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Association of acetazolamide infusion with headache and cranial artery dilation in healthy volunteers

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ABSTRACT

The carbonic anhydrase inhibitor acetazolamide causes extracellular acidosis and dilatation of cerebral arterioles. In this study, we tested the hypothesis that acetazolamide also may induce headache and dilatation of cranial arteries. In a randomized double-blind crossover study design, 12 young healthy women were allocated to injection of 1 g acetazolamide or placebo on 2 separate days. We recorded headache on a verbal rating scale from 0 to 10 during an immediate phase (0–90 minutes) and a delayed phase (2–12 hours). The circumference of cranial arteries was measured using 3T high-resolution magnetic resonance angiography 30 and 60 minutes after injection. Acetazolamide provoked immediate headache in 9 participants compared to 3 participants after placebo ($P = .031$). Eleven participants reported headache in the delayed phase after acetazolamide, compared with 4 after placebo ($P = .016$). The area under the curve for headache was increased after acetazolamide compared to placebo in the delayed phase (2–12 h) ($P = .005$). Compared to placebo, arterial circumference increased after acetazolamide in the basilar artery ($P = .002$) as well as the cerebral ($P = .003$), cavernous ($P = .002$), and cervical ($P = .005$) parts of the internal carotid artery, but no other extracranial arteries changed after acetazolamide. In conclusion, acetazolamide caused immediate and delayed headache as well as dilatation of intracranial arteries in healthy volunteers. It is possible that extracellular acidosis induced by acetazolamide causes sensitization of cephalic perivascular nociceptors, which, in combination with vasodilatation, leads to delayed headache.

1. Introduction

Acetazolamide was the first synthesized carbonic anhydrase inhibitor and has been used clinically since 1954 [8]. Acetazolamide is widely used to prevent or reduce the symptoms of altitude sickness [30] and idiopathic intracranial hypertension [32], but studies in humans also indicate that it may have headache-inducing properties [5,14,45]. In a previous study, healthy volunteers were pretreated with 1 g intravenous (i.v.) acetazolamide followed by infusion of the nitric oxide (NO) donor glyceryl trinitrate (GTN) [14]. The study showed that acetazolamide together with GTN induced significantly higher headache scores in the delayed phase than GTN alone [14]. Whether acetazolamide per se provokes immediate and delayed headache in healthy subjects has not previously been systematically investigated.

Measurement of acetazolamide-induced increase in cerebral blood flow (CBF) is commonly used to assess the dilator capacity of the cerebral circulation [40,50]. The vasodilator effects of acetazolamide are complex, and it has been suggested that acetazolamide dilates only arterioles [46]. However, there are conflicting results about arterial dilation from indirect measurements. Two studies of blood flow velocities in cerebral arteries and regional CBF have suggested a constricting effect [29,46], whereas 1 study

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reported no effect [13]. A dilator effect of acetazolamide has also been suggested based on measurements of flow volume in the common carotid arteries and flow velocities in the middle cerebral artery (MCA) [15]. To date, no high-resolution 3-dimensional (3D) magnetic resonance angiography (MRA) studies have investigated the effect of acetazolamide on intra- and extracranial arteries.

We hypothesized that acetazolamide would induce headache and dilatation of cranial arteries. To test this hypothesis, we conducted a double-blind, placebo-controlled, crossover study in healthy volunteers using high-resolution MRA.

2. Methods

2.1. Study participants

We recruited 16 healthy women (mean age 25 years, range 19–33 years) via an announcement on a Danish website for recruitment of volunteers to health research. Exclusion criteria were as follows: a history of migraine or any other type of headache (except episodic tension-type headache less than 5 days per month); first-degree relative with migraine; any daily medication apart from oral contraceptives; any somatic or psychiatric disease; contraindications for magnetic resonance imaging (MRI) scan; any headache 48 hours before the start of each scan; and intake of coffee, tea, cocoa, alcohol, tobacco, or other methylxanthine-containing foods or beverages 12 hours before the study days. All participants used reliable contraceptive methods.

The study was approved by the Ethics Committee of the Capital Region of Denmark (H-3-2012-137) and registered at Clinicaltrials.gov (ID: NCT01750723). All participants gave informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki of 1964, as revised in Edinburgh in 2000.

2.2. Study design

In a double-blind, placebo-controlled, crossover design, the participants were randomly allocated to receive 1 g intravenously of acetazolamide dissolved in 10 mL saline or placebo (10 mL saline) infused over 2 minutes on 2 separate days, with a minimum interval of 1 week. This produced an effective mean acetazolamide dose of 16 mg/kg (range 13–19 mg/kg). Two physicians (F.M.A. and A.H.) performed the infusion procedure according to a randomization scheme. The participants and 1 physician (N.A.) were blinded to the infusion substance. Headache intensity and characteristics, associated symptoms, and adverse events were monitored by a blinded physician (N.A.). Before the experiment, each participant underwent a general physical and neurological examination. The participants were told that we were investigating the possible headache inducing effects of acetazolamide. We did not specify the timing of the headache (ie, whether the possible headache would appear in the immediate or delayed phase). Half of the studies were initiated in the morning (9 AM–12 PM) and the other half in the afternoon (12–18 PM). All participants arrived headache-free at the laboratory at the same time on each study day (±2 h). All procedures were performed in the MRI scanner room. The participants were placed in a supine position, and a venous catheter was inserted in the antecubital vein for drug infusion. On each study day, we collected blood samples to determine baseline levels of potassium, sodium, and hematocrit. We obtained repeated MRA measurements of extra- and intracranial arteries 30 and 60 minutes after infusion (Fig. 1). Headache intensity and vital signs were monitored with regard to electrocardiogram (ECG), blood pressure (BP), heart rate (HR) (Veris Monitor; Medrad, USA), respiration frequency (RF), and end-tidal CO_2 ($P_{ET}CO_2$) (capnograh; Datex, Finland) before infusion (baseline) and then every 10 minutes until 90 minutes after the beginning of the infusion. After finishing the measurements, the participants were discharged from the hospital and asked to complete a headache diary every hour until 12 hours after the infusion (Fig. 1).

2.3. Headache

Headache intensity was recorded repeatedly on a verbal rating scale (VRS) from 0 to 10 (0 = no headache; 1 = a very mild headache (including a feeling of pressing or throbbing pre-pain); 10 = worst imaginable headache) [22]. In addition, we recorded headache characteristics (intensity [moderate to severe headache intensity was considered $\geqslant 4$ on VRS], quality, location, aggravation by physical activity), and associated symptoms (nausea, photophobia, and phonophobia). Two laboratory technicians (L.E. and W.G.) extracted data from the headache diaries blinded, and data was double-checked by a blinded physician (N.A.).

2.4. Imaging protocol

We used a 3.0 Tesla Philips Achieva MRI scanner (Philips Medical Systems, Best, Netherlands) with a 32-element phased-array receiver head coil to acquire single-slab 3D time-of-flight (3D TOF) MRA of extra- and intracranial arteries. Imaging was performed as described earlier [2]. We first performed a scout MRA using the following sequences: field-of-view (FOV) $180 \times 180 \times 120\ mm^3$; acquired matrix size (MxP) of 120×120; acquired voxel resolution $1.5 \times 1.5 \times 2.4\ mm^3$; reconstructed resolution $0.70 \times 0.70 \times 1.20\ mm^3$; repetition time (TR) 23 milliseconds; echo time (TE) 3.9 milliseconds; flip angle 20°; parallel imaging (sense) factor 3; 2 chunks; total scan duration 73 seconds. A subsequent high-resolution scan was planned from this scout MRA. This first high-resolution MRA scan was planned to include the middle cerebral artery (MCA), the basilar artery (BA), the cerebral part of the internal carotid artery ($ICA_{cerebral}$), the cavernous part of ICA ($ICA_{cavernous}$), and the external carotid artery (ECA), and used the following sequences: FOV $200 \times 200 \times 74\ mm^3$; MxP 800×406; acquired voxel resolution $0.25 \times 0.49 \times 1.00\ mm^3$; reconstructed resolution $0.20 \times 0.20 \times 0.50\ mm^3$; TR 25 milliseconds; TE 3.5 milliseconds; flip angle 20°; sense factor 2; 4 chunks; total scan duration 9 minutes 3 seconds. From this first high-resolution MRA, we planned another MRA scan with a higher spatial resolution to visualize the superficial temporal artery (STA), the middle meningeal artery (MMA) and the cervical part of the ICA ($ICA_{cervical}$), using following sequences: FOV $200 \times 200 \times 16\ mm^3$; MxP 800×571; acquired voxel resolution $0.25 \times 0.35 \times 0.70\ mm^3$; reconstructed resolution $0.20 \times 0.20 \times 0.35\ mm^3$; TR 25 milliseconds; TE 3.5 milliseconds; flip angle 20°; sense factor 3; 2 chunks; total scan duration 5 minutes 29 seconds.

2.5. MRA data analysis

The acquired MRA data were analyzed by LKEB-MRA vessel wall analysis software program (version 6.2007), which has been used in several studies [1,2,4]. The software provides automated contour detection and quantification of the luminal boundaries every 0.2 mm perpendicular to the centerline in the chosen vessel segments. The investigator (N.A.) and laboratory technician (L.E.) who performed the analyses were blinded to the experimental day and scan session. The blinding of data was done by F.M.A. We obtained an average of 26 values (ie, 5-mm-long vessel segments) for each arterial measurement (Fig. 1). If small side branches were included in a measurement or the contour was distorted, we manually corrected the measurement if possible. If not

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