Influence of Acetazolmide (Diamox) on breathing

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27371

Source
NTR

Brief title
Dia Study

Health condition

-High altitude disease
-COPD/OSAS
-Physiology: acid-base disturbances
-Control of breathing

Sponsors and support

Primary sponsor: Leiden University Medical Center
Source(s) of monetary or material Support: Leiden University Medical Center

Intervention

Outcome measures

Primary outcome

Comparisons that will be made

Hypoxic responses at alkalosis (placebo + bicarbonate), acidosis (acetazolamide) and normal pH (placebo as well as acetazolamide + bicarbonate)

Hypoxic responses at normal pH: placebo versus acetazolamide + bicarbonate.

Hypoxic responses: effect of acetazolamide on isocapnic versus poikilocapnic hypoxic ventilatory response.

A-aDO2 gradients and arterial O2 saturations at various pH's without and with acetazolamide.

Secondary outcome

None

Study description

Background summary

Acetazolamide is widely used in Acute Mountain Sickness and is effective against central sleep apnea and in some patients with lung disease able to increase their ventilation sufficiently to improve their acid-base status. In a clinical dose, acetazolamide causes metabolic acidosis and may also affect the hypoxic ventilatory response, but the underlying mechanisms of the latter are unclear.

We will examine the influence of acetazolamide on hypercapnic and acute hypoxic responses (AHR), and more specifically on the O2-CO2 interaction, i.e. the effect of rising PCO2 to increase the AHR. Isocapnic bicarbonate infusions will be performed to see if ventilatory isocapnic pH sensitivity reduces indicating inhibiting effects on the carotid bodies

Study objective

The peripheral chemoreceptors in the carotid bodies are sensitive to changes in the tensions of oxygen and carbon dioxide in the arterial blood and protect the body against hypoxia, hyper- and hypocapnia and acidosis/alkalosis. The ventilatory response to hypoxia (O2-chemoreflex) is initiated by a mechanism involving inhibition of potassium channels in chemosensitive cells in the carotid bodies, followed by membrane depolarisation, influx of Ca2+ ions and release of neurotransmitters. Other important adaptations of ventilation that are mediated by the carotid bodies occur during acidosis (rise in ventilation) and alkalosis (decrease in ventilation), acting to restore pH homeostasis.

In previous studies we examined the effect of acetazolamide (DiamoxTM) on the control of breathing in healthy volunteers. This agent causes mild acidosis due to inhibition of renal

carbonic anhydrase and thus induces a rise in normoxic ventilation. In clinical practice, diamox is used to prevent/treat the cerebral symptoms of acute mountain sickness (insomnia, headache, fatigue, anorexia, nausea, breathlessness, lightheadedness). The mechanism by which acetazolamide exerts its beneficial effect at high altitude is not clear. The common view is that the improved oxygenation in blood and tissues is due to a rise in ventilation. Interestingly, however, at altitude (characterised by a situation of poikilocapnic hypoxia, i.e. a condition in which the arterial CO2 tension will fall as a result of the hypoxia-induced hyperpnea) acetazolamide appears not to induce a consistent rise in ventilation. In a recent study (in collaboration with the Universities of Birmingham (UK) and Calgary (Canada)), we found that a clinical dose of acetazolamide reduces hypoxia-induced vasoconstriction in the lung (hypoxic pulmonary vasoconstriction, HPV). Since HPV is an uneven phenomenon, it may result in mismatches of ventilation and perfusion in the lungs and this will tend to decrease the arterial O2 tension. Consequently, acetazolamide may improve arterial oxygenation at altitude by reducing HPV rather than by increasing ventilation (or by a combination of both?).
Acetazolamide is also used to improve blood gases in patients with chronic obstructive pulmonary disease, to treat central sleep apnea and to improve extracellular volume status in cases of edema.

Our previous studies showed that a clinical dose of acetazolamide (250 mg 3 times/day) caused a rise in ventilation in normoxia (as expected) but did not change the ventilatory response to changes in CO2 tension. A low intravenous dose, however appeared to have an inhibitory effect on the O2-chemoreflex and data in the literature indicate that this may also occur after a usual oral clinical dose. This would be remarkable because the agent almost invariably causes a rise in ventilation in normoxia, that, similar to the O2 chemoreflex, is initiated by the same chemosensitive cells in the carotid bodies. This may indicate that, in contrast to the common view, acidosis and hypoxia follow different stimulus-response cascades in the carotid bodies.

Study design

Hypoxic responses after treatment with placebo or Acetazolamide

Intervention

Ventilatory response to isocapnic hypoxia:
What is the effect of a clinical oral dose of acetazolamide on the isocapnic hypoxic response (IHR), i.e. an exposure to hypoxia (end-tidal PO2 ~ 5.8 kPa) during 30 min? Does the agent increase the IHR as would be expected from the state of acidosis? To answer this question, we measure the IHR at two constant PCO2 levels (end-tidal concentration 5.5 and 7 kPa).

Ventilatory response to poikilocapnic hypoxia
How does acetazolamide influence the ventilatory response to poikilocapnic hypoxia (~ 30

min)? At a controlled inspired oxygen level of ~ 10.5 kPa (simulating an altitude of ~4800 m), how do the levels of ventilation, arterial PO2 and saturation compare after placebo and acetazolamide?

Bicarbonate infusion
What would be the ventilatory response if the acetazolamide-induced acidosis is acutely neutralized by infusion of bicarbonate? We follow (normoxic) ventilatory behaviour during ~ 30 min, during which we take arterial blood samples at time intervals of ~ 10 min. Thereafter, the subjects are exposed to isocapnic hypoxia (30 min) and the response compared with that seen before the acid-base correction.

Contacts

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Eligibility criteria

Inclusion criteria

1. Healthy volunteers aged 18-45 years

Exclusion criteria

1. Obesity (BMI > 30)

2. Presence of medical disease (heart-, lung-, liver-, kidney- and logic disease; diabetes M.)

3. Presence of psychiatric disease

4. History of chronic alcohol or drug use

5. Allergy to study medications

6. Possibility of pregnancy

7. Lactation

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Non controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2008
Enrollment:	9
Type:	Actual

Ethics review

Positive opinion

Date:	23-05-2007
Application type:	First submission

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
NTR-new	NL1277
NTR-old	NTR1323
Other	: Diamox001_2008
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results

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