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Nitrates and Bone Turnover: Trial to select the best nitrate preparation

Submission date
17/06/2011

Recruitment status
No longer recruiting

Registration date
27/07/2011

Overall study status
Completed

Last Edited
15/04/2019

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Thinning of the bones (osteoporosis) affects 1 in 4 Canadian women. While the rates of osteoporosis among Canadians are stabilizing, worldwide the number of people with osteoporosis continues to rise.
The most serious complication of osteoporosis is a broken bone or fracture. Fractures due to osteoporosis can result in long hospital stays, dependence on others, and premature death. While there are several medications that prevent osteoporosis they all have side effects and most cannot rebuild bone. In addition, drugs to prevent osteoporosis are expensive and not available worldwide. It is therefore essential that researchers continue to identify and test new medications for the prevention of osteoporosis. A previous study by our research group determined that nitrates, common and inexpensive agents used to treat chest pain or angina can increase bone strength by forming new bone. Nitrates are extremely safe medications and the only side effect, while common (20% of patients), is the development of headaches. It is not known whether nitrates can improve formation in women who have recently stopped treatment with drugs called antiresorptives. This is an important subgroup, as these women represent a large number of women at risk for osteoporosis and fracture. The purpose of our study is to identify the ideal dose and formulation of nitrate by comparing the effects of five different formulations of nitrates on headaches and markers of bone formation and resorption (NABT). We will also determine if nitrates affect these markers in women who have recently stopped treatment with alendronate, risedronate or zoledronate (NABT-B).

Who can participate?
We are looking for postmenopausal women 50 years of age or older, not currently taking estrogen or other prescription medications for osteoporosis, to participate in the NABT study. For the NABT-B study, we are looking for postmenopausal women 50 years or older who were previously treated with alendronate but stopped within 2 years of study commencement, risedronate but stopped within 1 year of study commencement, or zoledronate.

What does the study involve?
The NABT study has 2 treatment periods: an initial phase lasting 18 days and the main treatment phase lasting 3 months. The study involves a total 4.5 months and 3 study visits to hospital. At your first study visit, you will receive 5 different formulations of nitrates; 3 of these are tablets,

one is a patch and one is an ointment. You will be asked to take each of these 5 formulations in a certain order for 2 days, with a 2-day break in between treatments. You will be given a Visual Analogue Scale which you will use at home to evaluate the frequency and severity of headaches if they occur, and a Ranking Form to indicate preferences for the formulations. You will also be asked to provide a blood and urine sample for the measurement of bone turnover markers. At the end of 18 days you will come back for your second visit. If you had intolerable headaches while taking the nitrates, you will be withdrawn from the study. If you did not have headaches or had mild headaches that were tolerable, we will enter you into the main treatment phase of the study. If you are continuing, you will take a brief Food Frequency Questionnaire in order to determine how much calcium and vitamin D you need. If you require supplements, a 3 month supply of calcium and vitamin D will be provided. You will be randomly allocated by a computer program to receive one of 6 different treatments (one of the 5 formulations previously tried in the initial phase or a dummy ointment). You will have an equal chance of being assigned to any of the 6 treatments. The dummy ointment is an inactive ointment that will look and smell exactly like the nitroglycerin ointment. You will be asked to take your assigned medication once daily for 3 months. After 3 months, we will ask you to come back for your final study visit. You will be asked to provide a blood and urine sample for the measurement of bone turnover markers.
The NABT-B study involves a 3 month treatment phase. It involves 2 visits to hospital. At the first visit, you will receive a 3 month supply of nitroglycerin ointment. You will be asked to take this medication once daily for 3 months. You will take a brief Food Frequency Questionnaire in order to determine how much calcium and vitamin D you need. If you require supplements, a 3 month supply will be provided. You will also be asked to provide a blood sample and urine sample for the measurement of bone turnover markers. After 3 months we will ask you to come back to Womens College Hospital for your final study visit. You will be asked to provide a blood sample and urine sample for the measurement of bone turnover markers. You will also be asked to return any unused calcium and vitamin D or study medication.

What are the possible benefits and risks of participating?
You may not benefit directly from participation in this study. However, you will obtain health information on the use of calcium and vitamin D for the prevention of osteoporosis. Possible risks of participating are headaches (often described as a pressure sensation, worst on the first day and gets better daily, gone after 3 to 4 days, with no lasting effects), and other side effects of the nitrates that occur less frequently and include: lightheadedness going from lying/sitting to standing (postural hypotension), increased heart rate, faintness, flushing, dizziness, nausea, vomiting and skin redness or irritation (dermatitis). When the blood is taken at Visits 1 and 3 there may be a small amount of bleeding when blood is taken from a vein and there may be slight discomfort, bruising or redness that will usually disappear in a few days.

Where is the study run from?
Womens College Hospital, Toronto, Canada

When is the study starting and how long is it expected to run for?
December 2011 to April 2014

Who is funding the study?
The Canadian Institutes of Health Research, the Physicians Services Incorporated Foundation, the Ontario Academic Health Science Centres Alternate Funding Plan Innovation Fund and California Pacific Medical Center Research Institute.

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT01387672

Protocol serial number
062011

Study information

Scientific Title
Nitrates and Bone Turnover: A randomised controlled trial to select the best nitrate preparation

Acronym
NABT

Study objectives
Current study hypothesis as of 10/01/2013:
NABT: To compare the effects of five formulations and doses of nitroglycerin on two markers of bone formation (serum Bone-specific alkaline phosphatase [BALP] and procollagen type 1 amino-terminal propeptide [P1NP]) and two markers of bone resorption (serum C-terminal telopeptide [CTX] and urine collagen-type I N- telopeptide [NTX]) and on the frequency and severity of headaches they cause.
Nitrates and Bone Turnover Bisphosphonate Sub-Study (NABT-B): To determine if nitrates (15 mg of nitroglycerin [NTG] ointment) affect markers of bone formation (serum Bone-specific alkaline phosphatase [BALP] and procollagen type 1 amino-terminal propeptide [P1NP]) and resorption (serum C-terminal telopeptide [CTX] and urine collagen-type I N- telopeptide [NTX]) in women who have recently discontinued treatment with alendronate, risedronate or zoledronate.

Previous study hypothesis until 10/01/2013:
To compare the effects of five formulations and doses of nitroglycerin on two markers of bone formation (serum Bone-specific alkaline phosphatase [BALP] and procollagen type 1 amino-terminal propeptide [P1NP]) and two markers of bone resorption (serum C-terminal telopeptide [CTX] and urine collagen-type I N- telopeptide [NTX]) and on the frequency and severity of headaches they cause.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Women's College Hospital Ethics Board, 27/07/2011, ref: 2011-0028-B, amendment approved on 16/11/2012, ref: 2011-0028-B

Study design
NABT: Randomized controlled trial with an 18 day run-in phase and a 90 days treatment phase
NABT-B: Controlled trial with a 90 days treatment phase

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Osteoporosis

Interventions
Current interventions as of 10/01/2013:
NABT: 1. Nitrol® (Nitroglycerin Ointment 2% USP)
2. Nitro-Dur® (Nitroglycerin Extended Release Patch 160mg)
3. Nitrostat® (Nitroglycerin 0.3mg Sublingual tablet)
4. Nitrostat® (Nitroglycerin 0.6mg Sublingual Tablet)
5. Ismo® (Isosorbide Mononitrate 20mg Oral Tablet)
6. Placebo ointment
Each drug/placebo is to be taken once daily for a 12 week intervention period
NABT-B: Nitrol® (Nitroglycerin Ointment 2% USP)
The drug is to be taken once daily for a 12 week intervention period

Previous interventions until 10/01/2013:
1. Nitrol® (Nitroglycerin Ointment 2% USP)
2. Nitro-Dur® (Nitroglycerin Extended Release Patch 160mg)
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6. Placebo ointment
Each drug/placebo is to be taken once daily for a 12 week intervention period

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Nitroglycerin, isosorbide mononitrate

Primary outcome(s)
Current primary outcome measures as of 10/01/2013:
Mean percent change, from baseline, in two markers of bone resorption (CTX and NTX) and two markers of bone formation (BALP and PINP) within each treatment arm, measured at baseline and at the end of the 12 week intervention.

Previous primary outcome measures until 10/01/2013:
Mean percent change, from baseline, in two markers of bone resorption (CTX and NTX) and two markers of bone formation (BALP and PINP) among each of the five treatment arms and the placebo arm. Measured at baseline and at the end of the 12 week intervention.

Key secondary outcome(s))
Headache frequency and severity assessed by Visual Analogue Scale

Completion date
31/12/2013

Eligibility

Key inclusion criteria
Current inclusion criteria as of 10/01/2013:
1. Women aged 50 years and older whose last menstrual period occurred at least 3 years ago
2. Women without a uterus will be eligible after age 55
3. Women previously treated with alendronate but stopped within 2 years of study commencement; or previously treated with risedronate but stopped within 1 year of study commencement; or previously treated with zoledronate (NABT-B only)

Previous inclusion criteria until 10/01/2013:
1. Women aged 50 years and older whose last menstrual period occurred at least 3 years ago
2. Women without a uterus will be eligible after age 55

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Key exclusion criteria

Current exclusion criteria as of 10/01/2013:
1. Previous fracture of the hip, wrist, spine or ankle
2. Diagnosis of Osteoporosis (NABT main study only)
3. History of bone disorders such as hyperparathyroidism or Pagets disease
4. Treatment within 12 months of study entry with any agent that may influence bone metabolism including any hormone, anti-estrogen or raloxifene and prednisone (equivalent to 5 mg/d for 12 months or greater)
5. Treatment with any antiresorptive agent, including alendronate, risedronate, use for at least four weeks, within the last three years and any previous treatment with intravenous zoledronate (NABT only)
6. Treatment with etidronate or denosumab use for at least four weeks, within the last three years and any previous treatment with parathyroid hormone
7. Current treatment with nitrates
8. Any history of migraine headaches (nitrates can exacerbate migraines)
9. History of angina or cardiovascular disease
10. Inability to give informed consent
11. Hypersensitivity to nitroglycerin
12. Allergies to the adhesive used in nitroglycerin patches
13. Acute circulatory failure associated with marked hypotension (shock and states of collapse)
14. Postural hypotension
15. Increased intracranial pressure
16. Increased intraocular pressure
17. Severe anemia.

Previous exclusion criteria until 10/01/2013:
1. Previous fracture of the hip, wrist, spine or ankle, or those who report a diagnosis of osteoporosis, (osteopenia will not be excluded)
2. History of bone disorders such as hyperparathyroidism or Pagets disease
3. Treatment within 12 months of study entry with any agent that may influence bone metabolism including any hormone, anti-estrogen or raloxifene and prednisone (equivalent to 5 mg/d for 12 months or greater)
4. Treatment with an antiresorptive agent, including alendronate, risedronate, etidronate or denosumab use for at least four weeks, within the last three years
5. Any previous treatment with intravenous zoledronate or parathyroid hormone
6. Current treatment with nitrates
7. Any history of migraine headaches (nitrates can exacerbate migraines)
8. History of angina or cardiovascular disease
9. Inability to give informed consent
10. Hypersensitivity to nitroglycerin

Date of first enrolment
01/09/2011

Date of final enrolment
31/12/2013

Locations

Countries of recruitment
Canada

Study participating centre
Women's College Hospital
Toronto
Canada
M5G 1N8

Sponsor information

Organisation
Women's College Research Institute (Canada)

ROR
https://ror.org/03cw63y62

Funder(s)

Funder type
Research organisation

Funder Name
Physicians Services Incorporated Foundation (Canada)

Alternative Name(s)
PSI Foundation, PSI

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Canada

Funder Name
Ontario Academic Health Science Centres Alternate Funding Plan Innovation Fund (Canada)

Funder Name

Canadian Institutes of Health Research (Canada)

Alternative Name(s)
Instituts de Recherche en Santé du Canada, The Canadian Institutes of Health Research (CIHR), Canadian Institutes of Health Research (CIHR), Canadian Institutes of Health Research | Ottawa ON, CIHR - Welcome to the Canadian Institutes of Health Research, CIHR, IRSC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Canada

Funder Name
California Pacific Medical Center Research Institute (USA)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	08/09/2013		Yes	No
Basic results				No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes