Randomized, double-blind, placebo-controlled trial on the effectiveness and safety of dapagliflozin for blood glucose control during glucocorticoid treatment for acute exacerbation COPD

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The purpose of this study is to investigate the effectiveness and safety of dapagliflozin for glucose control in patients with exacerbation COPD on high dose glucocorticoids.Effectiveness of glucose control in clinical practice is measured by the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON41812

Source
ToetsingOnline

Brief title
GluCon-COPD

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Glucocorticoid induced hyperglycemia, high blood glucose due to glucocorticoid therapy

Research involving
Human

Sponsors and support

Primary sponsor: Slotervaartziekenhuis
Source(s) of monetary or material Support: AstraZeneca,Stichting klinisch wetenschappelijk onderzoek Slotervaartziekenhuis

Intervention

Keyword: COPD, Glucocortcoid-induced hyperglycemia, Glucose

Outcome measures

Primary outcome

Effectiveness: The difference in mean percentage time spent within glucose target range on 2nd till 7th day of treatment, between the dapagliflozin group and the control group as measured by subcutaneous continuous glucose monitor. Target range is defined as random glucose 4-10 mmol/l according to ADA guidelines for non-critically ill inpatients (20).

Safety: Incidence rate of hypoglycaemic events per patient-day. A hypoglycaemic event is defined according to Whipple*s criteria (i.e. symptoms known or likely to be caused by hypoglycaemia, interstitial glucose <= 3.9 mmol/l continuing until the interstitial glucose is >3.9 mmol/l, relief of symptoms when glucose is raised to normal).

Secondary outcome

1. Patient satisfaction measured by Diabetes Treatment Satisfaction Questionnaire for inpatients (DTSP-IP) (21) specifically directed at glucose lowering treatment.

2. Clinical outcomes: duration of hospitalisation, need for intensification of treatment for AECOPD, change in body weight and blood pressure during investigational treatment.

3. Other parameters of glucose control:

- Glucose variability by mean amplitude of glycaemic excursion (MAGE)

- Total daily dose of insulin

- Mean daily glucose concentration

- Mean percentage time spent within glucose target range from start till end of

treatment

4. Safety: incidence rate of asymptomatic hypoglycaemia, incidence of genital

infections and urinary tract infections, incidence of other adverse events.

Study description

Background summary

Glucocorticoids are a causative factor for severe hyperglycaemia in patients treated for acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Hyperglycaemia during AECOPD is associated with increased risk for death or prolonged hospitalization, and this risk is independent of age, sex and disease stage. Also, GCIH may increase disease burden and costs in patients with COPD by the need for frequent monitoring of glucose levels, and the need for frequent contact with caregivers to adjust glucose lowering treatment. In preclinical studies, acute hyperglycaemia has been shown to cause immune dysfunction and a procoagulant state which might explain the association between hyperglycaemia and adverse outcomes in AECOPD.
The world-wide prevalence of chronic obstructive pulmonary disease (COPD) is 10% in adult patients. Patients with COPD frequently need high dose glucocorticoid agents to combat sudden worsening of COPD symptoms - AECOPD. In international guidelines, treatment with 30-40mg prednisone for 5-14 days is advised for such episodes.
Glucocorticoids are synthetic adrenal glucocorticoid hormones that inhibit pro-inflammatory gene expression. This inhibition of inflammation is beneficial for the outcome of AECOPD. A complication of short-term high dose glucocorticoids in AECOPD is acute hyperglycaemia. Glucocorticoids cause hyperglycaemia by inducing insulin resistance, diminishing beta cell function and increasing hepatic glucose production. These effects lead to a glucocorticoid-specific pattern of hyperglycaemia with pronounced postprandial hyperglycaemia and normal or near to normal fasting glucose. Forty percent of patients with AECOPD develops severe hyperglycaemia, and in patients with known

diabetes the incidence is even higher.
There is little evidence on how to treat GCIH. Sliding scale insulin regimens are most frequently used to treat GCIH (Gerards et al., manuscript in preparation), although guidelines recommend against it. In SSI therapy, subcutaneously short-acting insulin is prescribed in a variable dose based on the current grade of hyperglycaemia. A major limitation of SSI is the failure to prevent glucose excursions and thereby high glucose variability. The reactive approach of SSI is especially popular in residents with low level of clinical experience. Barriers for proactive treatment of inpatient GCIH are absence of easily applicable treatment options, vigilance for hypoglycaemia and the difficulty that an inpatient therapy regimen needs to be combined with eventual pre-existing glucose lowering therapy.

SGLT-2 inhibitors lower blood glucose by blocking glucose reabsorption in the proximal tubule leading to urinary glucose excretion, and thereby to a reduction of blood glucose. There are 3 important reasons why SGLT-2 inhibitors are an interesting treatment option for acute GCIH. In contrast to other classes of glucose lowering agents the efficacy of SGLT2-inhibitors is insulin-independent, and therefore can have a complementary instead of a competing action to other glucose lowering agents. Secondly, SGLT-2 inhibitors have a rapid onset of action compared to other oral glucose lowering drugs. Thirdly, SGLT-2 inhibitors have a strong capacity to reduce postprandial glucose. Most importantly, SGLT-2 inhibitors carry a lower risk of hypoglycaemia in contrast to sulfonylurea derivatives and insulin. Altogether, this make SGLT-2 inhibitors an ideal agent for treatment of temporary high dose glucocorticoid induced hyperglycaemia that can be prescribed irrespective of eventual pre-existing insulin resistance or glucose lowering therapy.

Study objective

The purpose of this study is to investigate the effectiveness and safety of dapagliflozin for glucose control in patients with exacerbation COPD on high dose glucocorticoids.
Effectiveness of glucose control in clinical practice is measured by the time spent within target range between 2nd and 7th day of study, as measured by subcutaneous continuous glucose measurement (hypothesis that dapagliflozin treatment is superior to placebo).
Safety is measured by as incidence rate of hypoglycaemic events (hypothesis that dapagliflozin treatment is non-inferior to control treatment).

Study design

Multi-centre, double-blind placebo-controlled clinical trial with the objective to investigate the difference in control of high-dose GCIH between subjects treated with dapagliflozin 10mg or placebo

Intervention

Dapagliflozin 10mg or placebo

Study burden and risks

The burden of participation consists of the extra capillary glucose measurements that will be done 3-4 times daily and wearing a coin size glucose sensor. Furthermore, patients have to fill out a treatment satisfaction questionnaire. There will be no extra site visits for participants. Dapagliflozin (experimental group) carries a risk of hypoglycaemia, especially for patient who have concomitant therapy with insulin or sulfonylurea derivatives. Patients will be instructed to anticipate, and if required dosing of glucose lowering therapy will be adjusted. Furthermore, dapagliflozin carries an increased risk of urogenital infections, increased haematocrit and LDL cholesterol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age >= 18 years and <=100 years at baseline
- Informed consent
- Hospitalization due to AECOPD
- Treatment with >=30mg prednisone daily or equivalent dose of glucocorticoid for AECOPD
- An expected duration of glucocorticoid treatment of 3-14 days at study entry
- Known type 2 diabetes or glucose >= 10 mmol/l at admission

Exclusion criteria

- Glucocorticoid pulse therapy started >=7 days before study entry
- Need for ICU admission
- Chronic kidney disease stage G3 (glomerular filtration rate <60ml/minute)
- Recurrent genital or urinary tract infection
- Current use of any SGLT-2 inhibiting agent
- Suspected volume depletion
- Congestive heart failure functional classification NYHA class IV/IV or instable heart failure
- Acute stroke within 2 months before inclusion.
- Recent cardiovascular event: acute coronary syndrome, hospitalisation for unstable angina or coronary revascularisation within 2 months before inclusion
- Suspected liver disease, confirmed by AST/ALT > 3x ULN or bilirubin >2.0mg/dl (34.2 µmol/l) or serologically proven infection with hepatitis B or hepatitis C
- Pregnancy or breast feeding

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-02-2015
Enrollment:	46
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Forxiga
Generic name:	Dapagliflozin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-08-2014
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	12-01-2015
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	26-02-2015
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	14-08-2015
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	27-08-2015

Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	21-10-2015
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-002370-36-NL
CCMO	NL49690.048.14