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Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 549–556

Progress In Neuro-Psychopharmacology & Biological Psychiatry

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Influences of caffeine, acetazolamide and cognitive stimulation on cerebral blood flow velocities

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Accepted 28 January 2005
Available online 8 March 2005

Abstract

Assessment of cerebral blood flow velocities (CBFV) can be used as a non-invasive tool to evaluate specific drug effects, like caffeine (CAF), acetazolamide (AA) as well as cognition. Their influences on each others CBFV were evaluated in detail, using a randomized, double-blind, double-dummy, placebo-controlled three-fold cross-over study design in 18 right-handed healthy male volunteers. CBFV (maximal, mean, minimal) and pulsatility index of both middle cerebral arteries were recorded by transcranial Doppler ultrasound simultaneously, during a verbal memory test, oral CAF, intravenous AA or placebo. AA led to increase in CBFV of 25–32%. Caffeine resulted in decreased V_{mean} and V_{min} of 10–13%. Cognitive stimulation resulted in a slight increase of CBVF of about 4%, but was overruled by effects of AA and CAF.

We conclude that pharmacological effects can easily be assessed by TCD during clinical pharmacological studies of vasoactive drugs. However intraindividual variability and effects of neuropsychological stimulation needs to be taken into account.

Keywords: Acetazolamide; Caffeine; Cerebral blood flow velocity; Cognition; Transcranial Doppler ultrasound

1. Introduction

Cerebral hemodynamics can be assessed non-invasively using transcranial Doppler ultrasound (TCD) (Deppe et al., 2004; Haase and Diener, 1998; Lunt et al., 2000; Stoll and Hamann, 2002; Vollmer-Haase et al., 1998; Zunker et al., 1998). Although cerebral blood flow is strongly auto-regulated in healthy persons, variations can be measured applying intrinsic triggers, e.g. carbondioxide, cognitive tasks or various drugs. In order to monitor drug effects on cerebral blood flow velocities (CBFV) alteration in CBFV were induced either in resting positions, positional changes (tilt-table testing), voluntary movements (e.g. extremities) or cognitive-mental testing. For cognitive tasks TCD has been proven to be a reliable tool to explore CBFV changes (Deppe et al., 2004; Droste et al., 1989; Hartje et al., 1994; Kelley et al., 1992; O'Dell et al., 1992; Perod et al., 2000; Schmelzeis et al., 1994). Depending on the nature of the task either the right, left or both hemispheres became activated, resulting in increased CBFV of 7–10% for the left and 3–11% for the right hemisphere. While verbal tasks lead to significant differences in CBFV in favor to the left hemisphere, word memory produced bilateral CBFV increase of the middle cerebral artery (MCA) (Droste et al., 1989; Hartje et al., 1994). In healthy volunteers, cerebral auto-regulation has to be challenged by activation of cerebral blood flow (CBF) via either cognitive or pharmacological stimuli, in order to increase CBFV in both MCA (Kelley et al., 1992; O'Dell et al., 1992; Perod et al., 2000; Schmelzeis et al., 1994).

Abbreviations: AA, acetazolamide; AMG, Arzneimittelgesetz (German drug law); BW, body weight; CAF, caffeine; CBF, cerebral blood flow; CBFV, cerebral blood flow velocities; CI, confidence interval; CVR, cerebral vasoreactivity; GCP, good clinical practice; ICH, international conference on harmonization; MCA, middle cerebral artery; PI, pulsatility index; TCD, transcranial Doppler ultrasound.

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0278-5846/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2005.01.006

Pharmacological influences on the cerebral vessels have been extensively examined under various conditions in healthy volunteers and patients with cerebrovascular diseases using acetazolamide (AA-Diamox®) for clinical testing of the cerebral reserve capacity/ vasoreactivity (CVR) and CAF for the testing of vasodilatating effects (Couturier et al., 1997; Grossmann and Koeberle, 2000; Haase and Diener, 1998; Perod et al., 2000; Piepgras et al., 1990; Stoll and Hamann, 2002).

Caffeine is a xanthin-derivative, acting at adenosinergic auto-receptors, inhibiting the intracellular phosphodiesterase, resulting in increased intracellular levels of cAMP and Ca^{2+}. Already low doses of 150–250 mg can lead to agitation, headache, increase of physiologic tremor, sleeplessness and irritability. An optimal effect–time relation was achieved by moderate doses of 200 mg caffeine ingested around 30–60 min before testings. Caffeine effects on CBFV, 0.5 h after oral intake, resulted in lowering of average CBFV by 5–8%, which were restored after about 2 h (Lieberman et al., 2002; Lunt et al., 2000).

Acetazolamide (AA-Diamox®) is a thiazide derivative acting as an inhibitor of the enzyme carboanhydrase resulting in increased cellular CO_2 and elevated CBF. After injection, AA has a t_{max} of about 0.2 h and $t_{1/2}$ of 2–6 h. Doses used for testing cerebral vaso-reactivity are 1 g per person or 13 mg/kg body weight (BW). The effects of AA on CBFV are caused by the metabolic acidosis followed by small vessel vasodilatation. In order to supply the acidic tissue with oxygen and defer CO_2, blood flow velocities in the basal and peripheral cerebral arteries increase. The optimal dose–effect relationship to CBFV was provided using 13 mg/kg body weight (BW), resulting in increased average CBFV of 14–21%. Adverse events of AA included effects of increased diuresis, like hypovolemia, hypotonia, increased urinating pressure, as well as headache, nausea, vertigo, dizziness and changed taste (Grossmann and Koeberle, 2000; Piepgras et al., 1990; Stoll and Hamann, 2002). Apart from these adverse, little is known of AA influencing cognition or vice versa.

In order to assess the influence of caffeine and AA on cognition as well as on cerebral blood flow velocities, we examined healthy male volunteers at rest and during psychometric testing under the influence of either caffeine, acetazolamide and placebo in a double-blind, double-dummy cross-over design.

2. Methods

2.1. Subject population

A total of 18 right-handed male healthy subjects participated in this study. Mean age was 31.6±6.0 years, with a range of 21–41 years and a mean weight of 83.7±8.2 kg. All participants gave their informed written consent prior to the study, after approval of an external ethics committee had been achieved. The study was conducted in accordance with the Declaration of Helsinki (1964) in the revised version of 1996 (Somerset West), the ICH GCP Guideline (Note for Guidance on Good Clinical Practice) and the German drug law (AMG). Exclusion criteria determined at the pre-study examination included: Participation in another clinical trial during the preceding 3 months; Subjects with conspicuous findings in medical history and pre-study examination; Donation of more than 100 ml of blood (e.g. for the reference pool of an analytical laboratory) in the preceding 4 weeks; Blood donation of more than 500 ml or plasma donation in the preceding 3 months; A history of relevant diseases of internal organs, of the central nervous system or other organs, including migraine and other forms of chronic headache; Subjects with a medical disorder, condition or history of such that would impair the subject's ability to participate or complete this study in the opinion of the investigator or the sponsor; Febrile illness within 1 week before the start of the study; Subjects with a history of severe allergies, non-allergic drug reactions, or multiple drug allergies; Subjects with a hypersensitivity to the investigational drug, the control agent and/or to inactive constituents; Use of caffeine-containing beverages 24 h before the study day; caffeine-containing forms exceeding a daily consumption of 7 cups/ day (3 mg/kg body weight); regular daily consumption of more than 1 l of usual beer or the equivalent quantity of approx. 40 g of alcohol in another form; regular daily consumption of more than 1 l of xanthin-containing beverages; regular daily consumption of more than 25 cigarettes; smoking or consumption of tobacco-like products 12 h before the study day; regular use of therapeutic or recreational drugs; use of medication within the 2 weeks preceding the study which could interfere with the investigational product; relevant deviation from the norm in the clinical examination; relevant deviation from the norm in clinical chemistry, hematology or urinalysis; resting heart rate in the awake subject below 45/min or above 90/min; systolic blood pressure below 100 mm Hg or above 145 mm Hg; diastolic blood pressure above 85 mm Hg; relevant pathological changes in the ECG such as a second or third-degree AV block, prolongation of the QRS complex over 120 ms or of the QTc-interval over 450 ms for males and over 470 ms for females; subjects testing positive in the drug screening. Before and after the study a thorough physical examination was performed. The study was conducted under fasting condition. Heart rate, and respiratory rates were measured continuously, blood pressures were recorded in parallel to TCD measurements and up to 4 h after administration of the study drugs. Study periods of this cross-over study were performed at least 1 week apart to avoid carry-over effects. In order to ensure subject's compliance to remain abstinent to caffeine for ca. 24 h before the study, plasma samples for the measurement of caffeine concentrations were taken at the morning of the study day at each of the periods and 4 h after study drug