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Remifentanil versus fentanyl for analgesia-based sedation to provide patient comfort in the intensive care unit

Submission date	Recruitment status	[_] Prospectively registered
20/10/2003	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
22/10/2003	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
26/03/2008	Signs and Symptoms	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

USA30206

Study information

Scientific Title

Study objectives
This randomised, double-blind study compared the safety and efficacy of remifentanil (REMI - 9 mcg/kg/h) with fentanyl (FEN - 1 mcg/kg + 1.5 mcg/kg/h). One hundred and ninety six Intensive Care Unit (ICU) subjects with normal renal function or mild renal impairment requiring mechanical ventilation were studied. A pre-defined dosing algorithm permitted initial titration of the opioid followed by the addition of propofol (0.5 mg/kg/h) if required. A REMI-based regimen was very effective in the provision of optimal sedation and analgesia. The mean % hours of optimal sedation was 88.3% in the REMI group. Similar results were observed when using FEN. There was no statistically significant difference in the overall between-subject variability in the duration of optimal sedation. However for those subjects who achieved a Sedation Agitation Scale (SAS) score of four, variability was significantly lower when using REMI.

Propofol was not required in 65% of subjects. When propofol was administered there was a trend towards less use in remifentanil subjects. The dosing algorithm facilitated rapid extubation in both treatment groups. REMI provided comparable haemodynamic stability compared to FEN. The adverse event profile observed for REMI was similar to FEN and was not unexpected for ICU subjects receiving an opioid agonist. The pharmacokinetic (PK) profile of REMI was unaltered in subjects with renal impairment. Although the elimination half-life of remifentanil acid was doubled and the clearance was reduced by half in subjects with mild renal impairment, no evidence of prolonged opioid effects were seen. REMI is therefore considered to effective and well tolerated in ICU subjects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from local and national ethics committees.

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Analgesia in the critically ill

Interventions
Assessment of sedation and pain scores with initial titration of the opioid to effect, monitoring of haemodynamics.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Remifentanil, fentanyl

Primary outcome measure
Between-subject variability around the mean percentage of hours of optimal sedation (Sedation Agitation Scale [SAS] score of 4).

Secondary outcome measures
Efficacy:
1. Mean percentage of hours subjects were optimally sedated (SAS score of 4) during the treatment and post-treatment periods
2. Mean percentage of hours subjects were inadequately sedated (SAS score of 5, 6 or 7) during the treatment and post-treatment periods
3. Mean percentage of hours subjects were excessively sedated (SAS score of 1, 2 or 3) during the treatment and post-treatment periods
4. Mean percentage of hours subjects were dangerously agitated (SAS score of 7) during the treatment and post-treatment periods
5. Mean percentage of hours subjects were unarousable (SAS score of 1) during the treatment and post-treatment periods
6. Mean percentage of hours of no/mild pain during the treatment and post-treatment periods
7. Time between start of the extubation process and actual extubation
8. Total time on mechanical ventilation within the treatment period
9. Time between extubation and ICU discharge
10. Time from the start of study drug until ICU discharge

Other:
1. Weighted mean infusion rates of remifentanil, fentanyl and propofol
2. Total exposure to study opioid and propofol including frequency of opioid infusion rate changes, and propofol infusion rate changes (from starting the opioid infusion until it was discontinued)
3. Incidence of supplementary open-label propofol and fentanyl bolus doses administered for stimulating procedures during the treatment period
4. Incidence of open-label propofol and fentanyl bolus doses administered for rescue treatment during the maintenance phase
5. Incidence of supplementary open-label propofol, fentanyl, morphine and bupivacaine bolus doses administered for analgesia/sedation during the extubation and post-extubation phases

Safety:
1. Haemodynamic parameters during and after treatment (mean arterial pressure [MAP] and heart rate [HR])
2. Respiratory function (post-extubation only - respiratory rate [RR], fractional inspired oxygen concentration [FiO2] and peripheral oxygen saturation [SpO2])
3. Clinical adverse events

Pharmacokinetics:
Remifentanil and remifentanil acid blood concentrations.

Overall study start date
12/07/1999

Completion date
19/06/2000

Eligibility

Key inclusion criteria
A subject will be eligible for inclusion in this study only if all of the following criteria apply:
1. Admitted into the ICU within the previous 24 hours
2. Intubated and expected to require short-term mechanical ventilation (i.e. for at least a further 12 hours and up to 72 hours after starting the study drug infusion)
3. Aged over 18 years old
4. A female is eligible to enter and participate in this study if she is of:
4.1. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal) or,
4.2. Child-bearing potential, has a negative pregnancy test (urine or serum) at screen, and agrees to one of the following:
4.2.1. Complete abstinence from intercourse from two weeks prior to administration of study drug, throughout the study, and for a time interval after completion or premature discontinuation from the study to account for elimination of the investigational drug (minimum of 7 days)
4.2.2. Female sterilisation
4.2.3. Sterilisation of male partner
4.2.4. Implants of levonorgestrel
4.2.5. Injectable progestogen
4.2.6. Oral contraceptive (combined or progestogen only)
4.2.7. Any intrauterine device (IUD) with published data showing that the highest expected failure rate is less than 1% per year (not all IUDs meet this criterion)
4.2.8. Any other methods with published data showing that the highest expected failure rate for that method is less than 1% per year
4.2.9. Barrier method only if used in combination with one of the above methods
5. Weighs an estimated 120 kg or less
6. Informed consent: a signed and dated written informed consent or assent must be obtained from the subject or the subject's legally acceptable representative, respectively, prior to study participation
7. Language: fluent and literate in the language spoken by the investigator and staff

Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
152

Key exclusion criteria
A subject will not be eligible for inclusion in this study if any of the following criteria apply:
1. Concurrent medications:
1.1. Requires neuromuscular blocking agents to facilitate mechanical ventilation
1.2. Has or is likely to receive an epidural block during the maintenance phase
2. The use of remifentanil, fentanyl or propofol is contraindicated
3. Concurrent disease or disorder:
3.1. Has or is likely to require a tracheostomy within 96 hours after admission to the ICU
3.2. Has a neurological disease or other medical condition that may affect the ability to assess the SAS score and PI (e.g. stroke, stupor or coma, dementia)
3.3. Predicted creatinine clearance of <50 mL/min indicating moderate or severe renal impairment
3.4. Modified ICU admission simplified acute physiology score (SAPS) II score of greater than 43
4. Drug allergy: history of allergic hypersensitivity to fentanyl analogues, morphine, benzodiazepines or propofol
5. History of alcohol abuse
6. History of drug abuse: clinically significant abuse of opioid or sedative containing substances, defined as:
6.1. Patterns of substance intake consistent with disruption of normal function in society
6.2. Past or current impairment of organ function reasonably related to substance intake
7. Previous entry into this study or participation in any other investigational drug study within 30 days of randomisation
8. Concurrently participating in another clinical study in which the subject is or will be exposed to an investigational or a non-investigational drug or device
9. Protocol specified treatment regimens would be inappropriate for the management of the subject
10. The subject will have been in the ICU for longer than 24 hours at the time of starting the study drug infusion

Date of first enrolment
12/07/1999

Date of final enrolment
19/06/2000

Locations

Countries of recruitment
Belgium

England

Germany

Netherlands

Spain

United Kingdom

Study participating centre
GlaxoSmithKline
Middlesex
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Sponsor information

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Sponsor type
Industry

ROR
https://ror.org/01xsqw823

Funder(s)

Funder type
Industry

Funder Name
GlaxoSmithKline (UK)

Alternative Name(s)
GlaxoSmithKline plc., GSK plc., GlaxoSmithKline plc, GSK

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Results	01/02/2004		Yes	No