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ORIGINAL

Intracranial hemodynamics during intravenous infusion of glyceryl trinitrate

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Abstract The mechanisms of glyceryl trinitrate (GTN)-induced headache are not fully elucidated. In this study we administered GTN 0.5 μg/kg/min i.v. for 20 min in six healthy volunteers. Before, during and 60 min after the infusion, we investigated regional cerebral blood flow (rCBF), cerebral blood volume (CBV), both estimated with SPECT, and blood flow velocity (BFV) in the middle cerebral artery (MCA), measured with transcranial Doppler. Headache was scored on a numerical verbal rating (0–10) scale. rCBF was unchanged, CBV was slightly increased (13%) during GTN infusion, whereas BFV decreased both during (20%) and 60 min (15%) after GTN. Headache was short-lived and maximal during infusion. This discrepancy of time-effect curves for the effect of GTN on headache and dilatation of MCA indicates that MCA is most likely not the primary source of pain in GTN-induced headache. The time-effect curves for the effect of GTN on headache and on dilation of MCA differed markedly. This indicates that MCA is most likely not the primary source of pain in GTN-induced headache.

Keywords Glyceryl trinitrate · Headache · Cerebral blood flow · Cerebral blood volume · Transcranial Doppler

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Introduction

The glyceryl trinitrate (GTN) headache model with intravenous administration of the drug is well established [1–4], and has been used to evaluate acute and prophylactic anti-migraine drugs [5–9]. GTN causes an immediate mild to moderate headache during infusion in normal subjects [1]. Migraine patients are supersensitive to GTN [3] and GTN causes a delayed headache in 80% of patients. This headache resembles the usual migraine attacks [2, 10] the patients suffer.

The cause of pain in the NO-induced headache is still not fully elucidated. In the present study, we therefore investigated the effect of intravenous GTN in healthy subjects on intracranial hemodynamics: regional cerebral blood flow, cerebral blood volume and blood flow velocity in the middle cerebral artery.

Methods

Material and measurements

Six healthy subjects, F:M = 2:4, with a mean age of 27.5 years (range 22–38 years) participated in the study. Subjects with migraine and subjects with more than one tension-type headache day per month were excluded. The subjects were to be free from any medication for at least a week. They arrived in the laboratory in the morning after abstaining from alcohol and caffeine for 12 h. Following the placing of a catheter in a cubital vein, they rested supine for 30 min after which baseline measurements were done.

Glyceryl trinitrate in a dose of 0.5 μg/kg/min was infused intravenously via the catheter in a cubital vein for 20 min by a volume-directed pump (Braun perfusor).

Headache was scored on a numerical verbal rating scale from 0 to 10 (0 = no headache and 10 = worst possible pain) [1] every 10 min before, during, and up to 60 min after GTN infusion.

The time-averaged mean of the maximal blood velocities (V_{mean}) in the right middle cerebral arteries (MCA) was measured with transcranial Doppler (EME TC28) [11]. The fixpoint measurements of V_{mean} was a point along the MCA, which was free of the bifurcation between the MCA and the anterior cerebral artery, but as close to it as possible [12]. Due to technical reasons and limitation of space in the scanner, the measurements were performed only on the right side.

Regional cerebral blood flow (rCBF) was measured with a highly sensitive, brain-dedicated, fast-rotating, single photon emission computerised tomograph (Tomomatic 232). Each study lasted 4.5 min. A mixture of atmospheric air and ^{133}Xenon was re-breathed during the first 1.5 min through a closed system from a 4-litre reservoir (740 Mbq/l). During the last 3 min the ^{133}Xenon mixture was expired against atmospheric air. rCBF was recorded simultaneously in two slices positioned 50 and 90 mm above and parallel to the orbito-meatal plane. Each slice was 16-mm thick and the distance between the centres of slices was 40 mm. The full width half maximum resolution of the instrument is about 16 mm in the horizontal plane. rCBF was calculated according to Celsis et al. [13].

A fixed matrix of regions of interest was superimposed on the rCBF picture. The shape and size were fitted to the outlines of the brain excluding extracranial flow and regional mean values were calculated within the predefined regions of interest. The matrix was divided into regions of interest representing the hemispheric rCBF regions and the vascular territories of supply by the anterior-, middle- and posterior cerebral arteries. The maximum whole body radiation was approximately 0.6 mSV per rCBF measurement [14]. rCBF and CBV were measured simultaneously with a highly sensitive, brain-dedicated, fast-rotating single photon emission computerized tomograph, SPECT, equipment (Tomomatic 232) with dual energy window facilities enabling separation of peak energies from Tc-99 m and Xe-133. rCBF was measured after Xe-133 inhalation and with 4 1/2 min data sampling. CBV was recorded after intravenous injection of Tc-99 m labeled erythrocytes [14] and data were corrected for physical and biological decay. Mean rCBF and CBV values from the MCA perfusion territory were calculated from a transverse section of the brain obtained 50 mm above the orbito-meatal plane. During the rCBF measurements end-expiratory pCO_2 was monitored using a capnograph. Data were corrected for pCO_2. Heart rate and blood pressures were measured every 2 min, except during the rCBF measurements, with an automatic inflatable arm cuff (Tonoprint®) during the GTN infusion and thereafter every 5 min. Blood samples for determination of counts in the blood were collected at 0, 15, 30, 60, 120, 150 and 180 min.

V_{mean}, rCBF and CBV were measured before and after 20 min of GTN infusion and 60 min after the infusion.

Statistical evaluation

Responses were calculated in percent of baseline and expressed as mean and standard error of the mean (±SEM). Statistical analysis was done with paired t test. $P < 0.05$ was considered statistically significant.

Results

During GTN infusion five of six subjects experienced headache. The median maximum headache score was 3 (range 0–5). The median headache was 0 (range 0–1) 60 min after termination of the infusion. The cerebral hemodynamic response was, however, the same in all subjects. The cerebral blood volume was slightly increased 13 ± 2% (mean SEM) during GTN infusion ($P < 0.05$) and returned to baseline, −0.3 ± 3%, 60 min after the end of infusion (Fig. 1). The regional cerebral blood flow (rCBF) in the perfusion territory of the middle cerebral artery (MCA) was used, and rCBF values from the second and third measurements were corrected 2% for each mmHg the end-tidal pCO_2 deviated from the control value. There were no significant changes in rCBF during and after GTN

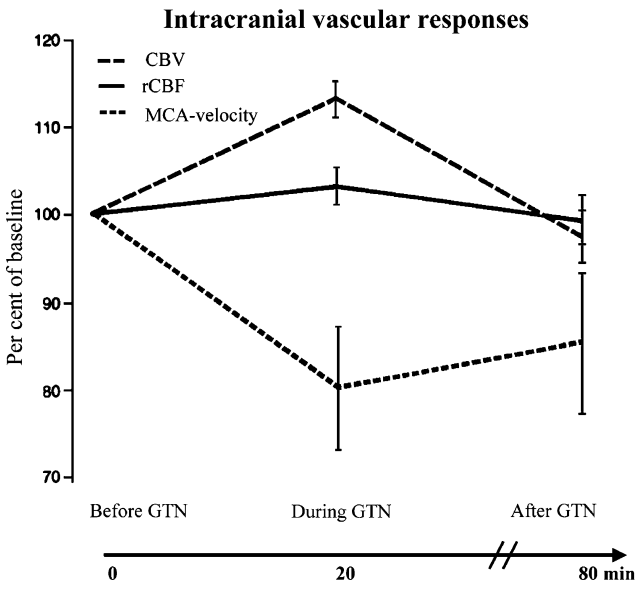

Fig. 1 The effect of glyceryl trinitrate (0.5 μg/kg/min) i.v. for 20 min in six healthy volunteers on cerebral blood volume, regional cerebral blood flow and blood flow velocity in the middle cerebral artery

in fusion (Fig. 1). The mean maximal velocity (baseline = 68 ± 3 cm/s) in the MCA decreased by 20% ($P < 0.05$) during infusion (from 68 ± 3 to 55 ± 5 cm/s) and was still decreased by 15% (56 ± 5 cm/s, $P < 0.05$) 60 min after infusion (Fig. 1).

Mean systolic BPs were 116, 119 and 120 mmHg ($P = 0.42$). Mean diastolic BPs were 72, 84, and 84 mmHg ($P = 0.013$). Mean heart rate, 69, 80 and 66 bpm, was unchanged ($P = 0.10$).

Discussion

Glyceryl trinitrate, an exogenous nitric oxide-donor, is known to cause headache as a side effect when used in cardiovascular diseases [15]. A headache model with intravenous GTN has been developed and evaluated [1–3, 5–10]. The bioavailability after sublingual GTN (0.4 mg) was 36 ± 25% (mean ± SD), range from 3 to 113% [16]. The time to peak concentration also varied considerably [16]. In our work with the experimental headache model we have therefore chosen to use intravenous administration of GTN, in order to decrease variability of doses given.

In healthy subjects the headache is dose-dependent with a ceiling effect at 0.5 μg/kg/min [1]. Migraine patients are more sensitive to GTN than tension-type headache patients and controls [17]. The cause of headache in the GTN model is not fully elucidated and it has been suggested that GTN-induced headache is caused both by vascular and by neuronal effects of NO [18, 19].

In the present study five of six subjects experienced headache during the GTN infusion. However, GTN induced equal hemodynamic responses in all subjects. Median maximal headache score was 3, and the headache decreased when the infusion stopped. That the bother of lying in the scanner amplified the induced headache, cannnot be ruled out. The headache did not fulfil the criteria for migraine, and no delayed headache was observed, as can be observed when GTN is administered to migraine patients [2].

Changes in regional cerebral blood flow (rCBF) are unlikely to cause headache. Thus during attacks of migraine with aura there is oligemia when the headache begins and there is a late hyperemia which persists after the headache [20]. In the present study, rCBF was unchanged during headache induced by GTN (Fig. 1). Similar results, that is unchanged CBF after GTN, were found in one SPECT study [21] and one PET study [22]. In one PET study [23] a 23% increase in CBF was found after GTN. This PET examination [23] showed, however, a decrease in occipital rCBF and it is unclear how a general vasodilatator like GTN should cause regional changes in CBF.

This is the first time cerebral blood volume (CBV) after GTN has been investigated. GTN is a potent dilator of peripheral veins [24]. CBV was slightly but statistically significantly increased (13%). Clinically, it is observed in migraine that headache is usually aggravated by coughing, straining, or undergoing the Valsalva test, which could infer a venous component to the migraine attack [25, 26]. We did not test for this during the GTN-headache. Applying pressure on the internal jugular veins (Queckenstedt's manoeuvre) during migraine attacks did cause an increase in migraine pain in two studies [27, 28] whereas this was not the case in one study [29]. This indicates that there could be a venous component to migraine pain.

Although the Doppler technique does not allow direct measurements of the diameter of the middle cerebral artery (MCA), the relative change in diameter can be estimated from the relation: regional cerebral blood flow (rCBF) = mean velocity × cross sectional area of the artery [21, 30]. When rCBF is unchanged (Fig. 1) a decrease in V_{mean}, as in the present study (Fig. 1), will indicate a dilatation of MCA. The decrease in mean blood flow velocity in MCA (Fig. 1) was still present 60 min after GTN infusion indicating dilatation. In contrast, the headache had disappeared at this time point making it unlikely that dilation per se of MCA is the cause of NO-induced headache. This is supported by findings in another study on GTN, where MCA velocities remained decreased (14%, $P < 0.001$) at the time of headache resolution [31]. In addition, dilation of the MCA outlasted the headache response after intravenous dipyridamole [32] and sildenafil-induced migraine in migraine patients, but did not affect MCA velocity [33].

A limitation of this study is the lack of a placebo-control but it was not considered feasible to expose the healthy subjects to the double dose of radiation from a total of six SPECT examinations.

In conclusion, regional cerebral blood flow was unchanged after GTN whereas the middle cerebral artery was dilated after GTN. However, because of the discrepancy of the time-effect curve for dilation of MCA and the effect on headache the dilation of the MCA is unlikely to cause NO-induced headache. Alternative causes for headache such as an effect of NO on extracerebral arteries or an effect of NO on perivascular nerves should be investigated.

Conflict of interest None.

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