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Melatonin associated to acid inhibition for chemoprevention in Barret esophagus (Melatonina asociada a inhibición ácida como estrategia de quimiprevención en esófago de Barrett)

Submission date
20/03/2012

Recruitment status
No longer recruiting

Registration date
18/04/2012

Overall study status
Completed

Last Edited
01/12/2015

Condition category
Digestive System

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

Plain English summary of protocol

Background and study aims
Barrett's oesophagus is a disease where the cells lining the lower part of the oesophagus (food pipe) are damaged by acid and bile travelling upwards from the stomach (reflux). It can progress to oesophageal cancer. At present, treatment of Barrett's esophagus is based on reducing acid reflux with drugs such as omeprazole. However, this treatment does not completely eliminate the risk of cancer. Therefore, it is necessary to find new drugs that prevent progression of the disease. New research suggests that antioxidants could be used, such as melatonin. This study will determine the effectiveness of melatonin in the prevention of oesophageal cancer.

Who can participate?
Patients aged 18 to 80 with Barrett's esophagus.

What does the study involve?
Participants are randomly allocated to receive one of the following two treatments: omeprazole alone, or omeprazole with melatonin.

What are the possible benefits and risks of participating?
This treatment produces hardly any adverse effects - the most frequent adverse effects of omeprazole are headache and stomach ache. For melatonin no adverse effects have been reported.

Where is the study run from?
Hospital Clinico Lozano Blesa (Spain)

When is the study starting and how long is it expected to run for?
March 2012 to March 2013

Who is funding the study?
Aragon Institute of Health Sciences (Spain)

Who is the main contact?
Dr Angel Lanas Arbeloa

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
ICS10/0273

Study information

Scientific Title
Melatonin associated to acid inhibition for chemoprevention in Barret esophagus: a pilot study

Study objectives
Gastroesophageal reflux disease (GERD) is one of the most prevalent pathologies in the digestive tract. Barrett's esophagus, a complication of chronic GERD, has attracted the attention of researchers due to its condition of pre-neoplastic lesion. At present, treatment of Barrett's patients is limited to acid inhibition with proton pump inhibitors (PPIs). Although there are several studies which indicate that treatment with PPIs could decrease the incidence of high grade dysplasia and esophageal adenocarcinoma (EAC), treatment with PPIs does not eliminate the risk of EAC in these patients. Therefore, it is necessary to find chemo-preventive agents that stop neoplastic progression of Barrett's esophagus. Among them, antioxidants have become the most promising agent. This pilot study will determine the efficacy of melatonin in the chemoprevention of EAC.

The main objective of this study is to determine whether melatonin decreases oxidative stress in Barretts esophageal mucosa after 6 months of treatment.

To evaluate whether melatonin modifies other mechanisms associated to neoplastic progression in BE patients: proliferation and apoptotic index, molecular markers of progression: 17pLOH, 9pLOH, p16 methylation and DNA ploidy (tetraploidy and/or aneuploidy).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Clinical Research Ethics Committee of Aragon (Comité Ético de Investigación Clínica de Aragón) (CEICA), 27/07/2011

Study design
Open randomized pilot clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Barretts esophagus

Interventions
Patients who agree to participate in the study will be randomized to one of the two following therapies:

Group 1: Omeprazole 40 mg/day. Patients will take the capsule once in the morning before breakfast. This is the standard therapy for patients suffering from Barretts esophagus.

Group 2: Omeprazole 40 mg/day + Circadin® 6 mg/12 hours. Patients will take the omeprazole capsule once in the morning before breakfast together with 3 tables of 2 mgs of Circadin® (melatonin). In the evening, before dinner, patients will take 3 tablets of 2 mg of Circadin®.

These medications will be delivered to the hospital pharmacy at each clinical visit, till the end of the study or until the patient leaves the study.

Four visits per patient providing the following procedures at each one:
1. Baseline assessment: Basal endoscopy and biopsies, revision of entry and exclusion criteria and signed informed consent.
2. Visit 1 (Day 0): Review of clinical history, hemogram and biochemical analysis, randomization based on a previously computer assigned allocation of treatment, and prescription of treatment omeprazole 40 mg once daily plus melatonin 3 mg/12 h vs. omeprazole 40 mg alone.
3. Visit 2 (Day 30±5) and Visit 3 (Day 90 ±7): Clinical visit to assess symptoms, pill count and new prescriptions.
4. Visit 4 (Day 180±14): Clinical visit to assess symptoms, pill count and new prescriptions and endoscopy plus biopsies.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Circadin® (melatonin), omeprazole

Primary outcome measure
1. Oxidative stress
1.1. Peroxynitrite production. This variable will be measured by immunohistochemistry (IHQ) with a monoclonal Ab against nitrotyrosine residues in biopsy specimens taken from the metaplastic mucosa of patients with Barretts esophagus (four samples every 2 cm) (Chemicon, Temecula, CA, USA).
1.2. DNA oxidative damage: We will determine levels of 8-hydroxy-2-deoxyguanosine in biopsy specimens form patients with Barretts esophagus, as described above. DNA will be extracted with a commercial kit from Qiagen (QIAamp DNA Mini Kit). 8-hydroxy-2-deoxyguanosina quantification will be carried out by enzyme immunoassay (EIA) (Bioxytech 8-OHdG-EIA kit, OXIS Health Products).

Measured at day 0 and final measurement 180 days since the beginning inclusion of patient.

Secondary outcome measures
1. Biological markers of diseases progression
1.1. Cell proliferation (Ag ki67-mib1) measured by automatic morphometry NIH-Image 6.1
1.2. Apoptosis: measured by IHQ with cysteine-dependent aspartate-directed proteases (caspase)
1.3. Molecular markers of neoplastic progression
2. The presence of DNA anomalies (tetraploidy and aneuploidy) will be determined by static cytometry

Measured at day 0 and final measurement 180 days since the beginning inclusion of patient.

Overall study start date
01/04/2012

Completion date
01/04/2013

Eligibility

Key inclusion criteria
1. Patients (males and females) with Barretts esophagus (>18 years and <80) without macroscopic esophagitis at endoscopy
2. A length of the metaplasic mucosa of 2 cm or longer
3. Who agree to participate in the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
80

Key exclusion criteria
1. Presence of carcinoma or high grade dysplasia at basal endoscopy
2. Oprevious gastric or esophageal surgery
3. Patients on nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin treatment (a maximum of 5 days per month is allowed. Paracetamol will be used as the standard analgesic treatment)
4. Neoplastic malignancies
5. Hematological serious diseases (coagulation disorders and anemia with Hb < 9.5 gr/dL)
6. Serious/moderate cardiac, liver or renal diseases
7. Need of corticosteroid therapy (a minimum of 5 days per month is allowed, as well as topical or inhaled treatment)
8. Patients on misoprostol or anticoagulants
9. Patients with inflammatory bowel disease and allergy to investigational drugs

Date of first enrolment
01/04/2012

Date of final enrolment
01/04/2013

Locations

Countries of recruitment
Spain

Study participating centre

Hospital Clínico Universitario Lozano Blesa
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Sponsor information

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Aragon Institute of Health Sciences (Instituto Aragonés de Ciencias de la Salud) (Spain)

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Sponsor type
University/education

ROR
https://ror.org/05p0enq35

Funder(s)

Funder type
University/education

Funder Name
Aragon Institute of Health Sciences (Instituto Aragonés de Ciencias de la Salud) (Spain)

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

Not provided at time of registration