Case Report

Efficacy of Candesartan in the Treatment of Migraine in Hypertensive Patients

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Triptans are usually administered for migraine, but cannot be given to patients with malfunctioning cardiac or cerebral vascular systems, which commonly accompany hypertension. This article focuses on 8 cases in which treatment with candesartan was successful in reducing both the incidence and severity of headache in hypertensive patients with migraine. The cases reported in this article showed a mean improvement in Migraine Disability Assessment score from 29.4 to 9 points and in blood pressure from 154.9/90.4 to 129.5/81.9 mmHg, suggesting that candesartan is an extremely attractive option for the treatment of migraine. Although recent studies have reported the efficacy of candesartan for treating migraine, there has been no description of its potential advantages over other prophylactic drugs. The present study included patients who could not tolerate triptans for whom triptans were contraindicated, several patients for whom other migraine prophylactic drugs showed little or no effect, and one patient for whom candesartan was prescribed initially for hypertension, but was also found to be therapeutic for migraines. Thus candesartan is considered to be a unique, attractive choice of prophylactic agent for migraine complicated by hypertension. (Hypertens Res 2004; 27: 441–446)

Key Words: angiotensin II receptor blocker, candesartan, migraine, hypertension

Introduction

Migraine affects approximately 10% of the adult population and is particularly common in women. The disease principally affects people in their prime working years, often striking those who have experienced headache from childhood. During a migraine attack patients often must curtail their work and other activities, so that the disease has high economic and social costs. Migraine differs considerably from tension headache, and is thought to be precipitated by excessive cerebral vasodilation and localized inflammation. Attacks, which occur from once or twice a month to several times a week, are characterized by repeated pulsating headache that persists for 4 to 48 h and then resolves without treatment. The classical migraine attack occurs in a characteristic manner (1). Triptans provide noticeable improvement in headache intensity and duration when administered during the headache phase of the migraine (2, 3). However, these drugs are associated with specific adverse drug reactions (ADRs) such as precordial distress and drowsiness, which cannot be tolerated by some patients (4). A variety of drugs are currently being used for migraine prophylaxis, but none of them are 100% successful in preventing migraine attacks.

Meanwhile, hypertension is recognized as a serious risk factor in the development of a variety of diseases and is the single highest risk factor for stroke. Thus, antihypertensive therapy is of extreme importance, and a variety of drugs are being used for this purpose. Today the angiotensin II receptor blockers (ARB) are coming into widespread use and have attracted considerable attention due to their organ-protective actions and other specific effects. Recent reports on the cardioprotective effects of the ARB candesartan have highlighted the unique characteristics of this drug (5). More recently,
candesartan has also been reported to provide migraine prophylaxis (6), which has further sparked the interest of researchers. The present case study series focuses on the therapeutic effects of candesartan in patients with hypertension and migraine. Selected patient profiles are used as a basis for discussion of the significance of candesartan as an antimigraine drug.

Case Studies

Case 1
A 35-year-old woman. From the age of 18 years, the patient began to notice occasional severe headaches, sometimes accompanied by vomiting. From April 2003, headaches increased to an average of 3 or 4 per month; the incidence increased again in June, and she was treated with nonsteroidal anti-inflammatory drugs (NSAIDs). When the headaches became still more frequent she was referred to our hospital as an outpatient. At her initial examination, her blood pressure was 148/88 mmHg and her Migraine Disability Assessment score (MIDAS) was 20 points. A regimen of sumatriptan was prescribed. Although this treatment was somewhat effective, frequent headaches continued, so concomitant therapy with candesartan 8 mg was added. Approximately 1 week after the start of candesartan administration, the frequency of her headaches declined, and in the second week her headaches vanished completely. After 1 month, her blood pressure was successfully controlled at 118/88 mmHg, and she experienced no headaches for several months under candesartan administration. In August she underwent surgery for uterine myoma, with no recurrence of migraine attacks. At present (October 2003), her migraines continue to be prevented by oral candesartan monotherapy.

Case 2
A 44-year-old woman. From the age of 15 years, the patient experienced occasional pain behind the eyes and pulsating unilateral headache, sometimes accompanied by vomiting. Beginning in November 2002, the pulsating headaches worsened, sometimes persisting for 2–3 h, and sumatriptan was prescribed. Although the drug relieved her headaches, she was unable to tolerate the precordial distress that she experienced with its use. When she presented at our hospital for treatment for headache, her blood pressure was 150/90 mmHg and her MIDAS was 26 points. An MRI scan was performed, with results indicating a cerebral aneurysm in the anterior communicating artery, so intra-arterial coil embolectomy was performed in January 2003. However, because her migraine attacks persisted after surgery, candesartan 8 mg therapy was initiated. This treatment brought a sharp reduction in headache frequency to approximately 1 headache per month. The patient strongly desired treatment with a triptan, so out of consideration for her previous experience of precordial distress, her prescription was changed from sumatriptan to zolmitriptan. She currently takes zolmitriptan about once a month, and is experiencing very few attacks.

Case 3
A 45-year-old man. The patient’s mother also had a history of headaches. From 20 years of age the patient became aware of headache attacks, but took no medication. From the age of 38, attacks began to occur 1–3 times weekly. At the age of 45 years, in addition to 4 or 5 attacks per month, he began to experience vomiting and dizziness along with headache and was referred to our department. NSAIDs were prescribed and were somewhat effective against the headache attacks. Because he also complained of left chest pain during the course of the disease, angina pectoris was suspected. In July his blood pressure was 174/86 mmHg, he was experiencing 1–2 migraines per week, and his MIDAS was 16 points, so a prescription for candesartan 8 mg was added to his treatment regimen. On his visit to the hospital in August, his blood pressure was 152/86 mmHg, and the headache attacks that had plagued him for over 10 years had nearly vanished. To control his hypertension, he was switched to amlodipine 5 mg. In September his blood pressure was 140/100 mmHg, but he experienced a recurrence of headache attacks 1–2 times weekly. When his antihypertensive medication was switched back to candesartan 8 mg, the headaches again vanished. His blood pressure is now being satisfactorily controlled at 134/68 mmHg.

Case 4
A 47-year-old woman. From 34 years of age the patient noticed headaches occurring once or twice a week. These attacks began with scintillating scotoma, followed by intense pulsating headache that persisted for 1 to 2 days. In 2003 the headaches worsened. The patient was referred to our hospital for in-depth testing, and her condition was diagnosed as migraine. On examination at our hospital, her blood pressure was 144/76 mmHg and her MIDAS was 22 points. She was started on a course of sumatriptan, with NSAIDs to be taken as needed, but the incidence of headache remained high. Mild hypertension had been detected, so candesartan 8 mg was added to her treatment regimen, at which point her headaches were reduced to approximately 1 per month. Improvement was also noted in headache severity, to the extent that the patient obtained adequate relief from NSAIDs alone, without the use of sumatriptan.

Case 5
A 54-year-old woman whose daughter also suffered from headaches. The patient first noticed headache in her 30s. At onset, she experienced pain behind the eyes, and sometimes
the headaches became so severe that she could not open her eyes. At 53 years of age she was examined at an urban university hospital and migraine was diagnosed. Sumatriptan was prescribed. Lomerizine was tried for migraine prophylaxis, but with no effect. When she was referred to our hospital for headache treatment, her MIDAS was 41 points. On examination, her blood pressure was 156/108 mmHg, so treatment with candesartan 8 mg was initiated. The incidence of headaches dropped to approximately 2 per month, and her sumatriptan use decreased. There was also a decrease in the intensity of the headaches occurring 2 to 3 times per month, and the patient no longer experienced attacks so severe that she could not open her eyes. During a 2-week interval when she was prevented from taking candesartan, the headaches returned.

**Case 6**

A 42-year-old man. The patient became aware of migraines in his 20s, and received a prescription for sumatriptan from his local physician. He came to our hospital because of intense precordial distress associated with the use of sumatriptan, and his prescription was changed to zolmitriptan. Up to this point the patient had used a variety of drugs for migraine prophylaxis, including valproate, β-blockers, and calcium antagonists, without effect. He was experiencing 8 to 10 migraines per month, and the headaches were accompanied by vomiting approximately twice a month. Even when he took zolmitriptan twice daily, migraine attacks occurred 4 to 5 times per month, and his MIDAS was 58 points. His blood pressure was 148/78 mmHg, so treatment with candesartan 8 mg was initiated. After beginning candesartan therapy, his blood pressure stabilized at 122/80 mmHg. There was also improvement in the incidence of headaches. He stopped taking zolmitriptan twice daily and no longer experienced headache with vomiting, and his MIDAS dropped to 31 points.

**Case 7**

A 43-year-old man. The patient became aware of headache at 41 years of age and went to a local physician. MRI and other tests were performed, and migraine was diagnosed. He experienced a feeling of dizziness followed by pulsating headache at the back of his head and behind his eyes. Because the headache attacks were occurring approximately 10 times per month, the local physician prescribed lomerizine (5 mg twice daily), but the headaches did not improve, and the patient was referred to our hospital. On initial examination, his blood pressure was 164/78 mmHg, and his MIDAS was 39 points. Treatment with candesartan 8 mg was initiated, and after 2 months the incidence of headaches had dropped to approximately 1 per month, indicating that candesartan was more effective than lomerizine for migraine prophylaxis.

**Case 8**

A 49-year-old woman. From somewhat after 30 years of age, the patient began experiencing 1 to 2 headaches per month. The headaches began with pain behind the eyes, followed by intense pulsating pain. The patient took commercially available headache preparations such as aspirin 330 mg with di-aluminate or diclofenac sodium 25 mg, but these were ineffective, so she came to our hospital. On initial examination, the patient’s blood pressure was 180/100 mmHg. Migraine was diagnosed on the basis of clinical symptoms, and her MIDAS was 19 points. Because migraine attacks were occurring once or twice a month, candesartan 8 mg was prescribed initially without sumatriptan, the patient was given NSAIDs to be taken when headache occurred, and progress was monitored. By the next month, the patient’s blood pressure had stabilized at 136/86 mmHg, and she had experienced only 1 mild migraine that did not require the use of NSAIDs. The following month no migraines occurred. The patient currently experiences approximately 1 mild headache every 2 months, and her MIDAS is approximately 6 points without the use of sumatriptan.

**Results**

The clinical features of these 8 patients are summarized in Table 1, and the MIDAS are shown in Fig. 1. The administration of candesartan apparently decreases MIDAS scores (cases 1–8) and can reduce the effective dosage for triptans and/or NSAIDs (cases 1–7). Candesartan was effective in cases where other prophylactic agents were ineffective (cases 5–7), and it alleviated migraine attacks in patients for whom triptans were restricted (cases 2, 3, 8). Patients were relieved of the adverse effects of the triptans by taking candesartan (cases 2, 6, 7). In one case, a successful treatment of hypertension by candesartan nearly eliminated migraine attacks (case 8).

The average MIDAS was 29.4 points (grade IV, severe disability) prior to administration of candesartan, and 9 points (grade II, mild or infrequent disability) after administration (Fig. 1).

**Discussion**

Triptans are contraindicated in patients with a history of myocardial infarction, with ischemic heart disease or related symptoms and signs, with variant angina pectoris (coronary vasospasm), with a history of cerebrovascular injury or transient attacks of cerebral ischemia, with peripheral vascular injury, with transient uncontrolled hypertension, or with isch-emic heart disease including myocardial infarction and angina pectoris, and in patients in whom cerebral infarction is suspected (7). Such arteriosclerotic lesions occur commonly in patients with hypertension, and no conventional therapies have been available for the treatment of migraine.
in patients with these complications.

When a migraine attack occurs it places severe limitations on the patient’s work and other interactions, so there is considerable interest in effective prevention. A variety of drugs have been tried for the prevention of migraine, including calcium channel blockers, β-blockers, antiepileptics, and antidepressants (8–10). Soon after reports on the prophylactic effects of the angiotensin II converting enzyme (ACE) inhibitor lisinopril (11), migraine prophylaxis was also reported for the ARB candesartan (6).

In the present series, candesartan treatment was used for each of 10 hypertensive patients with complications of migraine. The results showed candesartan to be effective for the treatment of migraine in 8 patients, and in the remaining 2 patients, although this treatment provided no apparent benefit, it did not provoke a worsening of migraine attacks. The 8 patients receiving candesartan showed an improvement in MIDAS from an average of 29.4 points (grade IV, severe disability) to 9 points (grade II, mild or infrequent disability), indicating that treatment was highly effective (Fig. 1). In contrast to previous studies, which have indicated that the migraine-preventing effects of candesartan are similar to those of other migraine prophylactic agents (6), our findings indicate that candesartan has unique advantages for migraine prevention in the following clinical settings: 1) when used as a migraine prophylactic in patients taking sumatriptan frequently, as in cases 1–5; 2) when used as a migraine prophylactic in patients for whom other prophylactic medications were ineffective, as in cases 5–7; 3) when used to treat

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### Table 1. Summary of 8 Patients in Whom Migraine Was Successfully Treated by Candesartan

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)/sex</th>
<th>MIDAS score before/after treatment</th>
<th>Blood pressure before/after treatment (mmHg)</th>
<th>Able to reduce dose of triptan and/or NSAID</th>
<th>Invalidity of other prophylactic drugs</th>
<th>Usage restrictions of triptans (causes)</th>
<th>Adverse effect of triptans</th>
<th>Special mention</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>35/F</td>
<td>20/0</td>
<td>144/88 ☐ 118/88</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>44/F</td>
<td>26/4</td>
<td>150/90 ☐ 138/84</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>45/M</td>
<td>16/0</td>
<td>153/107 ☐ 134/68</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>47/F</td>
<td>22/6</td>
<td>144/76 ☐ 110/70</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>54/F</td>
<td>41/16</td>
<td>156/108 ☐ 132/90</td>
<td>Yes</td>
<td>Lomerizine</td>
<td>After surgery for cerebral aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>42/M</td>
<td>58/31</td>
<td>148/78 ☐ 122/80</td>
<td>Yes</td>
<td>Lomerizine, valproate, β-blockers, dihydro-ergot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>43/M</td>
<td>39/9</td>
<td>164/78 ☐ 140/81</td>
<td>Yes</td>
<td>Lomerizine, lofazepate</td>
<td>Precordial distress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>49/F</td>
<td>19/6</td>
<td>180/100 ☐ 136/86</td>
<td>Not applicable</td>
<td>Mild bilateral lacunar infarction</td>
<td>Heavy-headed feeling</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male; MIDAS, Migraine Disability Assessment score; NSAID, nonsteroidal anti-inflammatory drugs.

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**Fig. 1. Changes in Migraine Disability Assessment score (MIDAS) before and after candesartan treatment. Significant reductions were seen in 8 of 10 patients with hypertension and migraine, and were particularly remarkable in 2 cases. This figure shows data from 8 patients whose migraine symptoms were reduced with candesartan treatment.**
headache in patients for whom sumatriptan use was limited, as in case 2; 4) when used in patients unable to tolerate sumatriptan ADRs, such as precordial distress or drowsiness, as in cases 2 and 6; and 5) as an alternative to be tried before prescribing sumatriptan in patients with hypertension presenting with the primary complaint of migraine, as in case 8 (Table 1). In particular, sumatriptan preparations are of limited use in patients with migraine after surgery for cerebral aneurysm or cerebrovascular injury, as in case 2, and for these patients candesartan is a particularly attractive treatment option. Also, our experience of giving precedence to hypertension treatment and finding that this treatment resulted in amelioration of migraine, as in case 8, suggests the usefulness of employing antecedent hypertension treatment with candesartan in some cases.

Although the mechanism of migraine disease is not yet fully understood, several factors appear to contribute. In particular, recent findings appear to indicate involvement of the trigeminovascular system, suggesting that the trigeminal nerves in the vicinity of the epidural vasculature release neuroptides that elicit neural inflammation and result in headache. The trigeminovascular theory was first propounded in 1984 by Mososkowitz (12) and colleagues, who were able to clearly show that stimulation of the trigeminal nerves around the epidural vasculature caused an inflammatory response. These findings suggest that the trigeminal nerve endings release serotonin when stimulated, which results in vasoconstriction. The aura would appear at this stage, and after exhaustion of the serotonin supply, neurogenic inflammation would be elicited in the epidural vasculature, giving rise to severe headache. Simultaneously, the excitation of the trigeminal nerves would be transmitted to the central nervous system, producing nausea, vomiting, and autonomic nervous system symptoms.

Candesartan is an angiotensin II type 1 (AT1) receptor blocker (ARB) that was initially developed as an antihypertensive agent to block the action of angiotensin II (13). It has been reported that the renin-angiotensin system has the potential to produce organ damage independent of hypertension (14), and administration of candesartan is reported to inhibit oxidative stress (15). Candesartan has also been reported to preserve the function of target organs, to improve patient prognosis after myocardial infarction, to reduce cardiomegaly (organ-protective effects), to delay progressive kidney failure, and to improve insulin resistance (16, 17). Recently, additional attention has been focused on the specific effects of this drug on the central nervous system (18). Based on these reports and because of their organ protective effects, the ARBs are considered drugs of first choice in cases complicated by diabetes (19).

Our results showed that an 8 mg dose of candesartan was quite effective in headache prophylaxis, almost completely eliminating migraine attacks in 2 patients (cases 1 and 3). Of these 2 patients, migraine recurred in 1 patient who was temporarily switched to the antihypertensive drug amlodipine, even though there was no change in the patient’s blood pressure. We thus theorize that the mechanism of migraine prophylaxis provided by candesartan cannot be attributed solely to the drug’s antihypertensive effects. Candesartan was also effective in one case where lomerizine showed no effect.

Based on the migraine mechanisms described earlier, the characteristics specific to candesartan, and the efficacy of treatment in these cases, I hypothesize that the mechanism of candesartan migraine prophylaxis involves either or both of the following: 1) inhibition of excessive vasoconstriction due to serotonin release, and 2) inhibition of neurogenic inflammation. Candesartan inhibits vasoconstriction by blocking the stimulation of AT1 receptors in vascular smooth muscle. It is possible that this action breaks the vicious circle of migraine by inhibiting excessive cerebrovascular constriction. Also, recent reports indicate that pretreatment with candesartan acts to regulate the progression of vascular permeability (20) and to deactivate the inflammatory nuclear transcription factor NF-κB induced by angiotensin II (21). These points suggest that candesartan may suppress neurogenic inflammation in the cerebral vasculature that is conducive to migraine.

Also, in addition to the confirmed antihypertensive action reported in these 8 case studies, candesartan has recently been shown to provide effective protection against death from heart failure. This makes candesartan an extremely attractive option for the treatment of both headache and hypertension in patients who find it difficult to tolerate triptans and who have ischemic heart disease, such as heart failure or angina pectoris, or cerebrovascular injury, or in those who are recovering from cerebrovascular surgery. The numerous adverse reactions associated with conventional migraine prophylactics (bradycardia with the β-blockers, cough with the ACE inhibitors, and drowsiness and lightheadedness with the antiepileptics) are seen only rarely with candesartan, making this drug easier to tolerate than the other migraine prophylactic drugs.

We found considerable dispersion in efficacy among patients, although candesartan was effective for headache in most of the patients receiving this treatment at our facility (8 of 10 cases). Clearly there is a need for further verification of the effectiveness of this treatment, including findings from multicenter, double-blind trials. No reports are currently available that provide direct comparison of the ACE inhibitor lisinopril and the ARB candesartan. However, because some angiotensin II production is non-ACE-dependent and ARBs are capable of blocking the effects of angiotensin II at the receptor level, and because ARBs are also useful in providing numerous organ-protective effects while provoking few ADRs, such as ACE inhibitor cough, candesartan may prove more useful than the ACE inhibitors in the treatment of migraine. Also, candesartan may prove more beneficial than has been currently reported for headache prophylaxis in cases complicated by hypertension. It will also be important to provide additional explication of the mechanisms of migraine prophylaxis, such as how angiotensin II...
contributes to migraine attacks, the effects of candesartan on the cerebral vasculature, and the effects of neurogenic inflammation in animal models of migraine disease.

References