The effects of low-dose analgesics on cardiovascular function (STU-2021-0579)
NCT04959812
8/18/2023

STU-2021-0579

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

The objective of this study is to identify whether sublingual sufentanil decreases tolerance to a simulated hemorrhagic insult in humans.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Hemorrhage is the leading cause of battlefield and civilian trauma deaths. In the early stages of a hemorrhagic injury, autonomic compensatory mechanisms are engaged that are vital to maintain blood delivery to vital organs.

Hemorrhagic injuries are virtually always accompanied with pain. Pain management of an injured soldier is a critical component of the medical care of that casualty. It is critical that the employed analgesic not compromise autonomic responses requisite to maintain arterial blood pressure, and thus blood flow, in a hemorrhaging individual. Sublingual sufentanil was recently approved by the FDA and is being deployed on the battlefield as and analgetic. No studies have evaluated the effects of analgesic doses of sufentanil on tolerance to a simulated (or actual) hemorrhagic insult in humans.

We propose that if sufficient doses of commonly employed analgesics are administered to humans, otherwise appropriate cardiovascular responses to the hemorrhagic insult will be suppressed, thereby reducing the ability of the individual to tolerate that insult. That said, the effects of analgesic doses of such agents (i.e., doses that are recommended for the pre-hospital setting) on physiological responses necessary to preserve tolerance to a hemorrhagic insult in humans is entirely unknown. Thus, the objective of this work is to identify the effects of sublingual sufentanil on tolerance to a simulated hemorrhagic challenge in humans.

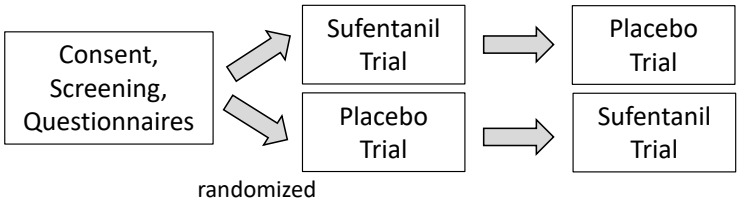
b. Current practice

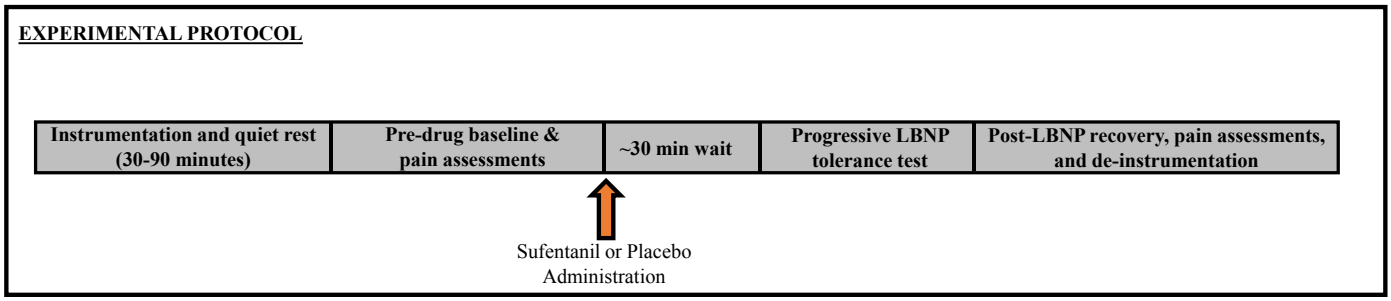
A 30 microgram dose of sufentanil (trade name: Dsuvia) is administered sublingually for the management of acute pain.

3. Study Design.

Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

We will conduct a double-blind, placebo-controlled, crossover study. Following informed consent and screening, eligible participants will be randomized to complete the sufentanil or the placebo trial first, with the other "agent" administered during the subsequent visit. During these experimental visits, we will administer two assessments of pain perception (described in greater detail below), then administer sufentanil sublingually or a placebo pill also sublingually, perform the simulate hemorrhagic tolerance assessment (lower-body negative pressure), and then re-assess the measures of pain perception. The graphics below depicts the study design and experimental protocol, respectively.





4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,

2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.

3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

Inclusion:

- 18-45 years of age
- Healthy
- Body mass index less than 33 kg/m^2
- Body mass greater than or equal to 60 kg
- Speak English

Exclusion:

- Subjects not in the defined age range
- Subjects who have cardiac, respiratory, neurological and/or metabolic illnesses
- Any known history of renal or hepatic insufficiency/disease
- Pregnancy or breast feeding
- Body mass less than 60 kg
- Current smokers, as well as individuals who regularly smoked within the past 3 years
- Subjects who cannot speak or read English
- Positive urine drug screen
- Currently taking pain modifying medication(s)

Although this study requires relatively uncomplicated procedures, inclusion of non-English speaking subjects would compromise subject safety. Consequently, it is imperative that the research and medical staff can communicate instantly and effectively with subjects, without the need of a translator. Therefore, the investigators feel that inclusion of non-English speakers would markedly and unnecessarily increase the risk to those participants.

Healthy adults will be recruited via online and paper flyers, emails to the Texas Health System (reaches over 18,000 people), local universities (inclusive of UTSW), and our institutional participant database. Participants must be free from underlying serious medical conditions (detailed via medical history, physical exam), non-smokers, have a body mass index less than 33 kg/m^2, and will be excluded if they have any current cardiometabolic diseases (e.g., diabetes, heart disease). Individuals who are pregnant, planning to become pregnant, or breastfeeding will be excluded. We will also exclude those with a history of drug abuse.

As described above, all participants will complete an informed consent and screening for eligibility. Participants will be randomized to complete either the sufentanil or placebo trial first. During these experimental visits, we will administer two assessments of pain perception (described in greater detail below), then administer sufentanil sublingually or a placebo pill also sublingually, perform the simulate hemorrhagic tolerance assessment (lower-body negative pressure), and then re-assess the measures of pain perception.

The setting for all visits will be the Institute for Exercise and Environmental Medicine. Trials will be conducted in controlled laboratory settings. During the experimental visits (sufentanil and placebo), we will record baseline cardiovascular measures. UT-Southwestern anesthesiologist Joseph Hendrix, MD, or a research nurse (with direct oversight from Dr. Hendrix) will administer sufentanil (30 microgram tablet) or placebo tablet during each experimental visit (i.e., participants will receive only one 30 microgram tablet of sufentanil). We will assess brachial blood pressure, nervous system activity via ultrasound-guided microneurography from the upper arm, beat-to-beat arterial blood pressure via photoplethysmography, cerebral perfusion via transcranial Doppler, limb blood flow via Doppler ultrasound, heart rate via electrocardiogram, respiration rate and end-tidal CO_2 via capnography from a nasal cannula, peripheral oxygen saturation via pulse oximetry, compensatory reserve via photoplethysmography, and plasma catecholamine concentrations from serial blood samples collected throughout the visit (~4 tablespoons per experimental visit). In addition, both before and after sufentanil/placebo administration, pain perception will be accessed via a cold pressor test (2-3

minutes of a hand placed in a water/ice slurry) and via a pressure algometer assessment (pressure applied to the hand to the point if discomfort).

Data analysis will be performed as done previously in Dr. Craig Crandall's laboratory in companion studies addressing the same questions but with ketamine (STU 092017-068), fentanyl (STU 092017-069), and morphine (STU 092017-070). Specifically, we will compare cardiovascular data (inclusive of nervous system activity data) between time points (baseline and post-drug/placebo administration) and conditions. We will also assess tolerance to the simulated hemorrhage challenge between sufentanil and placebo trials. All data will be analyzed while blind to condition and with proper co-variate analysis

Personal health information (PHI) that is collected will be kept in a key-lock filing cabinet in a key-lock room only accessible to study team members within a numeric-padlocked laboratory. As described in the eIRB portal, a coded number system will be used in place of the participants name to de-identify their research information collected. A participant ID key, only accessible to study team members, will link the participants 'information with the coded number. Additionally, we follow all applicable University of Texas Southwestern IRB and Institute of Exercise and Environmental Medicine (i.e., where the research will take place) guidelines for protecting research participant privacy.

Up to 60 participants are anticipated to enroll in this study. No study has evaluated the effects of sufentanil on lower-body negative pressure (LBNP) tolerance in humans. The power and sample size estimates are based on findings from Dr. Crandall's laboratory showing reduced LBNP tolerance in the heat-stressed individuals. In that study heat stressed reduced LBNP tolerance by ~70% ($P<0.001$). Though we expect sufentanil to likewise reduce LBNP tolerance, we do not anticipate as large of a reduction as that observed with heat stress. The power analysis was calculated using G*Power [Ttests – Means: Difference between two dependent means (matched pairs)] using an estimated reduction in the cumulative stress index to sufentanil of 25% relative to LBNP tolerance of a normothermic subjects taking a placebo (i.e., placebo: 988±402 units; sufentanil: 741±300 units). These predictions resulted in an effect size of 0.68. Having a correlation of 0.5, with a study power=0.80 at an adjusted alpha=0.05, yielded an estimated subject size of 15 individuals. That value was inflated to 30 subjects (15 male and 15 female) to permit a comparison in the primary responses within sexes. Given the potential for subject dropouts, we propose to recruit up to 60 individuals to obtain complete datasets from 30 subjects. Since the effects of sufentanil on LBNP tolerance has never been assessed, the indicated values are estimates and thus interim power analyses will be performed, with the number of required subjects adjusted based upon the variance of the obtained data.

4.b. List of the study intervention(s) being tested or evaluated under this protocol			
☐	**N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.		
#	**Study intervention(s) being tested or evaluated under the protocol** *Add or delete rows as needed*	**Affiliate** Place a check next to institution(s) where the intervention will be performed	**Local Standard Practice?** Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	**Sufentanil/Placebo administration**	☐ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☒THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

4.c.
Study Intervention #1
Sufentanil/Placebo Trials

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
All subjects	Learning of screening information (e.g., resting blood pressure) may positively contribute to the participant's well being

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious). (include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	• N/A	• N/A
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	• N/A	• N/A
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		• N/A

		4.d. List ALL other research procedures or components not listed in table 4.b. ***The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.*** Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)		
#	**Research component** • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Eligibility assessments**			
	Body height and mass, waist and hip circumference	0	Body height = 1, body mass recorded at each visit, waist and hip circumference = 1	
	Heart rate and rhythm via 12-lead ECG	0	1	
	Brachial blood pressure	0	Usually 3 to 5 measures	
2	**Other assessments**			
	Health history assessment	0	1	
	Lower-body negative pressure tolerance assessment	0	2	
3	**Blood sampling**			
	Blood sampling	0	Up to 10 draws (up to 5 draws per visit; baseline, and up to 4 time points post-drug/placebo administration). Total blood withdrawn: ~8 tablespoons.	

4	**Cardiovascular and other physiological measures**			
	Heart rate and rhythm via ECG	0	continuous throughout visits	
	Brachial blood pressure	0	several throughout visits, several in the 24-hour period after experimental visits	
	Finger blood pressure	0	continuous throughout visits	
	Microneurography for nervous system activity assessment	0	continuous throughout visits (needles placed at beginning of visits and removed before discharge)	
	Brain blood flow	0	continuous throughout visits	
	Limb blood flow	0	several throughout the experimental visits	
	End-tidal carbon dioxide	0	continuous throughout visits	
	Pulse oximetry	0	continuous throughout visits	
	Tissue oxygen saturation	0	continuous throughout visits	
	Urine sample	0	once each visit	
5	Sufentanil Administration	0	Once	

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Sufentanil administration: 30 micrograms of sufentanil will be administered once during one of the two experimental visits. The product that will be used will be a Dsuvia™ sublingual tablet, or similarly packaged placebo.

Risks and their mitigation: After sufentanil administration, it is possible participants will temporarily (e.g., to several minutes) experience low blood pressure, high heart rate, disorientation, become tired or dizzy, and/or develop a headache. While some individuals may feel discomfort from one or more of these sensations, it is expected that they will subside within a few minutes. In rare cases subjects may become nauseous or vomit. In extremely rare conditions individuals may have difficulty breathing. In such extreme cases, when medical treatment is needed, we will immediately stop testing and monitor the participant until all vital signs are within safe limits. Naloxone will completely reverse all opioid effects within 2 minutes of IV administration and 5 minutes of intramuscular administration. However, at the dose in the study proposed, we do not expect that significant respiratory depression will occur. We will monitor the patient's vital signs continuously. We will monitor pulse oximetry and end tidal carbon dioxide continuously. These two monitors will provide sufficient accuracy and robustness to administer this medication safely. An anesthesiologist will be present whenever sufentanil is administered to observe and intervene should the patient exhibit the slightest evidence of respiratory depression well before any

patient danger should arise. Standard airway intervention equipment will always be readily available. We have safely performed similar trials, using identical experimental procedures, with ketamine (STU 092017-068), fentanyl (STU 092017-069), and morphine (STU 092017-070) administrations without major complications in 40+ young adults in the previous two years.

Upon the conclusion of the protocol, subjects will not be permitted to leave the laboratory until all of the following discharge variables are met:

- The subject presents with an Aldrete score (post-anesthesia discharge scoring system) matching baseline,
- The subject demonstrates a awareness of time, person, and place and is able to answer questions appropriately
- The subject is able to stand up and walk for 5 minutes without assistance (supervised)
- The subject is able to drink water and eat crackers without reports of nausea
- The subject able to void

To be consistent with THR/UTSW hospital guidelines—the subject will be required to have a responsible adult bring them home. The responsible adult can either drive the subject home or accompany the subject home using ground transportation (bus, train, uber, or taxi service). The subject will also receive the recommendation to have someone observe them for the rest of the day and overnight.

Lower-body negative pressure (LBNP): LBNP to pre-syncope will be used to simulate a hemorrhagic injury. LBNP is performed by the subject lying on a table with their lower body (from iliac crest) inside an airtight container. A vacuum source is connected to that container. 40 mmHg negative pressure will initially be applied to the chamber for 3 min, with this pressure decreasing by 10 mmHg every 3 min until signs and/or symptoms of pre-syncope are observed (e.g., bradycardia, sustained systolic blood pressure <80 mmHg, nausea, lightheadedness, and/or diaphoresis). This approach is a validated method to simulate a hemorrhagic challenge (see PMID: 15016789). Dr. Crandall's laboratory has performed this procedure on hundreds of individuals (inclusive of 40+ individuals who received ketamine, morphine, or fentanyl) without any adverse incidents.
Risks and their mitigation: The possible risks of this procedure are light-headedness, feeling faint, nausea and rarely a subject may faint. If this occurs, the procedure will be stopped and the subject will begin to feel better almost immediately.

Cold pressor test: This widely used technique for pain assessment presents minimal risk. For this test, immersion of the hand in ice cold water will elicit painful sensations as well as an increase in blood pressure.
Risks and their mitigation: These typical responses are immediately reduced to pretest levels with the removal of the subject's hand from the ice water. The maximum duration for this test is three minutes and the subject can voluntarily remove the hand from the ice water at any time.

Pressure algometry: This pain assessment technique is conducted by applying the rubber tip of a hand-held digital algometer on the subject's digit. Force will be gradually increased and the peak force is recorded when the subject first reports a painful sensation.
Risks and their mitigation: Removal of the applied pressure immediately relieves the painful sensation, and the subject can voluntarily stop the test at any time. A pre-set maximum of 3 kg of pressure will ensure there is no damage to the tissue.

Microneurography: Nerve signals from the nerves in the arm [i.e. median nerve (inside portion of the middle part of the arm), radial nerve (inside portion of the forearm), or posterior cutaneous nerve (outside portion of the forearm)] will be measured. To locate the nerves, we use ultrasound imaging. When the nerve is located, we insert a small sterile needle (an electrode about the size of an acupuncture needle) through the skin. The participant may feel some slight discomfort during needle insertion. The recording needle is advanced into the nerve. When the tip of the needle enters the nerve, the participant may notice a tingling,

pins and needles, cramping, or dull achy sensation. A second needle serves as a reference electrode and is inserted just under the skin, a couple of inches away from the nerve. Once the needles are in place it is extremely unlikely the participant will feel any discomfort. This method of recording nerve signals in human participants has been used in over 3000 studies since 1979. We have performed over 300 recordings in our laboratory without any major complications. In rare cases, individuals may have tenderness, soreness, or numbness in the nerve recording area for a few days that subsides without treatment.
Risks and their mitigation: Consistent with published guidelines for microneurography, we will limit the nerve search time (from needle insertion until an adequate signal is acquired) to 60 minutes. Also, we will not record from the same nerve within one 28-day period. While not anticipated, we will stop this technique if they feel too much discomfort from microneurography. Participants will be instructed not to perform heavy lifting and to avoid rubbing/massaging the upper arm for ~24 hours to reduce the potential for inflammation-related acute neuropathy (occurs in fewer than 1% of cases).

Blood draws: A sterile catheter will be inserted into an arm vein for blood collection of plasma catecholamine concentrations. A total of ~8 tablespoons of blood will be withdrawn across all visits.
Risks and their mitigation: There is a small risk of infection and a still smaller risk of a blood clot or breakage of the catheter. The likelihood of these complications is remote (less than 1 in 10,000) when the procedure is carried out by trained personnel and proper equipment is used, as during this study. There is also a small risk of the catheter perforating the vein or not being inserted into a blood vessel. The participant may have discomfort, bleeding, and/or bruising and on rare occasions, a person may feel dizzy or faint.

Health history assessment: Participants will fill out a survey related to their physical well-being.
Risks and their mitigation: It is possible individuals may feel uncomfortable while completing this survey. We will ensure all participants are aware of this procedure during the informed consent visit. If a participant is uncomfortable completing all of the survey, they will be reminded that 1) their participation is entirely voluntary, 2) that only study investigators will have access to the surveys and their results, and 3) only de-identified results will be shared in scientific meetings and/or in future scientific manuscripts.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

When the participant is undergoing any testing, they will be supervised by an ACLS trained nurse and/or physician. Of note, a board-certified anesthesiologist will always be present when sufentanil is administered. There is a fully stocked “crash cart” with a defibrillator and medications (including naloxone) within 50 feet of the laboratory. IV anti-arrhythmic medications are rapidly available if a sustained but not life-threatening arrhythmia were to occur. Airway management equipment is also stocked in that cart. Furthermore, the Texas Health Resource Emergency Room is minutes away if an escalation of care is required.

Upon screening, participants will be given contact information for a nurse to contact in case any adverse event occurs following discharge from experimental days. However, this is unlikely to occur given the short-acting effects of sufentanil and the fact that participants are not discharged until vital signs are similar to that of baseline values.

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No

Statistical Analysis

Data was assessed for normality and are presented as means ± SD or medians [interquartile ranges], when appropriate. Based on our prior data investigating pharmacologic agents' effects on tolerance to LBNP (12, 24, 25), a sample size of $n = 15$ was estimated, but to maintain consistency with the previous studies, we recruited 29 individuals. Paired t-tests or Wilcoxon Signed-Rank tests were used for all paired comparisons (e.g., Urine-specific gravity, CSI, pain ratings, differences in CSI between the sexes etc.). Plasma catecholamine concentrations were compared between trials (placebo vs. sufentanil) using mixed-effects model analyses. Cardiovascular and cerebrovascular responses were evaluated every 30 seconds for the cold pressor test [time x trial], and the last minute of each LBNP stage [LBNP stage x trial], with the variables with each challenge compared using repeated-measures two-way ANOVAs or mixed-effects model. If a significant interaction was identified, a post hoc Šidák multiple comparison test was employed. $A < 0.05$ was considered statistically significant. Data were analyzed using GraphPad Prism 9 (GraphPad Software Inc., La Jolla, CA, USA).