Name of Sponsor/Company
University of Dundee / NHS Tayside

Title of Study
Evaluation of any steroid sparing effect of beta blocker therapy on airway hyper-responsiveness in stable, mild to moderate, asthmatics

Investigators
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Publication (reference)
ANDERSON WJ, SHORT PM, WILLIAMSON PA, MANOHARAN A, LIPWORTH BJ. The inverse agonist propranolol confers no corticosteroid sparing activity in mild to moderate persistent asthma. **Clin Sci** 2014;127:635-643

Date of first enrolment	**Phase of development**
04.04.2012 **Date of last completed** 25.05.2013	Phase II

Objectives
To evaluate any steroid-sparing effect of concomitant chronic dosing with beta blockers with low dose ICS on airway hyper-reactivity in stable mild to moderate asthmatics compared to high dose ICS alone.

Methodology
A randomised, double-blind, placebo-controlled, crossover trial in mild-moderate persistent asthmatics.

After a run-in (2weeks) on hydrofluoroalkanebeclometasone dipropionate (HFA-BDP) 100µg/day, patients received randomised treatments (4weeks) with propranolol 80mg/day plus HFA-BDP 100µg/day; versus placebo plus HFA-BDP 400µg/day. Propranolol was up-titrated to 80mg/day over initial 2weeks. Tiotropium was co-administered until 5 days before each histamine challenge (the primary outcome).

Number of patients planned
Approximately 24 enrolled to ensure 16 completed per protocol

Number of patients analysed
16

Diagnosis and main criteria for inclusion
Stable, histamine responsive (PC20<8mg/ml) persistent asthmatics receiving ≤1000µg/day of ICS (beclometasone dipropionate equivalent)

Test product dose
Arm A
Propanolol 10 mg bid + HFA-BDP 100mcg/day (1 week)
Propanolol 20 mg bid + HFA-BDP 100mcg/day (1 week)
Propanolol 80mg LA od or max tolerated dose + HFA-BDP 100mcg/day (2 weeks)

Arm B
Placebo Propanolol 1 tab bid + HFA-BDP 400mcg/day (1 week)
Placebo Propanolol 2 tabs bid + HFA-BDP 400mcg/day (1 week)
Placebo Propanolol 1 tab od + HFA-BDP 400mcg/day (2 weeks)

Duration of treatment
8 weeks (2 treatment periods of 4 weeks)

Reference therapy
Tiotropium 18 mcg od

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Criteria for evaluation

Primary Endpoint
Change in Histamine PC20.

Secondary Endpoints
IOS; FEV1; salbutamol recovery post histamine challenge; serum BDNF and ECP; Blood eosinophils; HR and Serum K+ pre and post histamine challenge; Blood pressure; FeNO; OUCC; Domiciliary FEV1, symptoms and reliever use; AQLQ; ACQ.

Statistical methods
All data assessed for normality of distribution.

Non-normally distributed variables were logarithmically transformed or analyzed non-parametrically.

Analysis was performed using repeated measures analysis of variance, factoring treatment and sequence effects, followed by Bonferroni correction for all pairwise comparisons ($P<0.05$, two-tailed).

All analyses were performed using IBM SPSS v20 (San Diego,CA, USA).

Summary Conclusions

Results
Histamine PC20 was unchanged by adding propranolol to HFA-BDP100 compared to baseline (HFA-BDP100): 0.17 doubling dilution (dd) difference (95%CI -0.58-0.92), but there was a significant improvement with HFA-BDP400 compared to both baseline 1.05dd (95%CI 0.43-1.66), P=0.02; and propranolol + HFA-BDP100:0.88dd (95%CI 0.45- 1.30), P=0.006.

Significant improvements were also observed with HFA-BDP400 for exhaled nitric oxide, blood eosinophils, serum eosinophilic cationic protein and asthma quality of life questionnaire symptoms, compared to propranolol + HFABDP100.

Salbutamol recovery post-challenge was partially blunted by propranolol (median prolongation 5min, P=0.002).

Domiciliary evening FEV1 also fell with propranolol +HFA-BDP100: mean reduction from baseline 0.22L [95%CI 0.10-0.34L], P=0.012, while Asthma Control Questionnaire remained unchanged.

Conclusion
In summary the inverse agonist propranolol produced no improvements when given with low dose ICS, while further significant improvements in airway hyper responsiveness and inflammation were demonstrated with higher dose ICS. Thus propranolol does not confer corticosteroid-sparing activity in persistent asthma.

Date of the report: 24/06/2015