Do cardio selective β-Blockers Affect the Use of β-Agonist Inhalers in response to bronchoconstriction challenge in Asthma?

Study Protocol

AIMS

1. To describe the bronchodilator response to β-agonists following bronchoconstriction challenge in asthma patients receiving cardio selective β-blockers.

INCLUSION CRITERIA

- Physician diagnosis of asthma
- Airway hyper responsiveness. Demonstrated with post mannitol (a 15% decrease in FEV1 at a mannitol provocation dose of <635mg, PD15 <635mg or a 10% decrease in FEV1 at a mannitol provocation dose of <635mg if taking regular inhaled corticosteroid therapy)~~)~~
- Over 18 years of age

EXCLUSION CRITERIA

- Pre spirometry FEV1 < 60% predicted or < 1.5L
- Dyspnoea at rest
- Past history of hypotension (baseline BP <100/60)
- ECG abnormalities that could interfere with the interpretation of the study
- HR<60/min
- Symptomatic hypotension
- ECG findings of severe 1st degree, or 2nd & 3rd degree heart block (defined as PR interval > 0.28s)
- LBBB & RBBB are NOT excluded.
- Known adverse reaction to beta blockers or mannitol
- On other drugs that commonly interacts with β-blockers (amiodarone, verapramil, diltizem, disopyramide, cimetidine, digoxin, phenytoin, clonidine)
- Already taking β-blockers – including eye-drops.
- Smoking history of >10 pack years
- Recent exacerbation as defined by oral corticosteroid use/hospitalisation within 6 weeks of recruitment
- Pregnant (negative pregnancy test required) or breast feeding.
- Under 18 year of age
- Unsuitability as defined by the study doctor

STUDY DESIGN

Two way randomised, placebo-controlled, double-blinded cross-over trial

Arm 1: placebo once daily
Arm 2: cardio-selective β-blocker once daily (Bisoprolol titrating up to achieve beta blockade through 1.25mg PO OD, 2.5mg PO OD, 5mg PO OD)
Arm 3: open label cardio-selective β-blocker once daily (Bisoprolol titrating up to achieve beta blockade through 2.5mg PO OD, 5mg PO OD, 7.5mg PO OD then 10mg PO OD)

RECRUITMENT

- From a database of asthmatics who are known to be interested in research held by the department.
- Through facebook advertisement and university advertisement
- Check inclusion/exclusion criteria

SCREENING

Bronchoprovocation Screening

- Methacholine screening to be done on a separate day to initial pre-post spirometry.
- Prior to the challenge to abstain from:
    - SABA (salbutamol, terbutaline) for at least 8 hours
    - SAMA (ipratropium) Ipratropium bromide (atrovent, combivent), inhaled corticosteroids for at least 12 hours
    -
    - LABA (formoterol and any combination of)24 hours prior to challenge.
    - Please avoid caffeine, vigorous exercise or smoking for 6 hours.
- Include patient in trial if reaches 15% drop in FEV1 at <635mg mannitol (PD15 <635 or a 10% decrease in FEV1 at a mannitol provocation dose of <635mg if taking regular inhaled corticosteroid therapy)~~)~~
    - Protocol for recovery beta agonist to be followed to determine AUC:Immediatedly after last FEV1 to have Salbutamol 100mcg via MDI and spacer immediately after final FEV1 determined.
    - Repeat FEV1 after 5 minutes post dose, then salbutamol 100mcg via MDI and spacer immediately after FEV1.
    - Repeat FEV1 after 5 minutes post dose, ~~.~~ then salbutamol 200mcg via MDI and spacer immediately after FEV1.
    - STOP at this point if FEV1 >= baseline.
    - Continue with 200mcg via MDI and spacer at 5 minute intervals with FEV1 measure immediately before each dose until baseline achieved.
    - Can additionally use ipratropium 40mcg via MDI if required at clinician's discretion

We need the patients to be sensitive to mannitol so we can measure their bronchodilator response to β-agonists.

β-Blocker Screening

The main adverse events we are looking for are:

- Acute bronchospasm
- Symptomatic intolerance to the bradycardic and hypotensive effects of β-blockers
- Arrhythmias
- Acute allergic reactions (rare)

1 dose of short-acting IV metoprolol 5mg over 5 minutes followed by 20 minutes observation
Spirometry to be repeated after the period of observation and if FEV1 dropped by 20% from baseline patient to be excluded.

STUDY VISITS

Visit 1 – day 0

- Consent
- Check inclusion/exclusion criteria - if fits inclusion criteria, take baseline ECG, blood pressure & heart rate.
- Baseline Fractional exhaled nitric oxide (FeNO)
- Baseline spirometry
- **mannitol screening** (see above) to be recorded as baseline response.

- ACQ5 Asthma questionnaire

Visit 2 – day 1

- Short acting β-blocker screening (see above)
- Monitor for 20 minutes – measure blood pressure & heart rate if symptomatic only
- Post single dose β-blocker spirometry at 20 minutes
- Randomised to receive 32 unmarked capsules of either placebo or bisoprolol 1.25mg. Instructions to take one capsule OD until arranged phone call in 2-5 days
- Issue symptoms diary.

Call 1 – day 4+/-2 (minimum 48 hours from visit 2)

- First up titratation. Phone call by unblinded investigator to ask if any adverse effects (dizziness, loss of consciousness, palpitations)
- Either stop, continue on one capsule or increase to two capsules each morning until next visit in 3-5 days

Visit 3 – day 7+/-3

- Unblinded investigator to measure blood pressure, pulse & check symptoms diary
- If heart rate dropped by 10 beats per minute and or systolic blood pressure dropped by 10mmHg continue on two capsules each morning until next visit.
  If not satisfying above criteria and no adverse effects as mentioned before then double dose to either **two** or **four** capsules PO OD until next visit.

Visit 4 – day 10+/-3

- Monitor heart rate, blood pressure.
- ACQ questionnaire.
- Measure Fractional exhaled Nitric Oxide (FeNO)
- Mannitol challenge.
- Switch placebo/bisoprolol arm and provide 32 unmarked capsules.

Call 2 – day 13+/-3

- First up titratation. Phone call by unblinded investigator to ask if any adverse effects (dizziness, loss of consciousness, palpitations)
- Either stop, continue on one capsule or increase to two capsules each morning until next visit in 3-5 days

Visit 5 – day 16+/-3

- Unblinded investigator to measure blood pressure, pulse & check symptoms diary
- If heart rate dropped by 10 beats per minute and or systolic blood pressure dropped by 10mmHg, continue on two capsules each morning until next visit If not satisfying above criteria and no adverse effects as mentioned before then double dose to either **two** or **four** capsules PO OD until next visit.

Visit 6 – day 19+/-3

- Monitor heart rate and blood pressure.
- ACQ Questionnaire
- Measure Fractional exhaled Nitric Oxide (FeNO)
- Mannitol challenge.
- At this point either unblinded bisoprolol up titration begins OR if not tolerated at 5mg (four capsules) then the study will end here.
- 42 2.5mg bisoprolol tablets provided if continuing into last arm.

Call 3 – day 22+/-3

- First up titratation. Phone call by investigator to ask if any adverse effects (dizziness, loss of consciousness, palpitations)
- Either stop, continue on one or increase to **two** bisoprolol tablets PO OD, total 5mg, until next call in 3-5 days

Call 4 – day 25+/-3

- Second up titratation. Phone call by investigator to ask if any adverse effects (dizziness, loss of consciousness, palpitations)
- Either stop, continue on previous dose, or increase by one tablet from previous dose (max should be **three** bisoprolol tablets PO OD, total 7.5mg) until next visit in 3-5 days

Visit 7 – day 28+/-3

- Investigator to measure blood pressure, pulse & check symptoms diary
- Either stop, continue on current dose or increase by one tablet to a maximum of **four** tablets (10mg) PO OD until next visit in 3-5 days.

Visit 8 – day 31+/-3

- Monitor heart rate and blood pressure.
- ACQ Questionnaire
- Measure Fractional exhaled Nitric Oxide (FeNO)
- Mannitol challenge.
- Stop taking study drug – return all unused study drug

OUTCOME MEASURES

Main outcome measures

1. Area under curve for bronchodilator response post mannitol challenge – in Litres/%

Secondary outcome measures

1. PD15 mannitol – Provocation dose of mannitol required to cause 15% drop in FEV1 at baseline and then after study drug
2. Cardiovascular response – blood pressure and pulse
3. Dose of salbutamol required to reach 80% recovery of FEV1
4. Time to 80% recovery of FEV1
5. Symptoms & adverse events

BLINDING

This is a double-blind study. All medications (bisoprolol and placebo) will be blinded to the patient and lead investigator. The heart rate and blood pressure measurements during the study are to be taken by unblinded study nurse investigator and analysed by a separate respiratory clinician so as to maintain the blinding of the lead investigator.