Clinical Study Report Synopsis

Name of Sponsor/Company
Umeå University, Sweden

Title of Study
Recovery of gastric function after treatment with shortacting opioids.

Eudra-CT number
2015-005489-46

Study Center:
Sundsvall Hospital, Sweden

Investigator:
Jakob Wallden, M.D. Ph.D.

Study periods
First enrolment: 2017-09-18
Last completed: 2018-06-23

End-of-trial
2024-06-07 (Early/premature termination)

Reason: "This was an experimental study with volunteers, and we planned to perform 7 series of experiments with 10 participants in each. From September 2017 to May 2018, we completed 3 series (1: fentanyl 1µg/kg, 3: alfentanil 5µg/kg 5: remifentanil 0.1µg/kg/min) and included 5 patients in erie 6 (remifentanil 0.2µg/kg/min). After the summer 2018, the planned PhD student droped out from the project, and there were no persons available to conduct the experiments. We put the study on hold, and hoped to run the remaining series later. The pandemic was a factor delaying decisions regarding the study, and now we realize that we are not going to be able to "restart the trial". We hope to complete the analysis of data during 2024-2025. Today (240607), I formally decided, as the PI and sponsor of the trial, to end the trial and no further experiments will be performed."

Justification: We have data from three experimental series and data from five participant in a fourth serie. Analysis and publication are not dependent on the missing series. Further, we have no resources for completing the trial, and the EGG-equipment is now faulty. Therefore, there are no basis for continuing the trial.

Objectives of the trial:

The primary objective of the trial was to explore gastric recovery after treatment with short-actings opioids.

S

econdary objectives were to study the effects of opioids on gastric myoelectric activity and evaluation of safety variables

Methodology:

Experimental study in healthy volunteers given opioids and study gastric myoelectrical activity with electrogastrography (EGG) and evaluate time to recovery to the normal (baseline) EGG-activity of around 3 cpm.

We planned for these series:

Series F1: Intravenous bolus dose of fentanyl 1 µg/kg
Series F2: Intravenous bolus dose of fentanyl 2 µg/kg
Series A5: Intravenous bolus dose of alfentanil 5 µg/kg
Series A10: Intravenous bolus dose of alfentanil 10 µg/kg
Series R01: Intravenous infusion of remifentanil 0.1 µg/kg/min for 15 minutes
Series R02: Intravenous infusion of remifentanil 0.2 µg/kg/min for 15 minutes
Series R03: Intravenous infusion of remifentanil 0.3 µg/kg/min for 15 minutes

Before starting administration of opioid, baseline EGG was registered during at least 20 minutes. EGG-activity was evaluated visually and with a running spectral analysis. After administration of the opioid EGG was registrered continuously, and if/when the EGG returned to normal pattern, registration continued for further 15 minutes. Registration was discontinued 90 minutes after the administration of opioids.

As safety measures during the study, vital functions were monitored continuously.

As the short-acting opioids used have strong effects on vital functions, we expected side-effects like respiratory depression, decreased oxygen saturation, nausea/vomiting, hypotension and affected consciousness.

Measures were taken to monitor and act for compromised vital functions. Actions included oxygen supply, ventilatory support, discontinuation of study drug, antiemetic treatments, opioid-antidotes. Participant were fully informed and consented.

Primary endpoint:

- Time to recovery (minutes) of normal gastric electrical activity defined as dominant frequency (DF) +/-10% of dominant frequency before opioid administration.

Secondary endpoints:

- Changes in dominant frequency after opioid administration.
- Safety variables
  - Pulse, blodpressure, ECG changes
  - Oxygen saturation, respiratory rate
  - Consciousness

Method for evaluation of EGG-signal

Using an overall spectrum analysis, dominant frequency (DF) and dominant power (DP) were determined before administration and with 10-minute intervals, with a 5 minute overlap, after the administration of opioids until return of normal activity. The 10 minutes interval in which the activity returned to normal was identified and the mean time for that specific interval was used in the calculations as the time for the return of normal gastric activity. The dominant individual response of DF was classified as either bradygastria (-10% of baseline DF), tachygastria (+10% of baseline DF), unaffected (<±10% of baseline DF) or uncoordinated (loss of detectable frequency).

Number of patients

Serie	Planned	Included	Excluded	Opioid	Analysed
F1	10	11	1	10	10
F2	10	0	0	0	0
A5	10	11	1	10	10
A10	10	0	0	0	0
R01	10	10	0	10	0
R02	10	6	0	6	0
R03	10	0	0	0	0

Main criteria for inclusion/exclusion:

Inclusion criteria:

ASA-classification 1-2

Non-smokers

Men and women 18-65 years

Body Mass Index (BMI) 18-30

The subjects must be able to fulfil the study

Signed and dated written informed consent

Exclusion criteria:

Women that are pregnant or breastfeeding.

Pathophysiology concerning gastric motility, i.e. gastric surgery.

The subject is prescribed drugs that interfere with gastric motility.

History of drug abuse.

Other reason that the investigator finds essential.

Participated in another series during this study.

Test product, dose and mode of administration:

Fentanyl, bolus dose, intravenous.

Alfentanil, bolus dose, intravenous.

Remifentanil, continuous infusion, intravenous.

For doses, see section methodology.

Duration of treatment.

Experimental study, single-dose.

Reference therapy

Not applicable

Subject characteristics

	F1 ***Fentanyl 1µg/kg*** ***n=10***	***A5*** ***Alfentanil 5µg/kg*** ***n=10***	***R01*** ***Remifentanil 0.1*** ***µg/kg/min n=10***	***R02*** ***Remifentanil 0.2*** ***µg/kg/min n=6***
Age (years)	32 (9,6)	27 (5,5)	24 (3.2)	26 (4.1)
Males	4	4	4	3
Females	6	6	6	3
BMI (m^2/kg)	24,3 (1,8)	24,3 (2,5)	24.2 (2.2)	23,7 (3.3)
ASA class I	10	10	9	6
ASA class II			1	

Data are given as means and standard deviation. BMI = Body Mass Index. ASA = American Society of Anaesthesiologists Physical Status Classification System

Criteria for evaluation - Efficacy

Main parameters from the electrogastrografic (EGG) registration after intravenous bolus dose of a short-acting opioid.

EGG-signal from Serie R01 and R02 has not yet been analysed.

	F1 ***Fentanyl 1µg/kg*** ***n=10***	***A5*** ***Alfentanil 5µg/kg*** ***n=10***
Baseline dominant frequency (DF), cpm, mean (SD)	2,93 (±0,19)	2,98 (±0,21)
Baseline dominant power (DP), dB, mean (SD)	48,9 (±8,9)	45,7 (±6,8).
Main effect on EGG, number of subjects		
- Unaffected	1	2
- Bradygastria	1	3
- Tachygastria	1	0
- Uncoordinated	7	5
Time to loss of normal EGG activity, minutes, median (range)	5 (5-20) n=9	8 (5-15) n=8
Time to return of normal EGG activity minutes, median (range)	40 (15-60) n=9	20 (10-45) n=8

Cpm = cycles per minute; SD = standard deviation; dB = decibel; EGG = electrogastrography. Time to loss and return of activity are among the affected subjects.

Changes in electrogastrographic (EGG) dominant frequency (DF) during 10 minutes after administration of fentanyl and alfentanil (secondary endpoint):

	F1 Fentanyl 1µg/kg	A5 Alfentanil 5µg/kg
DF, Baseline	3,0 (2,6-3,3) cpm	2,9 (2,7-3,4) cpm
DF, 10 minutes after opioid	2,2 (0-3,4) cpm	2,6 (0-3,3) cpm
(p-value)	0,037	0,012

Values are given as median (range). DF= dominant frequency. Cpm = Cycles per minute. Wilcoxons signed rank test is used for comparisons of DF before and after administration of opioids. When no DF was detected, DF was set to 0.

Criteria for evaluation: Safety

Adverse events/observations

Events (numbers of subjects)	***F1 Fentanyl 1µg/kg n=10***	***A5 Alfentanil 5µg/kg n=10***	***R01 Remifentanil 0.1 µg/kg/min n=10***	***R03 Remifentanil 0.2 µg/kg/min n=6***
Allergic reactions	0	0	0	0
Loss of consciousness	0	0	0	0
Respiratory depression (RF <6/min)	0	0	0	0
Itching	0	0	2	0
Nausea	0	0	2	2
Dizziness			2	5
Other	1*	0	0	0

*Panic attack in a subject with history of anxiety.

During the experiments, breathing frequency, saturation, pulse and blood pressure were stable in all subjects. A few subjects not receiving additional oxygen, desaturated to approximately 90%, but after a verbal reminding to breathe normally and/or adding oxygen (1-2 L/min, nasal cannula), the saturation immediately returned to normal. In either of the series, none of the subjects were never deeper sedated than that they could easily be wakened if fallen asleep.

Statistical methods

Data is presented with descriptive statistics as mean (SD) for normally distributed data and medians (ranges) for non-normal distributed data. Non-parametrical statistical tests were used for the analysis of the effect of opioids on the dominant frequency (Wilcoxon signed rank test). The study is a physiologic descriptive study and therefore, we considered that a power-analysis was not needed.

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Summary/Conclusions - Efficacy

Significant change in gastric myoelectric activity after the administration of short-acting opioids with a high individual variation. The gastric effect was short and return of normal EGG-activity was observed in all subjects within one hour.

Summary/Conclusions – Safety

During this experimental study, there were no serious adverse reaction. Some expected adverse reactions related to the opioid administration occurred, mainly respiratory depression that was handled per protocol in the study. The expected side-effect occurred mainly during the series with remifentanil.

Date of the report:

2025-06-12

Jakob Wallden