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A study to compare the effect and safety of inhaled isoflurane to intravenous midazolam for sedation in mechanically ventilated children 3-17 years old

Submission date
28/01/2022

Recruitment status
No longer recruiting

Registration date
04/05/2022

Overall study status
Completed

Last Edited
07/06/2022

Condition category
Other

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Mechanical ventilation is a method that helps patients who can't breathe spontaneously, whereby a machine called a ventilator is used to help move air in and out of the lungs. Mechanically ventilated patients often need to be sedated to ensure comfort. Sedation is a reduced degree of consciousness or artificial sleep, induced by medication. Mechanically ventilated patients in the intensive care unit (ICU) are sometimes sedated with the same anaesthesia medication as used for surgery but at a lower dose and often over a longer time. Today, only a medication called midazolam, which is administered through the veins, is approved for sedation of mechanically ventilated children. However, studies in adults have shown that inhalation anaesthetics such as isoflurane (anaesthetic in the form of gas delivered via the lungs) can be used as an alternative to intravenous substances for sedation in ICUs. A prerequisite for this is an additional device connected to the ventilator, called AnaConDa-S, which allows the inhaled anaesthetics to be mixed with breathing air. Studies in adults have shown that inhaling isoflurane for sedation is equally good and shows promising advantages over standard intravenous sedation, such as shorter wake-up times, better tolerance, fewer side effects and a better ability to maintain the desired level of sedation. There is quite a number of reports and smaller trials in which isoflurane or another inhalation anaesthetic were administered safely and with great success. The aim of this study is to collect data on a larger scale to determine if inhaled isoflurane has the same level of effect and safety in children as intravenous midazolam. This is necessary as isoflurane has so far only been approved for anaesthesia in surgery, but not for sedation in ICUs.

Who can participate?
Children (aged 3-17 years) admitted to an ICU/with planned ICU admission undergoing mechanical (invasive) ventilation and sedation for at least 12 hours

What does the study involve?
There will be two treatment groups. One group will receive intravenous midazolam sedation as

used in standard practice. The other group will receive inhaled isoflurane using an additional device connected to the ventilator, called AnaConDa-S, which allows the inhaled anaesthetics to be mixed with breathing air. The participant will be randomly assigned to one of the treatments, which means that a computer programme chooses which treatment group the participant will be in (like the flip of a coin). The study doctor has no influence on what treatment group the participant will be in. The sedation period with study medication will be up to 48 hours, and only as long as sedation is required. After 48 hours, the treating doctor will decide whether to carry on with sedation, choose a different type of sedation, or cease sedation. After the study period, there will be a follow-up period of approximately 30 days.

What are the possible benefits and risks of participating?
Midazolam is commonly used in ICUs and is considered safe. All medications have side effects. Exposure to midazolam can cause withdrawal symptoms when stopped, such as headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. These side effects are treatable.
In relation to children, sedation can be associated with reversible neurological side effects, so-called psychomotor events, usually seen after 24 hours of sedation. These include involuntary twitching movements and hallucinations. They are reversible which means that they resolve spontaneously, usually within hours or maximum up to a few days.
In rare cases in patients with a genetic susceptibility, isoflurane may trigger a syndrome called malignant hyperthermia which is a life-threatening dysfunction of the skeletal muscles. The symptoms include increased body temperature, muscle rigidity, irregular heartbeat, unstable blood pressure and low oxygen levels in extremities (e.g. fingers or toes). Patients with known /suspected genetic susceptibility to malignant hyperthermia will not be included.
Isoflurane sedation in the intended dose for the intended duration is likely to be more effective than intravenous sedation with midazolam. The risks for severe immediate or prolonged side effects appear to be very small.
The participants' health will be closely monitored during the study treatment and after the end of the sedation with the study medication, the patient will be followed closely during a 48-hour post-study treatment period, e.g. assessment of safety laboratory parameters, delirium if applicable, and adverse events. After the 48-hour post-study treatment monitoring patients will be assessed on a weekly basis, e.g. follow up of all ongoing adverse events, recording adverse events which are assessed as severe, serious or assessed to be related to the study drug.

Where is the study run from?
Sedana Medical AB (Sweden)

When is the study starting and how long is it expected to run for?
January 2022 to December 2022

Who is funding the study?
Sedana Medical AB (Sweden)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2020-000578-31

Integrated Research Application System (IRAS)
1004579

ClinicalTrials.gov (NCT)
NCT04684238

Protocol serial number
SED002, IRAS 1004579, CPMS 51643

Study information

Scientific Title
A randomised active-controlled study to compare efficacy and safety of inhaled isoflurane delivered by the AnaConDa-S (anaesthetic conserving device) to intravenous midazolam for sedation in mechanically ventilated paediatric patients 3 to 17 (less than 18) years old

Acronym
IsoCOMFORT

Study objectives
To compare the percentage of time adequate sedation depth is maintained within the individually prescribed target range in the absence of rescue sedation as assessed according to the COMFORT-B scale, in isoflurane vs midazolam treated paediatric patients for an expected minimum of 12 hours.

Secondary objectives:
1. Compare the use of opiates and the development of tolerance to the sedative regimen as measured by the change in the dose of the study drug, opiates and other analgesics, over time in isoflurane- vs midazolam-treated patients
2. Compare the need for rescue sedatives and other sedatives in isoflurane- vs midazolam-treated patients

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/03/2022, Yorkshire & The Humber - Leeds West Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 972 2504, +44 (0)207 104 8134; leedswest.rec@hra.nhs.uk), ref: 22/YH/0036

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Sedation in mechanically ventilated paediatric patients

Interventions
There will be two treatment groups. One group of 53 children (1/3) will receive therapy with intravenous midazolam sedation as used in standard practice. The other group of 107 children (2 /3) will receive inhaled isoflurane using an additional device connected to the ventilator, called AnaConDa-S, which allows the inhaled anaesthetics to be mixed with breathing air.

The participant will be randomly assigned to one of the treatments, which means that a computer programme chooses which treatment group the participant will be in (like the flip of a coin). The study doctor has no influence on what treatment group the participant will be in.

The sedation period with study medication will be up to 48 hours, and only as long as sedation is required. After 48 hours, the treating doctor will decide whether to carry on with sedation, choose a different type of sedation, or cease sedation. After the study period, there will be a follow-up period of approximately 30 days.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Isoflurane, midazolam

Primary outcome(s)
The percentage of time adequate sedation depth is maintained within the individually prescribed target range is measured using the COMFORT-B scale hours after initiating study sedative treatment starting 2 hours after the initial study sedative treatment (or in case of ongoing sedation, 2 hours after terminating ongoing sedatives) until the study treatment is replaced with the standard treatment (at 48± 6 hours from study treatment initiation) or when the wake-up for extubation is started, whichever comes first.

Key secondary outcome(s))
1. The use of opiates and the development of tolerance to the sedative regimen as measured by the change in dose of study drug, opiates and other analgesics in isoflurane vs midazolam treated patients from a minimum of 12 hours up to 48 hours (± 6 hours)
2. The mean dose of study drugs, opiates and other analgesics required during the last 4 hours of study treatment as compared to the first 4 hours of study treatment after the first blinded COMFORT-B assessment is calculated
3. The mean dose of rescue propofol (mg/kg/24 hours) and mean dose of rescue ketamine /esketamine (converted to ketamine-equivalents mg/kg/24 hours), and mean dose of α2-adrenergic agonists (mg/kg/24 hours) to maintain the COMFORT-B score in the individually prescribed range in isoflurane- vs midazolam-treated children from 2 hours after initiating study sedative treatment to the end of sedative treatment
4. Number of doses of rescue sedation (propofol, ketamine, es-ketamine) given per 24 hours from the first blinded COMFORT-B assessment (at +2 hours) to the end of the study treatment period
5. The time from the end of study drug administration to extubation if the study drug is terminated for extubation, measured during the treatment
6. The proportion of observations with spontaneous breathing efforts, measured during study treatment
7. The need for additional inotropic/vasopressor agent measured using the Vasoactive-Inotropic Score (VIS) score during the study treatment period and at baseline.
8. The presence of withdrawal symptoms in patients exposed to more than a total of 96 hours sedation (including the pre-study sedation period) until the end of the 48-hour post-study treatment monitoring or ICU discharge, whichever comes first, is measured using the SOS-PD scale during treatment (every 8 hours), at the end of the study treatment (48± 6 hours from study treatment initiation) and at post-study treatment monitoring (up to 48 after the end of study treatment)
9. The presence of delirium in patients admitted to the ICU for at least 48 hours (including the period prior to study enrolment) until the end of the 48-hour post-study treatment monitoring or ICU discharge, whichever comes first, is measured using the SOS-PD scale at baseline, during treatment (every 8 hours), at the end of the study treatment (48± 6 hours from study treatment initiation) and at post-study treatment monitoring (Up to 48 after the end of study treatment)
10. The proportion of patients experiencing psychomotor dysfunction or neurological symptoms during sedation and/or in the 48 hours after discontinuation of isoflurane or midazolam treatment, in relation to the duration of exposure to isoflurane or midazolam, and to cumulative midazolam mg/kg or isoflurane exposure (MAC hours)
11. 30 days/hospital mortality calculated using data recorded from the patient’s medical records

on day 30 after the end of the study treatment period
12. Ventilator-free days at 30 days from the start of the study treatment period are calculated using data recorded from the patient's medical records on day 30 after the end of the study treatment period
13. Time in intensive care unit/hospital at day 30 from the start of the study treatment period is calculated using data recorded from the patient's medical records on day 30 after the end of the study treatment period
14. Days alive and not in the ICU at day 30 from the start of study treatment period are calculated using data recorded from the patient's medical records on day 30 after the end of the study treatment period
15. Proportion of patients with common as well as sedation-related adverse events, and frequencies of these adverse events from the start of study treatment to the end of 48-hour post study treatment monitoring. Recording of AEs starts at the initiation of IMP administration and will continue to the end of the 48-hour post-study treatment monitoring
16. Frequency and intensity of adverse events measured from the start of study treatment to day 30. Recording of AEs starts at the initiation of IMP administration and will continue to the end of the 48-hour post-study treatment monitoring. After this, the patient's general condition will be assessed at the weekly follow up visits/contact
17. Changes in vital signs, blood gases, body temperature and urinary output measured from baseline to end of study treatment. Respective assessments are taking place at baseline (except for urinary output), during treatment (every 2 hours [vital signs], or 8 hours [urinary output, body temperature, blood gases], respectively) and at the end of the study treatment (48± 6 hours from study treatment initiation)
18. Changes in clinical chemistry and haematology parameters measured from baseline up to the 48-hour post-study treatment monitoring. Respective assessments are taking place at baseline, 24 +-6 hours, at the end of the study treatment (48± 6 hours from study treatment initiation) and post-study treatment monitoring (up to 48 after the end of study treatment)

Completion date
10/12/2022

Eligibility

Key inclusion criteria
1. Paediatric patients at least 3 years to 17 (less than 18, patients who will turn 18 years during the study [including follow-up] will not be included) years at the time of randomisation, admitted to an ICU/with planned ICU admission
2. Expected mechanical (invasive) ventilation and sedation for at least 12 hours
3. Informed consent obtained from the patient, patient's legal guardian(s) as required by local regulations. Where applicable, assent obtained from the patient to participate in the clinical study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
3 years

Upper age limit
17 years

Sex
All

Key exclusion criteria
1. Ongoing seizures requiring acute treatment
2. Continuous sedation for more than 72 hours at the time of randomisation
3. Less than 24 hours post cardiopulmonary resuscitation
4. Uncompensated circulatory shock
5. Known hypersensitivity to isoflurane or to other halogenated anaesthetics (such ashalothane), benzodiazepines, non-investigational medicinal product(s) (analgesics, additional rescue sedatives that may be required during the study) or to any of their formulation ingredients
6. Known or suspected genetic susceptibility to malignant hyperthermia
7. Patients with acute asthma or obstructive lung disease symptoms requiring treatment at inclusion
8. Patient with tidal volumes below 30 ml or above 800 ml
9. Inability to perform reliable COMFORT-B assessment in the opinion of the Investigator e.g. due to (not limited to): severe traumatic brain injury, intracranial pathology (tumour, haemorrhage, infections), with a profound effect on the level of consciousness, severe mental retardation, major congenital anomalies of the central nervous system, severe myasthenia gravis, spinal muscular atrophy, or another severe neurologic disease, ongoing neuromuscular blockade which precludes COMFORT-B scoring.
10. Patients with intracranial pressure (ICP) monitoring or with a suspected increase in ICP
11. Patients with treatment-induced whole-body hypothermia
12. Patients with pheochromocytoma
13. Patients with prolonged QT interval or with significant risk for prolonged QT interval
14. Patient not expected to survive next 48 hours or not committed to full medical care
15. Female patients who are pregnant or breastfeeding
16. Previous participation in the study (a patient can only participate once)
17. Known participation in any other clinical study that included drug treatment within three months of the first administration of the IMP
18. Any for the study relevant medical history, or ongoing clinically significant disease, disorder or laboratory result which, in the opinion of the Investigator, precludes participation in the study for medical or ethical reasons

Date of first enrolment
20/11/2020

Date of final enrolment
10/12/2022

Locations

Countries of recruitment
United Kingdom

England

France

Germany

Spain

Sweden

Study participating centre
Royal Manchester Children's Hospital
Oxford Road
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Study participating centre
Leicester Royal Infirmary
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Study participating centre
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Sponsor information

Organisation
Sedana Medical AB

Funder(s)

Funder type
Industry

Funder Name
Sedana Medical AB

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes