Antimigraine drug sumatriptan increases blood flow velocity in large cerebral arteries during migraine attacks

J.F.V. Caekebeke, MD; M.D. Ferrari, MD; C.P. Zwetsloot, MD; J. Jansen; and P.R. Saxena, MD, PhD

Article abstract—Sumatriptan, a novel selective 5-hydroxytryptamine<sub>1D</sub> (5-HT<sub>1D</sub>) receptor agonist, which is highly effective in the acute treatment of migraine attacks, blocks dural neurogenic plasma extravasation and constricts cranial blood vessels in animal experiments. We measured intra- and extracranial blood flow velocities (BFV) with a transcranial Doppler device in 67 patients during a spontaneous migraine attack, before and after treatment with 3 mg or 6 mg subcutaneous sumatriptan or placebo. Sumatriptan, but not placebo, significantly increased BFV (cm/sec) in the internal carotid and middle cerebral arteries on both sides, without detectably changing the BFV in the common and external carotid arteries. The rise in BFV increased with the dose of sumatriptan, parallel to an increase in proportion of patients improved. There were no significant changes in heart rate, blood pressure, or respiratory frequency after treatment with sumatriptan. The increase in BFV probably reflects vasoconstriction of the large basal intracranial arteries, which may be a mechanism for the antimigraine action of sumatriptan.

Sumatriptan is a novel selective 5-hydroxytryptamine<sub>1D</sub> (5-HT<sub>1D</sub>)-like receptor agonist, highly effective in the acute treatment of migraine attacks. Following subcutaneous (sc) injection with 6 mg sumatriptan, nearly 90% of the patients improve within 2 hours.

Sumatriptan shows a remarkable selective pharmacologic profile. In animal experiments, it has a marked vasoconstrictor effect on cephalic arteriovenous anastomoses, redirecting the blood flow to the capillary bed. Sumatriptan also blocks neurogenic plasma extravasation from blood vessels in the dura mater of the rat, presumably by presynaptic inhibition of vasoactive neuropeptide release.

In humans, little is known about the pharmacologic actions of sumatriptan and its actual mechanism of action in migraine. A vasoconstrictor effect would be compatible with the vascular hypothesis for migraine, suggesting that vasodilatation of intracranial blood vessels is crucial for the development of the migraine headache. A neuronal effect would support the neurovascular hypothesis that the migraine headache is not due to vasodilatation but is caused by an axonal reflex mechanism in the trigeminovascular system. Both mechanisms may be involved.

The transcranial Doppler technique is a noninvasive and relatively easy technique to measure changes in blood flow velocity (BFV). With constant blood flow, increase of BFV indicates vasoconstriction, whereas decrease of BFV indicates vasodilatation.

We therefore investigated whether sumatriptan changes the BFV during spontaneous migraine attacks in the common carotid (CCA), external carotid (ECA), internal carotid (ICA), and middle cerebral (MCA) arteries. We also studied whether this effect would be different at the headache and nonheadache sides.

Methods. This study was performed as part of two consecutive, double-blind, placebo-controlled, in-hospital clinical trials in which patients were treated during spontaneous migraine attacks with various doses of sc sumatriptan. In the first trial, patients were treated with placebo or 1, 2, or 3 mg sc sumatriptan. If the patient had not improved sufficiently after 30 minutes, a second sc injection with 3 mg sumatriptan was given. In the second trial, patients received placebo or 6 mg sc sumatriptan. If the patient had not improved sufficiently after 60 minutes, a second sc injection with 6 mg sumatriptan was given.

We measured the BFV in the CCA, ECA, ICA, and MCA on both sides of the head, just before and 30 minutes after the final sc injection of sumatriptan with an
EME TC2-64B transcranial pulsed Doppler system (EME, Uberlingen, Germany). We used a hand-held 2-
MHz probe for the MCA and a 4-MHz probe for the CCA, ECA, and ICA. Repeated measurements within each
patient were obtained at an identical and vessel-specific depth. We determined both the systolic peak flow velocity
(cm/sec) and the mean velocity (cm/sec) over a period of 5
seconds.

In addition, blood pressure (BP), heart rate, and respira-
tory frequency were measured.

Patients. We included patients with migraine with or
without aura, aged 18 to 65 years. Demographic, clinical,
and study characteristics of the patients are summa-
rized in table 1. Inclusion and exclusion criteria were the
same as for the clinical trials. In summary, all patients
had a migraine history of at least 1 year with a
maximum attack frequency of six per month, but were
otherwise healthy. They typically had no cardiovascular
diseases or hypertension (≥160/95 mm Hg) and did not
regularly use opiates, major tranquilizers, ergots (≥10 mg per week), alcohol (315 g per week), or
other drugs. In addition, patients had not used migraine
prophylaxis within 2 weeks and ergot-containing prep-
rations within 24 hours before the study treatment.

Only patients who presented with moderate (grade 2)
or severe (grade 3) headache (on a 0 to 3 rating scale)
were included, and they were divided into three treat-
groups:

1. Low-dose group: Thirty-six migraine patients who
had participated in the first clinical trial and in whom
BFV was measured 30 minutes after an sc injection of 3
mg sc sumatriptan; 18 of these patients had also received
1 or 2 mg sc sumatriptan 30 minutes before the 3-mg
injection, ie, 60 minutes before the BFV measurement,
without clinical improvement. In this group, the MCA
was measured in all patients and the CCA, ECA, and
ICA in twenty-five.

2. High-dose group: Twenty migraine patients who
had participated in the second trial and in whom BFV
was measured 30 minutes after an sc injection of 6 mg
sc sumatriptan; 11 of them had received a first sc injection
of 6 mg sumatriptan 60 minutes before the second 6-mg
injection, ie, 90 minutes before the BFV measurement.
All four vessels were measured in all of these patients.

3. Placebo group: Eleven migraine patients who had
participated in the first trial and had received placebo.
The MCA was measured in all these patients and the
CCA, ECA, and ICA in seven.

The study was approved by the local ethics committee,
and patients gave written, informed consent.

Statistics. The effect of treatment on BFV in the dif-
f erent vessels was analyzed with repeated measurement
ANOVA, split-plot type. The vessels (CCA, ECA, ICA,
MCA) were analyzed separately in each of the three
treatment groups (low-dose, high-dose, and placebo).
Subjects were crossed with the repeated factors "treatment" (pre-
 and post-treatment) and "side" (right or left).
In the analysis of the low- and high-dose groups, subjects
were also nested within the nonrepeated factor "sub-
group dose" (3 mg only or 3 mg preceded by 1 mg or 2 mg
in the low-dose group; 6 mg or 6 mg plus 6 mg in the
high-dose group).

Differences in sumatriptan-induced BFV changes at
the headache and nonheadache sides were analyzed with
repeated measurement ANOVA in the 47 subjects with
unilateral headache. Subjects were crossed with the
repeated factors "treatment" (pre- and post-treatment) and
"headache side" (headache and nonheadache).

Differences in treatment effect between the three
treatment groups were analyzed with one-way ANOVA
and, when significant, followed by the Newman-Keuls
range test for multiple comparisons. We believe that,
although the data with high- and low-dose sumatriptan
were obtained in two separate studies, comparison of
these effects is allowed, because both clinical trials had a
similar design and comparable patient population (table
1) and only differed with respect to the dosage of drug
given.

Because of the multiple BFV measurements (four ves-
sels and two parameters) per patient, the strict level of
significance was set at 0.05/8 = 0.00625 (Bonferroni's
method).

Results. Clinical effect of sumatriptan. The clinical
effect of treatment on headache severity at the
time of BFV measurement is shown in table 1. In
the low-dose group, 24/36 (66%) of the patients had
improved from severe or moderately severe
headache to mild or no headache. In the high-dose
group, 20/20 (100%) had improved, and in the
placebo group 4/11 (36%). Clinical response rates
differed significantly between the low- and high-
dose groups ($\chi^2$, 8.5; $p < 0.005$) and between the
high-dose and placebo groups ($\chi^2$, 16.4; $p = 0.0001$).
The difference between the low-dose and placebo
groups was near significant ($\chi^2$, 3.2; $p = 0.07$),
probably due to small numbers in the placebo group.

Vital signs. In none of the treatment groups was
there a significant difference between measure-

Table 1. Demographic and clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Sumatriptan</th>
<th>Low dose</th>
<th>High dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Subgroup for CCA, ECA, ICA</td>
<td>25</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Age (mean ± SD; yrs)</td>
<td>43.8 ± 10.1</td>
<td>45.0 ± 8.8</td>
<td>43.9 ± 12.5</td>
</tr>
<tr>
<td>Female/male</td>
<td>24/12</td>
<td>18/2</td>
<td>6/6</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>31</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Duration of attack prior to treatment (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>300</td>
<td>420</td>
<td>240</td>
</tr>
<tr>
<td>Range (60-2,100) (180-3,000) (160-1,440)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache localization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>11</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Right/left sided</td>
<td>12/13</td>
<td>10/5</td>
<td>2/5</td>
</tr>
</tbody>
</table>
| Headache severity post-
treatment* | | | |
| Grade 0/1 | 24 | 20 | 4 |
| Grade 2/3 | 12 | 0 | 7 |
| Low dose: 3-6 mg sumatriptan; high dose: 6-12 mg sumatriptan. |
| MCA Middle cerebral artery. |
| CCA Common carotid artery. |
| ECA External carotid artery. |
| ICA Internal carotid artery. |
| * Headache severity: grade 0/1 = no or mild pain, grade 2/3 = moderate or severe pain; pretreatment, all patients had grade 2/3. |
Table 2. Peak and mean blood flow velocities (cm/sec; group means ± SD for the mean of the right and left vessels) before and after treatment with placebo or low- or high-dose sumatriptan during migraine attacks.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low dose</th>
<th>High dose</th>
<th>( p_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak BFV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA</td>
<td>(n = 7)</td>
<td>(n = 25)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>54.7 ± 21.7</td>
<td>52.9 ± 13.5</td>
<td>54.6 ± 10.7</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_1 )</td>
<td>0.06</td>
<td>0.07</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>ECA</td>
<td>(n = 7)</td>
<td>(n = 25)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>54.4 ± 11.2</td>
<td>48.9 ± 13.2</td>
<td>51.1 ± 10.1</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_1 )</td>
<td>0.02</td>
<td>0.1</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>ICA</td>
<td>(n = 7)</td>
<td>(n = 25)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>56.3 ± 13.2</td>
<td>53.4 ± 13.0</td>
<td>58.8 ± 13.0</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_1 )</td>
<td>0.4</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Mean BFV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA</td>
<td>(n = 7)</td>
<td>(n = 25)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>22.4 ± 5.8</td>
<td>23.0 ± 5.4</td>
<td>25.9 ± 5.7</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_1 )</td>
<td>0.9</td>
<td>0.1</td>
<td>0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>ECA</td>
<td>(n = 7)</td>
<td>(n = 25)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>22.0 ± 5.2</td>
<td>18.2 ± 4.9</td>
<td>21.2 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_1 )</td>
<td>0.09</td>
<td>0.8</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>ICA</td>
<td>(n = 7)</td>
<td>(n = 25)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>34.4 ± 7.6</td>
<td>32.6 ± 6.5</td>
<td>39.8 ± 10.0</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_1 )</td>
<td>0.5</td>
<td>&lt;0.01</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>MCA</td>
<td>(n = 11)</td>
<td>(n = 26)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>65.4 ± 12.2</td>
<td>60.9 ± 14.0</td>
<td>67.7 ± 15.2</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_1 )</td>
<td>0.05</td>
<td>0.04</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\( p_1 \) for intra-individual difference before and after treatment (repeated measurement ANOVA).

\( p_2 \) for difference between treatment effects in the three treatment groups (one-way ANOVA).

ments before and after treatment for systolic BP (overall mean, 132 ± 15 versus 128 ± 16 mm Hg), diastolic BP (54 ± 8 versus 85 ± 9 mm Hg), heart rate (68 ± 10 versus 66 ± 8 BPM), and respiratory frequency (12 ± 4 versus 11 ± 3 per minute). There were also no differences between the basal values of the three treatment groups.

**Effect on blood flow velocity.** There were no significant (\( p > 0.05 \)) interactions between the treatment effect and side of measurement (right or left), and no significant differences between the BFV values obtained in right- and left-sided vessels. Likewise, in the 47 patients with unilateral headache during the attack, the BFV values and the effect of sumatriptan on the BFV did not differ significantly between the headache and non-headache sides. Therefore, BFVs are presented as the mean BFV of the right and left vessels. Further, subgroup analysis did not disclose significant differences within the low-dose sumatriptan group between the changes in BFV in those patients who had received 3 mg only and those patients who had already received 1 or 2 mg 30 minutes previously. Likewise, there were no significant differences within the high-dose sumatriptan group between those patients who had received only one sc injection of 6 mg and those who had received two 6-mg injections with a 60-minute interval. Therefore, the data are grouped and presented for the whole low- and high-dose sumatriptan groups.

Table 2 shows the peak and mean BFV in the CCA, ECA, ICA, and MCA before and after treatment with placebo or sumatriptan. Moreover, \( p \) values are given for the treatment effects (difference between the pre- and post-treatment values; \( p_1 \)) and for the difference in treatment effect between the three treatment groups (\( p_2 \)).

Treatment effects were similar for the peak and mean BFV values. After treatment with placebo, BFV was unchanged in the CCA, ECA, and ICA, and decreased near significantly in the MCA. After low doses of sumatriptan, BFV was unchanged in the CCA and ECA, near significantly increased in the MCA, and highly significantly increased in the ICA. There were no significant differences in changes in BFV between the 12 nonresponders and the 24 responders. After high doses of sumatriptan, BFV was still unchanged in the CCA and ECA, but highly significantly increased in the ICA (24% to 25%) and MCA (13% to 16%).

The difference in degree of change in BFV (treatment effect) between the placebo and the low-dose and high-dose sumatriptan groups was statistically highly significant in the ICA and MCA (\( p < 0.0001 \) for overall difference). For both vessels, the Newman-Keuls multiple comparison test indicated highly significant intergroup differences between the three treatment effects. Thus, increase in BFV was significantly greater after high doses of sumatriptan than after low doses (\( p < 0.005 \) for mean and peak BFV values), and change after low doses of sumatriptan differed significantly from change following placebo (\( p < 0.005 \) for peak BFV values; \( p < 0.01 \) for mean BFV in MCA; \( p < 0.05 \) for mean BFV in ICA).

We also correlated total drug dose with increase in BFV in ICA and MCA. This produced highly significant (\( p < 0.005 \) in all comparisons), although rather poor, correlation coefficients (\( r \)) (about 0.40) and slopes (about +1).

Because the women:men ratio differed in the three treatment groups (table 1), we also analyzed the data by including only the values obtained in women. This produced similar results (data not shown).

**Discussion.** The main finding of our study is that sumatriptan selectively increased BFV in the internal (but not external) carotid arterial bed and markedly reduced the severity of headache during
spontaneous migraine attacks. Both effects were clearly more pronounced with the higher doses of sumatriptan and appeared dose related. In contrast, after placebo treatment, neither the clinical condition nor the BFV were significantly different.

We investigated our patients in a double-blind, placebo-controlled design as part of two of the first clinical trials with sumatriptan. This experimental design has added considerable validity to the measurements, but the tight time schedule and the lack of knowledge about exactly what to expect both in terms of clinical improvement and changes in BFV may have introduced some potential confounding factors.

First, to create sufficiently large study groups, without including the same patients in more than one treatment group, we regrouped sumatriptan-treated patients in two treatment groups. Thus, half of the patients in the low-dose group had already received 1 mg or 2 mg sumatriptan 30 minutes before the 3-mg injection, ie, 60 minutes before the BFV measurement, and 11 of the 20 patients in the high-dose group had received a first sc injection with 6 mg sumatriptan 60 minutes before the second 6-mg injection, ie, 90 minutes before the investigation. However, in both cases, subgroup comparison between those patients who were investigated after two injections and those patients who were investigated after only one injection did not disclose significant differences in the final effect on the BFV. In fact, in both the low- and high-dose groups, the subgroup that received two doses even tended to show less increase in BFV than the subgroup that received only one dose.

Further, 1 mg and 2 mg sumatriptan proved to be insufficient to cause a significant clinical improvement or change in BFV. We are therefore confident that grouping the patients in low- and high-dose treatment groups has not artefactually created nonexistent or greater differences.

A second potential confounding factor may have been the difference in time from treatment to investigation between the low-dose group (60 minutes to first injection, 30 minutes to final or single injection) and high-dose group (90 minutes to first injection, 30 minutes to final injection). We cannot exclude that this time difference may have contributed to the observed difference in BFV increase between high and low doses of sumatriptan, eg, secondary to a longer period of clinical improvement. However, both time frames are within the plasma half-life time of sumatriptan of about 2 hours. Furthermore, preliminary findings in 14 patients treated with 6 mg sumatriptan during an attack-free period have shown a similar 25% increase in BFV, which was not further increased by a second 6 mg sumatriptan injection 60 minutes later (in preparation). These observations would suggest that 6 mg is an optimal dose in terms of increase of BFV. A 6-mg dose is optimal for clinical improvement, and a second 6-mg dose does not cause additional improvement.

Third, we could not reliably measure Pco2. Sumatriptan-induced changes in Pco2 could have affected BFV. Although we cannot exclude this possibility, we believe that Pco2 was not greatly changed by sumatriptan; there are no pharmacologic clues to expect such a mechanism, and the respiration rate was not significantly altered. In addition, Friberg et al14 failed to demonstrate a significant change in end-tidal Pco2 after treatment with sumatriptan.

Blood flow through a vessel is positively related to the BFV and inversely related to the cross-sectional area of the vessel. An increase in BFV therefore suggests either a constriction of the investigated vessel, an increase in the total blood flow through that vessel, or a combination of both mechanisms. Admittedly, we cannot determine the precise mechanism of the sumatriptan-induced increase in BFV since we have not measured the cross-sectional area and blood flow. However, in animal experiments, sumatriptan decreases (and certainly not increases) total carotid blood flow and increases carotid vascular resistance. One would expect these effects to have decreased BFV, thus obscuring any increase in BFV. Notwithstanding, we observed a clear increase in BFV. Further, infusion of 5-HT causes a marked constriction of the ICA in baboons, without affecting rCBF. Finally, Friberg et al14 investigated seven patients during predominantly on pathologically distended arteries. In contrast, in a much larger and controlled study, we found no differences between the headache and attack-free period.14 Because rCBF was not changed, they concluded that sumatriptan acts predominantly on pathologically distended arteries. In contrast, in a much larger and controlled study, we found no differences between the headache and nonheadache sides. We also have found an increase in BFV during the attack-free period (in preparation). These discrepancies may be related to four of their patients being investigated during a migraine attack with aura, known to be associated with asymmetric rCBF changes. In contrast, our patients were investigated during predominantly migraine attacks without aura (table 1). In addition, Friberg et al used only 2 mg sumatriptan IV.
(which corresponds to about 2 mg sc) and did BFV measurements after 133Xe rCBF measurements, which in itself may increase BFV. 21 Diener et al investigated BFV after 4 mg sc sumatriptan in the MCA and basilar artery of six patients during the withdrawal phase from ergotamine-induced headache. Despite transient clinical improvement, there was no significant change in BFV. In our study, 3 mg sc sumatriptan was sufficient to increase BFV in normal migraine attacks. The lack of change in BFV in the study of Diener et al may have been related either to the small number of patients or to a counteracting action in ergotamine-dependent patients. This would suggest that the clinical effect of sumatriptan in treating ergotamine-withdrawal symptoms may be independent of its vasoconstrictor action. 7

We conclude that increasing sc doses of sumatriptan up to 6 mg cause both a greater increase in BFV in the MCA and ICA, presumably due to vasoconstriction, and a higher proportion of improved patients. Thus, 5-HT1\textsubscript{1} receptor-mediated vasoconstriction of the large basal arteries of the circle of Willis and the clinical efficacy of sumatriptan in the treatment of migraine attacks appear to be related. Our data, however, do not permit the conclusion that the two factors are causally related.

Acknowledgments

We would like to thank A.H. Zwinderman, Msc, Department of Medical Statistics, for statistical advice, and the Dutch Migraine Foundation, Glaxo Group Research, Greenford, UK, and Glaxo BV, Nieuwegein, NL, for financial support.

References

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*Neurology* 1992;42;1522
DOI 10.1212/WNL.42.8.1522

This information is current as of August 1, 1992