Cerebral blood flow changes in patients with probable medication-overuse headache

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Summary

Transcranial Doppler (TCD) is a non-invasive method for measuring blood flow velocity (BFV), and a marker of vessel diameter. In this study, intracranial BFV was investigated, by means of TCD, in patients suffering from probable medication-overuse headache (PMOH). Twenty-three female patients with probable ergotamine-overuse headache (PEOH), 23 female patients with probable analgesic-overuse headache (PAOH), and 15 healthy female controls participated in the study. The mean BFVs of the bilateral middle and anterior cerebral arteries (MCA and ACA) and basilar artery (BA) were measured by TCD.

The mean BFVs of the BA and MCA were found to be significantly increased in the PEOH group when compared with those of the PAOH and control groups (p<0.05). No significant differences in BFV of the ACA were observed between any groups (p>0.05). The mean BFV of all the vessels in the PAOH group was found to be lower than that of the control group but no statistical significance was found (p>0.05).

Our results show that ergotamine increases BFV via vasoconstriction, especially of the BA and MCA. We also suggest that 5HT1B/1D receptors are mainly localized in the BA and MCA, and that analgesic overuse results in a functional disorder of neuronal receptor and neurovascular reflexes and may cause a reduction of intracerebral vessel tone, leading to vasodilatation.

KEY WORDS: analgesic, cerebral blood flow, headache, ergotamine, overuse, transcranial Doppler.

Introduction

It has been known for a long time that frequent use of medications to relieve headache could worsen the pre-existing primary headache or give rise to a new type of daily headache. There has been extensive debate over the terminology to be used in these cases: chronic migraine, chronic daily headache, rebound headache, drug-induced headache, medication misuse headache, and analgesic overuse headache have all been used alternatively (1). The revised headache classification of the International Headache Society (IHS) has ended these conflicts, classifying the headaches secondary to overuse of drugs under the term medication-overuse headache (MOH) and probable medication-overuse headache (PMOH), irrespective of the type of headache. Six subgroups of MOH and PMOH have been identified (Table I) (2).

Transcranial Doppler sonography (TCD) is a non-invasive and repeatable bedside diagnostic tool, which was first used by Aaslid et al. in an attempt to detect blood flow in intracranial vessels (3). For intracranial use, ultrasonic waves sent by a 2 MHz Doppler probe are reflected back from the figured elements of the blood flowing in the vessel and converted to a wave form by means of a computer. Hence, blood flow velocity (BFV; cm/s) and flow direction can be determined. BFV may change in relation to age and gender (4). Although the normal range of BFV values has not been well documented, TCD has been used in many pathological conditions affecting the intracranial arteries (arteriosclerosis, sickle cell disease, vasospasm, etc.) (5,6).

Using TCD, the underlying pathophysiology of the headache can be discovered and the efficacy of the therapeutic intervention monitored (6-8).

Table I - The classification of ‘medication-overuse headache’ according to the International Headache Society criteria.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Headache Classification</th>
</tr>
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<tbody>
<tr>
<td>8.2.1</td>
<td>Ergotamine-overuse headache</td>
</tr>
<tr>
<td>8.2.2</td>
<td>Triptan-overuse headache</td>
</tr>
<tr>
<td>8.2.3</td>
<td>Analgesic-overuse headache</td>
</tr>
<tr>
<td>8.2.4</td>
<td>Opioid-overuse headache</td>
</tr>
<tr>
<td>8.2.5</td>
<td>Combination medication-overuse headache</td>
</tr>
<tr>
<td>8.2.6</td>
<td>Headache attributed to other medication overuse</td>
</tr>
<tr>
<td>8.2.7</td>
<td>Probable medication-overuse headache</td>
</tr>
<tr>
<td>8.2.7.1</td>
<td>Probable ergotamine-overuse headache</td>
</tr>
<tr>
<td>8.2.7.2</td>
<td>Probable triptan-overuse headache</td>
</tr>
<tr>
<td>8.2.7.3</td>
<td>Probable analgesic-overuse headache</td>
</tr>
<tr>
<td>8.2.7.4</td>
<td>Probable opioid-overuse headache</td>
</tr>
<tr>
<td>8.2.7.5</td>
<td>Probable combination medication-overuse headache</td>
</tr>
<tr>
<td>8.2.7.6</td>
<td>Headache probably attributed to other medication overuse</td>
</tr>
</tbody>
</table>
In this study, we used TCD to evaluate cerebrovascular changes in a group of patients with probable analgesic-overuse headache (PAOH) or probable ergotamine-overuse headache (PEOH) and compared the results with those of healthy subjects. This study also considered the effect of intracranial vascular tone changes on the pathophysiology of PMOH.

Materials and methods

Subjects

Forty-six female patients fulfilling the IHS 2004 criteria (2) for the PEOH and PAOH subgroups of PMOH (23 patients per group) were included in the study. The primary headache, in all cases, was found to be migraine without aura. Fifteen healthy volunteers, matched for age and sex with the patients, were enrolled in the study. Hypertensive patients were not included in the study, and no patient reported here was receiving anti-hypertensive medication. We also excluded patients i) with significant systemic and/or cerebrovascular disease, ii) who were on a regular drug therapy that might cause any hemodynamic change, and iii) with TCD findings of intracranial stenosis/reverse flow, vasospasm, or insufficient temporal/occipital acoustic window.

All the subjects gave their written informed consent to participate in the study, after the nature of the procedure had been fully explained to them. The study was approved by our institutional ethics committee and performed in accordance with the guidelines of the Declaration of Helsinki.

Transcranial Doppler sonography examination

Transcranial Doppler sonography examination, to evaluate the normal cerebral hemodynamic parameters and appropriate temporal and occipital window, was conducted using a 2 MHz Doppler probe, spectral analyzer, and TCD Multidop X4 DWL device (Electronische Systeme GmbH, Sipplingen, Germany). The subjects were taken into a quiet room in the morning. Following a rest of 20 minutes, the analysis was performed. Then, basal blood pressure, heart rate and TCD recordings from the anterior cerebral artery (ACA), middle cerebral artery (MCA) and basilar artery (BA) were obtained. The patients had been asked to stop taking their medications 8 hours before the procedure. Insonation was performed at a depth of 60-75 mm for the ACA, 40-65 mm for the MCA, and 75-90 mm for the BA. The TCD techniques and velocity criteria have been described and defined elsewhere (6-8).

Mean BFV was used as a parameter in the TCD measurements. TCD devices automatically calculate mean BFV as follows: BFVMean=(VMax+2V Min)/3. The mean values of the right and left-sided measurements were calculated and their average values were used for all the assessments.

Statistical analysis

The chi-square analysis of variance (ANOVA) and Mann-Whitney U-test were used to examine associations between categorical and continuous variables. Alpha was set at 0.05 to determine statistical significance.

Results

The demographic features of both the patients and the controls are shown in Table II. No significant differences were found in age or arterial blood pressure between the patient and control groups. The primary headache of all the patients enrolled in the study was migraine without aura. In addition, the duration of the primary headache and the PMOH and the number of tablets taken daily did not differ significantly between the patient groups (p>0.05). The mean BFV values of both the patient groups and the control group are shown in Table III. The mean BFVs in the BA and MCA recorded in the PEOH group were significantly increased when compared to those of the PAOH and control groups (p<0.05). The mean BFVs in the ACA, MCA and BA in the PAOH group were decreased in comparison to the control group findings but the differences were not statistically significant (p>0.05). The mean BFV in the ACA did not show any statistical significance between the groups, although the highest values were obtained in the PEOH group and the lowest in the PAOH group.

Table II - Demographic and clinical characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>PEOH</th>
<th>PAOH</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23 (females)</td>
<td>23 (females)</td>
<td>15 (females)</td>
</tr>
<tr>
<td>Mean age (years±SD)</td>
<td>42.5±4.81</td>
<td>41.3±6.59</td>
<td>41.1±4.16</td>
</tr>
<tr>
<td>Primary headache duration (years±SD)</td>
<td>15.45±5.9</td>
<td>11.86±6.79</td>
<td>–</td>
</tr>
<tr>
<td>PMOH duration (years±SD)</td>
<td>3.68±2</td>
<td>2.95±1.53</td>
<td>–</td>
</tr>
<tr>
<td>Mean daily intake of tablets (number±SD)</td>
<td>2.38±2</td>
<td>2.22±1.33</td>
<td>–</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg±SD)</td>
<td>125±4.9</td>
<td>122±4.3</td>
<td>123±4.2</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg±SD)</td>
<td>75.5±5</td>
<td>72.5±3.8</td>
<td>71.8±3.5</td>
</tr>
</tbody>
</table>

Abbreviations: PMOH=probable medication-overuse headache; PEOH=probable ergotamine-overuse headache; PAOH=probable analgesic-overuse headache.
Discussion

The etiopathogenesis of MOH is not clearly defined. Genetic factors, psychotropic effects and antinociceptive peripheral and central regulation (neural plasticity) are thought to be involved in the etiology (9-11). It is suggested that ergotamine may affect migraine headache in three ways: first, it may reduce the release of neurogenic inflammatory mediators by activating serotonin 5HT1B/1D receptors located in afferent nerve endings of the trigeminal nerve. Second, it may inhibit neuronal hyperactivity by activating serotonin 5HT1B/1D receptors located in the neurons of the trigeminal caudal nucleus, which is located at lower brain-stem level. Third, it may cause vasoconstriction of the meningeal vessels within the neurogenic inflammatory territory, again by activating serotonin 5HT1B/1D receptors (12-14). Although vasodilatation-related plasma protein extravasation is a prevalent hypothesis in migraine pathophysiology and vasoconstriction is suggested to be the mechanism of action of many antimigraine drugs such as ergotamine, there are reports in the literature which do not support this hypothesis. These reports suggest that the action of ergotamine is probably not mediated only by vasoconstriction of the cerebral arteries (4). In fact, our study supports these reports indirectly. In the PEOH group, the mean BFVs in the BA and MCA were significantly increased when compared with those of the PAOH and control groups. In addition, the BFV in the ACA was increased, although this increase was accepted as statistically insignificant. These results showed us that these vessels underwent vasodilatation. During the TCD examination, performed in the morning, all the patients reported headache even though their vessels were constricted. We hypothesized two explanations for this situation: first, that the effect of ergotamine on headache might not be mediated by vasoconstriction of the cerebral arteries – other authors, too, have advanced this hypothesis (15-17) –, and second, that although the mean BFVs of the PEOH group were significantly increased in comparison to those of the control group, it could be that even more vasodilatation is needed to achieve the antinociceptive effect in the PEOH group. In fact, it is known that chronic or frequent exposure to 5HT1B/1D agonists results in a decrease in the number of 5HT receptors and changes in the antinociceptive pathways (13). No statistical analysis was performed to evaluate possible correlations between changes in BFV and pain side or intensity in the patients as we did not observe any relationship between these parameters clinically. Another finding obtained in the PEOH group was that 5HT1B/1D receptors were localized mainly in the MCA and BA. Limmoth et al. reported similar results in their study (18). In animal models, it was shown that chronic use of drugs mediated via 5HT1B/1D receptors caused a significant decrease in the number of these receptors located in the cortex and brain stem (16).

The mean BFVs in the MCA and BA were found to be significantly decreased in the PAOH group when compared to the PEOH group. In addition, the mean BFVs in all the blood vessels in the PAOH group were found to decreased, although not statistically significantly, in comparison to the control group. This result showed us that the intracranial vessels of the patients in the PAOH group were more dilated than those of the controls. It is known that analgesic drugs act via inhibition of cyclooxygenase I or II, enzymes that mediate the synthesis of prostaglandin from arachidonic acid. Besides, acetaminophen and dipyrone have been suggested to provide an analgesic effect by acting on the serotonin and opioid peptide systems centrally (19,20). Chronic drug use in PAOH patients results in changes in the antinociceptive system receptors, activation of nociceptive “on-cells” facilitating nociceptive reflex responses in ventral medulla, and changes in the enzyme activities on which they show their effects (11,20).

A known vascular side effect of NSAIDs is their tendency to increase blood pressure in hypertensive patients due to their antidiuretic effects, which are associated with inhibition of prostaglandin synthesis and a tendency to vasoconstriction (21). On the basis of this observation of the effects of NSAIDs in hypertensive patients, it can be hypothesized that the increased BFV in the PAOH patients is correlated with the vasoconstriction mediated by chronic exposure to NSAIDs. However, since our patients were compared to controls, and hypertensive patients were not allowed to enter the study, we were not able to confirm this hypothesis. Also, the slight decrease in BFV, which indicates vasodilatation, is not the result we would have expected. This vasodilatation might be explained speculatively by receptor blockage or failure in the neural reflex mechanism in these arteries. In addition, it has been reported that changes in the receptor level and enzyme activities occur significantly faster in PAOH patients (11). Besides, we may draw a hypothesis from these results: it has been reported in many studies that after drug withdrawal, the most important factor predicting prognosis is the kind of the drug overused in MOH patients. Patients overusing analgesics not only suffer from severe withdrawal symptoms but also show a high recurrence rate (21-23). In addition to this in MOH patients, the critical duration of overuse is longest for analgesics (4.8 years), shortest for triptans (1.7 years) and between the two for ergotamine (2.7 years) (10). In our study group, to achieve ho-

### Table III - Mean blood flow velocity values (cm/sec±SD) of all vessels in patients and controls.

<table>
<thead>
<tr>
<th>Artery</th>
<th>PEOH</th>
<th>PAOH</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilar</td>
<td>46.81±9.79*</td>
<td>40.63±6.07</td>
<td>40.9±2.09</td>
</tr>
<tr>
<td>Middle cerebral</td>
<td>65.14±13.38*</td>
<td>53.8±12.14</td>
<td>56.25±3.77</td>
</tr>
<tr>
<td>Anterior cerebral</td>
<td>57.2±12.51</td>
<td>51.29±10.14</td>
<td>53.5±6.04</td>
</tr>
</tbody>
</table>

Abbreviations: PEOH=probable ergotamine-overuse headache; PAOH=probable analgesic-overuse headache. * p<0.05.
mogeneity, patients with similar duration of drug intake were chosen. Despite this similarity of duration, we found that more severe functional changes or disorders in neural receptors and nociceptive and vascular reflex were observed in the PAOH group. The severe and long-lasting withdrawal symptoms and the high recurrence rate in patients with PAOH seemed to correlate with these results. The increased BFV in PEOH patients was an expected result and it was related to increased rather than altered function. In this group, drug withdrawal symptoms were milder and short-lasting.

In conclusion, our results show that ergotamine increases BFV via vasoconstriction especially of the BA and MCA, but this predictable consequence is not effective in relieving the headache. We also suggest that 5HT1B/1D receptors are mainly localized in the BA and MCA, analgesic overuse results in a functional disorder of neuronal receptor and neurovascular reflexes and may cause a reduction of intracerebral vessel tone, leading to vasodilatation. We also think that this last finding may provide an explanation for the observation, reported in previous studies, that withdrawal symptoms are more severe and long lasting in PAOH patients. In our opinion, although the measurements in the PAOH patients did not statistically differ from those recorded in the control subjects in our study, further investigations including other neuroimaging techniques in larger patient groups are needed in order to observe minor changes in BFV.

References

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