, J.Y., Lim, B.G., Park, H.Y., Kim, N.S. (2012). Sufentanil infusion before extubation suppresses coughing on emergence without delaying extubation time and reduces postoperative analgesic requirement without increasing nausea and vomiting after desflurane anesthesia. *Korean Journal of Anesthesiology*, 62(6), 512-517. doi.org/10.4097/kjae.2012.62.6.512

Results:

- Groups S1 and S2 showed significantly lower cough scores and smaller hemodynamic changes on extubation compared to Group C.
- Pain score, PONV at 1 hour postoperatively, and the total volume of PCA administered at all evaluation times were significantly lower in Groups S1 and S2 than in the control group. However, pain score, and PONV at 6 hours and 24 hours postoperatively showed no significant differences.
- A sufentanil infusion (0.2-0.3 µg/kg/hr) during emergence from desflurane anesthesia may suppress coughing on extubation in patients with body mass indexes (BMI) of 21-26 without delaying extubation time. It may also reduce the postoperative analgesic requirement without increasing PONV.

Eslanian, L., Kabiri-Nasab, M., Agha-Hosseini, M., Azimzadeh, O., Barzin, G., & Movafegh, A. (2016). Adding sufentanil to TAP block hyperbaric bupivacaine decreases post-caesarean delivery morphine consumption. *Acta Medica Iranica*, 54(3), 185-190.

Methods:

- 50 ASA I-II term primiparous women aged 20-40 years scheduled for elective cesarean delivery under general anesthesia were enrolled in the randomized, double-blind, placebo-controlled trial.
- Ultrasound guided transversus abdominis plane (TAP) block was performed at the end of surgery. Patients were randomly enrolled into two groups.
- Patients in the study group received 20 ml of hyperbaric bupivacaine 0.25% plus 2 mL of sufentanil on either side while patients in the placebo group were administered 20 ml of hyperbaric bupivacaine 0.25% with 2 mL of placebo.

Islamian, L., Kabiri-Nasab, M., Agha-Hosseini, M., Azimaraghi, O., Barzin, G., & Movafegh, A. (2016). Adding sufentanil to TAP block hyperbaric bupivacaine decreases post-caesarean delivery morphine consumption. *Acta Medica Iranica*, 54(3), 185-190.

Results:

- The morphine consumption was significantly less in the study group (37.2 ± 16.1 mg) than the control group (52.8 ± 16.7 mg, $P=0.002$).
- Sufentanil added to 0.25% hyperbaric bupivacaine in TAP block decreases post caesarean delivery morphine consumption.

Yeganeh, N., Roshani, B., Latifi, H., & Almasi, A. (2013). Comparison of target-controlled infusion of sufentanil and remifentanyl in blunting hemodynamic response to tracheal intubation. *Journal of Injury & Violence Research*, 5(2), 101-107. doi:10.5249/jiv.v5i2.325

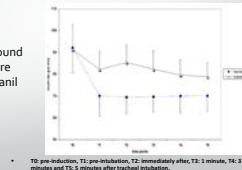
Methods:

- ASA I-II 40 normotensive patients
- Randomized double-blinded clinical trial study
- After BIS guided anesthesia with a target-controlled propofol infusion and muscle relaxation with cisatracurium, remifentanyl and sufentanil were infused using TCI with 2 and 0.2 ng.ml⁻¹ targets respectively
- BP and HR were recorded for five data points and compared with Fischer's exact test (T0: pre-induction, T1: pre-intubation, T2: immediately after, T3: 1 minute, T4: 3 minutes, T5: 5 minutes after tracheal intubation)

Yeganeh, N., Roshani, B., Latifi, H., & Almasi, A. (2013). Comparison of target-controlled infusion of sufentanil and remifentanyl in blunting hemodynamic response to tracheal intubation. *Journal of Injury & Violence Research*, 5(2), 101-107. doi:10.5249/jiv.v5i2.325

Results:

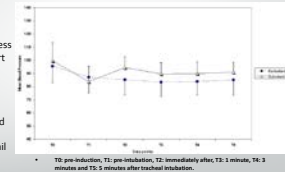
- Remifentanyl produced more profound preintubation bradycardia and more sustained bradycardia than sufentanil after tracheal intubation



Yeganeh, N., Roshani, B., Latifi, H., & Almasi, A. (2013). Comparison of target-controlled infusion of sufentanil and remifentanyl in blunting hemodynamic response to tracheal intubation. *Journal of Injury & Violence Research*, 5(2), 101-107. doi:10.5249/jiv.v5i2.325

Results:

- Both TCI produced stable hemodynamic conditions but sufentanil TCI was associated with less decrease in blood pressure and heart rate
- Sufentanil produced more common preintubation hypotension than remifentanyl in propofol anesthetized patients but this hypotension disappeared sooner than remifentanyl after tracheal intubation



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