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Dose assessment of melatonin in sepsis trial

Submission date
01/07/2014

Recruitment status
No longer recruiting

Registration date
29/08/2014

Overall study status
Completed

Last Edited
26/09/2022

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Sepsis is a common condition caused by an infection, whereby the bodys immune system goes into overdrive. It can lead to, among other things, widespread inflammation, body swelling and a drop in blood pressure. Low blood pressure can then result in a reduced blood supply to vital organs, such as the brain and the heart. If not treated quickly, sepsis can cause multiple organ failure and death. Sepsis is a major cause of death for patients in intensive care units (ICU). Some 30% of patients currently die from the condition. Melatonin is a hormone naturally produced in the body. It is often referred to as the sleep hormone as it is given as a medicine to help people with insomnia (difficulty sleeping). However, it has proved to be a very versatile molecule; scientists has shown that it may have many health benefits. One of these is its antioxidant effects, mopping up the otherwise cell-damaging free radicals in our bodies. Research has also found that it reduces the inflammatory response to infection. We have recently undertaken a study that showed that, in healthy people, doses of oral melatonin are well tolerated and have no side effects. In this study, we want to find out two things. The first is whether or not oral melatonin is well tolerated in patients with sepsis as well as in healthy people. The second is whether the hormone is safe and how well it treats sepsis in patients compared to a placebo, or dummy, pill. The ultimate aim is to reduce the number of patients that die from sepsis, but for this early study, we hope to be able to identify a substance we can measure in blood which reflects the beneficial effect of melatonin.

Who can participate?
Patients over 16 years of age that have, or are suspected of having, sepsis and showing signs of pneumonia.

What does the study involve?
The study has two stages. In stage 1, two small groups of patients are given one dose of either 50 mg or 100 mg of melatonin. This is done to see whether the doses are well tolerated in sepsis patients. In stage 2, patients are randomly allocated into one of two groups. Patients in group 1 are given melatonin for 72 hours. Patients in group 2 are given a placebo. The effects of the hormone compared to the placebo are then analysed, using a number of measures.

What are the possible benefits and risks of participating?
For those patients given melatonin there is possibility of benefit by reduction of inflammation.

Where is the study run from?
The University of Aberdeen (UK)

When is the study starting and how long is it expected to run for?
October 2014 to June 2017

Who is funding the study?
Chief Scientist Office for Scotland (UK)

Who is the main contact?
Prof. Helen Galley

Contact information

Type(s)
Public

Contact name
Prof Helen Galley

Contact details
Institute of Medical Sciences
School of Medicine, Medical Sciences and Nutrition
University of Aberdeen
Aberdeen
United Kingdom
AB25 2ZD
-
h.f.galley@abdn.ac.uk

Additional identifiers

ClinicalTrials.gov (NCT)
NCT02319265

Clinical Trials Information System (CTIS)
2014-002840-42

Protocol serial number
3/035/14

Study information

Scientific Title
Dose Assessment of Melatonin in SEpsis triaL: a pilot phase I/II study

Acronym
DAMSEL 2

Study objectives

DAMSEL 2 is a pilot Phase I/II study in patients with sepsis. Stage 1 will assess the pharmacokinetics of melatonin and its major metabolite after 2 doses of exogenous melatonin in order to make dosing and dosing interval decisions for Stage 2. Stage 2 is a double blind randomised controlled trial of melatonin in patients with sepsis at the dose and dosing interval decided after Stage 1. Measurements of melatonin and its major metabolite, and an array of biomarkers of inflammation and oxidative stress will be made.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland A REC, 16/12/2014, ref: 14/SS/1078

Primary study design
Interventional

Study design
Stage 1: Phase I open-label two-dose cohort study
Stage 2: Phase II pilot double blinded randomised controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Sepsis due to community acquired pneumonia

Interventions
Stage 1: Two small groups of patients will receive a single dose of either 50 mg or 100 mg of melatonin.
Stage 2: Patients will be randomly allocated into either:
Group 1 - these patients will receive melatonin for 72 hours
Group 2 - these patients will receive a placebo for 72 hours

Intervention Type
Other

Phase
Phase I

Primary outcome(s)
Stage 1: Adminstration of 2 oral melatonin doses with no SUSARs
Stage 2: Approval by the DMC of dose and dosing interval decisions
The ultimate goal of experimental therapies in sepsis is reduced mortality. However, using mortality as an endpoint in a pilot study such as this is clearly not feasible. A panel of biomarkers will be used which are surrogates of outcome from sepsis.

All outcomes other than final outcome will be measured daily during the ICU stay. Final outcome is mortality at 28d.

Key secondary outcome(s)

1. Tissue specific injury markers, cytokines, adhesion molecules and chemokines: IL-1 beta, IL-2, IL-4, IL-6, IL-8, IL-10, IL-18, pentraxin-3, RANTES, MCP-1, MIP1alpha NGAL, SP-D, MMP-9, VCAM-1, P-selectin and TIMP-1.
2. Key clinical parameters including: heart rate, mean arterial pressure, temperature, acute physiologial and chronic health evaluation (APACHE) II score, length of ICU stay, ICU- and 28 day-all cause mortality, daily sequential organ failure score, time on vasopressor support
3. Time on the ventilator and ventilator settings such as positive end expiratory pressure, peak inspiratory pressure and minute volume
4. Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FIO2 ratio)

All outcomes other than final outcome will be measured daily during the ICU stay. Final outcome is mortality at 28d.

Completion date
28/02/2022

Eligibility

Key inclusion criteria
Patients who are within 24h of fulfilling the criteria for sepsis with clinical suspicion of community acquired pneumonia and the presence of chest X-ray changes consistent with pneumonia will be recruited. The criteria for sepsis are clinical suspicion or evidence of acute infection plus systemic inflammatory response syndrome, defined by two or more of the following:
1. Core temperature <36 or >38°C
2. Tachycardia: heart rate > 90 beats/min
3. Tachypnoea: respiratory rate > 20 breaths/min or ventilated
4. Leucocyte count >12 x 10^9/L or <4 x 10^9/L

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
10

Key exclusion criteria
1. Anyone <16 years old
2. Life expectancy <24h
3. Metastatic cancer or immunosuppression
4. Taking steroids (>20mg/d prednisolone or equivalent, used regularly for >2 weeks prior to ICU admission)

5. Premenopausal females without a negative pregnancy test or a history of surgical sterilization.
6. Patients receiving fluvoxamine or nifedipine
7. Consent refusal

Date of first enrolment
08/01/2018

Date of final enrolment
30/04/2021

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Aberdeen Royal Infirmary
Intensive Care Unit
Aberdeen
United Kingdom
AB25 2ZN

Sponsor information

Organisation
University of Aberdeen/NHS Grampian (UK)

ROR
https://ror.org/016476m91

Funder(s)

Funder type
Government

Funder Name
Chief Scientist Office. ETM/358 (UK)

Alternative Name(s)
CSO

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Helen Galley. Type of data: pharmacokinetic data (biochemical analysis of melatonin and major metabolite in serum). When the data will become available: after publication. For how long: no restriction. By what access criteria data will be shared including with whom: bona fide researchers in the field of melatonin. For what types of analyses: to support other trials of melatonin. By what mechanism: email request with detailed description of reason/purpose. Whether consent from participants was obtained: yes. Comments on data anonymisation: all data completely anonymous. Any ethical or legal restrictions, any other comments: acknowledgement/citation of source of data.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		31/08/2022	20/09/2022	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 6.0	28/01/2020	20/09/2022	No	No