Clinical Study Report Synopsis

Study Code	D4411M00007
Edition Number	1
Date	2 February 2010

Pharmacological intervention in insulin resistance targeting autonomic nerve activity - a concept study in man

Study dates: First subject enrolled: 2 May 2007
Last subject last visit: 24 November 2008

Phase of development: Exploratory study

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This was a single centre study performed at Sahlgrenska University Hospital, Lundberg Laboratory, Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
The primary objective of this study is to study the effect of anticholinergic drug on insulin sensitivity by assessment of glucose infusion rate during hyperinsulinemic euglycemic clamp.	M-value, i.e. glucose infusion rate divided by lean body mass (estimated with bioimpedance) during steady state (60-120 min)
Secondary	**Secondary**
To study the effect of cholinergic stimulation on insulin sensitivity by assessment of glucose infusion rate during hyperinsulinemic euglycemic clamp.	M-value, i.e. glucose infusion rate divided by lean body mass (estimated with bioimpedance) during steady state (60-120 min)
To study the possible difference in effect of cholinergic (physostigmine) and anticholinergic (atropine) drugs on insulin sensitivity in a lean and abdominal obese subgroup of subjects.	M-value, i.e. glucose infusion rate divided by lean body mass (estimated with bioimpedance) during steady state (60-120 min)

Study design

This was an explorative, single-blinded, placebo-controlled, randomized cross-over study including 6 (abdominally obese) subjects with insulin resistance and 6 age- and gender matched lean controls with normal insulin sensitivity. Subjects received intravenous atropine, physostigmine and placebo as single infusions with 2-4 weeks wash-out in between.

Target subject population and sample size

Inclusion criteria:

- Signed written informed consent
- Male/female of Caucasian origin, 18-60 years
- BMI of lean (BMI < 25 kg/m^2) and abdominally obese subjects (BMI> 27 kg/m^2 and waist circumference >102 cm in men and >88 cm in women)
- Weight stable

Exclusion criteria:

- Ongoing clinically significant diseases
- History of repeated syncope
- Resting pulse <50 or systolic blood pressure <100

Sample size:

6 abdominally obese subjects and 6 age- and gender matched lean controls The aim of this hypothesis-generating study is to evaluate the effect of atropine and physostigmine on insulin sensitivity in obese and lean subjects.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Atropine® (Merck) and physostigmine (Dr F. Köhler Chemie, Germany) is used in the study as active drugs and saline as placebo

Table S2 Identity of investigational product

Investigational product	Content	Dosage form and strength	Manufacturer	Dosage
Atropine®	Atropine	Injection fluid 0,5 mg/ml	Merck	10 µg/kg bolus (however, maximally 1000 µg in total), 4 µg/kg/h infusion
Anticholium	Physostigmine	Injection 0.4 mg /ml	Dr F. Köhler Chemie, Germany	0.12 µg/kg/minute
Placebo	Saline NaCl			One single dose

Intravenous atropine® (15 µg/kg bolus, 4 µg/kg/h infusion), physostigmine (Anticholium; Dr F. Köhler Chemie, 0.4 mg/ml, 0.12 µg/kg/minute) and saline was given in random order on separate days and maintained for the duration of the clamp (totally 150 min). Infusion was started at 30 minutes before the start of the clamp procedure.

Duration of treatment

This cross-over study used 3 periods where subjects received intravenous atropine, physostigmine and placebo as single infusions with 2-4 weeks wash-out in between. The duration of each clamp procedure was 150 minutes and infusion was started at 30 minutes before the start of the clamp procedure.

Statistical methods

Insulin sensitivity was assessed as M-value (mg/kg lbm/min) (GIR), i.e. glucose infusion rate divided by lean body mass during steady state (60-120 min). Data were analyzed using analysis-of-variance (ANOVA).

Subject population

Table S3 Baseline characteristics of study participants (n=12)

	Lean subjects (n=6)	Obese subjects (n=6)
Age (years)	43.8±14.8	46.8±4.8
BMI (kg/m^2)	22.6±1.7	28.8±1.3

Data are mean ±SD

Summary of efficacy results

Primary objective:

Insulin sensitivity assessed as M-value (GIR) at steady-state (60-120 min) was higher during infusion with atropin than placebo; p=0.015.

Secondary objectives:

Physostigmine did not differ significantly from placebo in all subjects taken together.

M-values (GIR) were overall higher in lean vs obese subjects and higher during infusion with atropine than placebo in both subgroups. The incremental effect of atropine vs placebo did not differ consistently between subgroups.

Summary of safety results

One subject experienced an SAE during clamp procedure with physostigmine, reported by the investigator as vasovagal syncope. The clamp procedure was stopped and the subject was treated with atropine and saline. The subject recovered after about 2 hours. The event was considered by the investigator as probably precipitated by clamp procedure exaggerated by physostigmine. The subject had a history of syncope when participating in invasive research procedure.

There were no other significant safety findings in the study.