

THIS IS AN INVITATION FOR YOU TO PARTICIPATE IN A RESEARCH STUDY WHICH INVOLVES TESTING OF THE MEDICINE

DETERMINATION OF ANALGESIC EQUIPOTENT DOSES OF INHALED METOXYFLURANE VS. INTRAVENOUS FENTANYL USING COLD PRESSOR TEST (CPT) IN VOLUNTEERS: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY.

This is an invitation for you to participate in a research study at Oslo University Hospital. The research study involves testing of metoxyflurane and fentanyl. The purpose of the study is to determinate analgesic equipotent doses of inhaled metoxyflurane vs. intravenous fentanyl.

WHAT DOES THE STUDY INVOLVE?

At first attendance, you will receive oral information about the study. An interview will be performed to examine your health condition. The study consists of four separate sessions, each of approximately 2 hours. There must be at least 3 days between each session. You must be available for at least 3-4 weeks.

You should be in good health and not have any chronic illness. No use of pain medication and complementary medicine the last 2 days before a session are allowed. No use of alcohol last 24 h before each of the four experiments. Your sex, age, weight and height will be stored. Nødvendige opplysninger vi må ha og lagre om deg er: kjønn, alder, vekt og høyde. Former medical history will also be stored if it does not qualifies for exclusion from the study.

Each session starts with a CPT (cold pressor test). The CPT will be conducted using a temperature-controlled bath with circulating 3°C water. You submerge your right hand to the wrist with fingers abducted for up to 90 seconds. You will be asked for pain score every 10 s during the test. NRS (numeric rating scale) scores from 0 to 10; 0= no pain and 10=worst pain imaginable. After the first CPT you will receive a syringe in your left arm. The test (CPT) will be performed 3 times for each session. After the first CPT there will be a 10 minutes rest before you receive either NaCl or a dose of fentanyl intravenously. At the same time you begin to inhale either metoxyflurane or NaCl through the inhalator. You will first take 10 breath through the inhalator. This will take approximately 1-1.5 minutes. You take a break, and then inhale the rest of the dosage.

After the second CPT, you relax until the last CPT 15 min after the second CPT. The actual implementation of the study will take 30 minutes..

The study is double-blind: both the participant and the investigator do not know which medication you receive.

Session 1: Placebo (saline) intravenously and placebo (saline) inhalation.

Session 2: Fentanyl 0.025 mg intravenously and placebo (saline) inhalation.

Session 3: Fentanyl 0.05 mg intravenously and placebo (saline) inhalation.

Session 4: Saline intravenously and metoxyflurane 3 ml inhalation.

These four sessions will be performed in a randomized order. It is necessary to recruit 10 volunteers to this study. No blood samples will be taken. During each session pulsoxymetry (oxygen level in your blood), ETCO₂ (end-tidal CO₂ – carbon dioxide in your expiratory breath) and ECG will be continuously monitored. Respiration frequency and non-invasive blood pressure will be recorded every 5. min during the study.

POTENTIAL ADVANTAGES, DISADVANTAGES AND SERIOUS ADVERSE EVENTS

You will be exposed for pain: cold pain (ice water), called CPT (cold pressor test). The CPT is painful, but harmless. In addition to pain you will be exposed to a little risk of side effects of the drugs. (see chapter A). If unacceptable adverse effects occur, the session will be interrupted.

The most common side effects are sedation, dizziness, itching, nausea and vomiting. Respiration depression may occur. Metoxyflurane has one serious side effect: kidney failure in anesthetic (large) doses. In the dose you receive there has been no reports of kidney failure.

In two of four sessions you will receive two different doses of fentanyl. Fentanyl is a strong opioid (“morphine drug”) which can give a sense of intoxication. We can therefore not have participants with previously drug abuse. The doses you receive are small, and the feeling of intoxication will soon disappear when you perform the CPT, because the test is painful.

VOLUNTARY PARTICIPATION AND THE POSSIBILITY TO WITHDRAW CONSENT

Participation in the project is voluntary. If you wish to take part, you will need to sign the declaration of consent on the last page. You can, at any given time and without reason withdraw your consent. This will not have any consequences for any future treatment. If you decide to withdraw participation in the project, you can demand that your tests and personal data concerning health be deleted, unless however, the personal data concerning health and tests have already been analysed or used in scientific publications. If you at a later point, wish to withdraw consent or have questions regarding the project, you can contact:

Harald Lenz, principal investigator, Tlf 90549545. E-mail: harald.lenz@medisin.uio.no

Leiv Arne Rosseland, investigator, Tlf 92204274. E-mail: l.a.rosseland@medisin.uio.no

WHAT WILL HAPPEN TO YOUR PERSONAL DATA CONCERNING HEALTH?

No bloodsamples will be taken. Any personal data concerning health that has been recorded about you will only be used as described in the purpose of the project.

All information will be processed and used without your name or personal identification number, or any other information that is directly identifiable to you. A code links you and your personal data concerning health via an identifier list. Only personnel involved in the study will have access to this list. The identifier list will be stored at the hospital.

After publication of the study it will not be possible to identify you in the results.

APPROVAL

The Regional Committee for Medical and Health Research Ethics has reviewed and approved the Research Project. Reference number REC 2018/2500.

In accordance with the General Data Protection Regulation the project manager , Harald Lenz, is independently responsible to ensure that the processing of your personal data concerning health has a legal basis. This project has legal basis in accordance with the EUs General Data Protection Regulation, article 6a, article 9 nr.2 and your consent.

You have the right to submit a complaint on the processing of your personal health data concerning health to the Norwegian Data Inspectorate (Datatilsynet).

CONTACT INFORMATION

If you have any questions regarding the research project, you can get in touch with

Harald Lenz, Principal Investigator, Tlf 90549545. E-mail: harald.lenz@medisin.uio.no

Leiv Arne Rosseland, responsible for research, Tlf 92204274. E-mail: l.a.rosseland@medisin.uio.no

You can also get in touch with the Institution's Data Protection Officer (personvernombud) if you have any questions related to the use of your personal health data concerning health in the research project. E-mail address: personvern@ous-hf.no

Further information on the study can be found in Chapter A – *Elaboration of what the study involves.*

Further information about biobank, data privacy, finance and insurance can be found in Chapter B – *Data privacy, biobank, funding and insurance.*

The declaration of consent follows Chapter B. – *The declaration should be signed by i) the person who consents to participate in the study and ii) the person who has provided information about the study and who can confirm that such information has been provided.*

CHAPTER A – FURTHER EXPLANATION OF WHAT THE STUDY INVOLVES

The purpose of the study is to determinate analgesic equipotent doses of inhaled metoxyflurane vs. intravenous fentanyl.

You should be in good health and not have any chronic illness. No use of pain medication and complementary medicine the last 2 days before a session are allowed. No use of alcohol last 24 h before each of the four experiments. You cannot have participated in a medical scientific project the last six months.

Why do we conduct this study?

Background information:

Methoxyflurane (Penthrox®- inhalation) is a halogenated ether first used clinically as a volatile inhalational anesthetic when introduced in the 1960s. Gradually the use of methoxyflurane as an anesthetic agent declined because of serious dose-related nephrotoxicity. There have also been reports of hepatic failure or hepatitis. Therefore, methoxyflurane is contraindicated in patients with clinically renal impairment, and should be used with care in patients with hepatic dysfunction.

Common and more harmless adverse effects of metoxyflurane are: dizziness (over 10%), dry mouth, nausea, coughing, headache, sedation, euphoria, short-term memory loss and indistinct speech (under 10%).

Methoxyflurane also demonstrates an analgesic effect in doses much less than used during anesthesia. In the past 30 years, methoxyflurane has been used as an analgesic in Australia and New Zealand. The drug has mostly been used in the emergency department and in a prehospital setting in conscious patients. Methoxyflurane is inhaled via an inhalator similarly as you use asthma medication. The main difference is that you breath in- and out continuously for about 10 breath or to acceptable pain relief. The pain relief occurs after few minutes and last for about 30 min if you inhale repetitive times. A standard dose is 3 ml, which can be repeated once. In our study, you will receive 3 ml once during the 4 sessions.

There are no reports of renal toxicity in the literature at the current dose recommendation of 3 ml, repeated once with a maximum of 15 ml/week. It has been calculated that an adult dose of 20-24 g metoxyflurane is associated with subclinical nephrotoxicity (6.0 ml delivers < 1.5 g).

In Norway, methoxyflurane has recently been approved for the emergency relief of moderate to severe trauma pain in conscious adult patients. Methoxyflurane is easy to administrate, and the patient do not need a syringe. There exists no good data of how effective metoxyflurane is as an analgesic compared to an opioid. Therefore, there is of interest to investigate metoxyflurane against another pain drug.

An alternative pain drug is often an opioid (“morphine drug”). Prehospital fentanyl is often used as standard therapeutic treatment for acute pain. A single dose of fentanyl has a pain relief effect after approximately 5 min and has effect approximately the same length as metoxyflurane. Fentanyl, like all opioids, has some adverse effects, which is associated with risk prehospital. Fentanyl may lead to respiration depression and can in worst-case lead to apnea and death. This is luckily seldom. Fentanyl may also lead to hypotension, and can

therefore aggravate a situation where the patient is hypovolemic. Hypovolemia is difficult to detect prehospital and this often lead to insufficient analgesia with opioids.

The opioid fentanyl (Fentanyl® - intravenous, liquid) is used as standard therapeutic treatment for acute pain and acute operative pain. Fentanyl is a pure opioid receptor agonist with central and peripheral effects.

In addition, fentanyl has also adverse effects like nausea, vomiting and muscle rigidity (over 10%) and dizziness, sedation, low blood pressure, itching, low pulse and visual disturbances (over 5%).

If you experience some of these adverse effects, and that they are unpleasant, the experiment will be aborted. We must the consider whether we must exclude you from the rest of the study.

The table below represent the study's timeline:

Time (min)	- 15	-10	-5	0	5	10	15
Control (C)	CPT		placebo (NaCl) i.v. placebo (NaCl) inhal; continuous	CPT			CPT
Fentanyl (F1)	CPT		F1 0.025 mg i.v. placebo (NaCl) inhal; continuous	CPT			CPT
Fentanyl (F2)	CPT		F2 0.05 mg i.v. placebo (NaCl) inhal; continuous	CPT			CPT
Metoxyflurane (M)	CPT		placebo (NaCl) i.v. M 3 ml inhal; continuous	CPT			CPT

The CPT (cold pressor test – ice water 3°C) is performed by submerge the right hand to the wrist with fingers abducted for up to 90 s. You will be asked for pain scores every 10 s. This test will be performed 3 times for each session. You may retract your hand before 90 s. In case of this, we registered the time you manage to keep the hand in the ice-water. The CPT is painfull, but harmless.

As you can read from the table, the experiment lasts for 30 minutes. There are some preparation: a syringe has to be placed and other monitoring equipment connected like ECG, endtidal CO2 and pulsoxymetry.

We expect 30 min preparation and 1 hour with observation after each session. Totally 2 hours. You can not drive a car the same day. It must be at least 3 days between each session.

10 volunteers will be included in this study.

Allowance: You receive a remuneration of 300 n.kr pr. session, and 100 n.kr in travel expenses. Totally 1600 n.kr.

CHAPTER B – DATA PRIVACY, BIOBANK, FUNDING AND INSURANCEKAPITTEL

WHICH INFORMATION IS REGISTERED ?

Following information about you will be registered: sex, age, weight and height.

Representatives from sponsor for this study, the Norwegian Medicines Agency (NoMA) and domestic and foreign supervisory authorities may have study data released to them and be granted access to relevant parts of your medical records. The purpose is to check that the study data corresponds with the equivalent data in your medical records. Anyone who has access to this data is bound to secrecy.

The identifier list will not be extradited.

FUNDING

The study is funded by Oslo University hospital

The implementation of the study will be conducted by Harald Lenz (anesthesiologist) and Tomas Drægner (CRNA/research nurse). Both are funded by Division of Emergencies and Critical Care, Oslo University Hospital.

INSURANCE

You are insured in accordance with the Product Liability Act in the Drug Insurance.

INFORMATION ABOUT THE OUTCOME OF THE STUDY

You are entitled to receive information about the outcome/result of the study.

CONSENT FOR PARTICIPATION IN THE STUDY

I am willing to participate in the study.

(Signed by the study participant, date)

CONSENT THAT INFORMATION HAS BEEN GIVEN TO THE PARTICIPANT IN THE STUDY

I confirm that I have given information about the study.

(Signed, role in the study, date)