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Migraine, arterial hypertension and cerebrovascular disorders. A literature review and outcomes of candesartan (Ordiss) therapy in the prevention of migraine in patients with hypertension

Abstract

According to current guidelines, migraine should be treated for at least 12months. Therefore, compliance with therapy is the main prerequisite for making it successful. Yet 40% of patients receiving beta–blockers, anticonvulsants, or antidepressants refuse to continue therapy within one month, 24% to 25% are still on treatment in 6months, and 13% to 16% take medication for 12months. The main reason to refuse therapy, particularly during the first few weeks, is poor tolerability of these drugs (psychotropic effects, sedation, bradycardia).The goal of the study was to evaluate the efficacy and safety of candesartan (Ordiss) in patients with chronic migraine (diagnosed according to the ICHD III criteria, 2013) and hypertension (systolic blood pressure (BP) above 140mm Hg, diastolic–above 90mm Hg).Treatment was administered to 72 patients with chronic migraine and hypertension (9 men and 63 women, mean age 46.4±9.7years). Efficacy was assessed using analysis of headache diary data (number of days with headache, number of days with migraine). BP levels were recorded at each visit. Assessments were performed before treatment, at 1month, at 3months, and at 6months. Significant reductions were observed in the number of days with headache, from 22.3±6.0 days to 10.4±3.5days at one month, 8.8±3.1days at three months, and 6.2±2.7days at six months of therapy ($p<0.01$ for all comparisons). There were also statistically significant reductions in the number of days with migraine: from 16.9±5.4 days prior to treatment to 7.3±2.9days at one month, 6.5±2.7days at three months, and 4.9±1.8days at sixmonths. Treatment with candesartan (Ordiss) also resulted in normalization of BP in 92.8% of the subjects. Two patients stopped treatment after experiencing general weakness and increased fatigue. Five subjects (6.9%) also reported general weakness and increased fatigue, but these events proved to be transient. Candesartan (Ordiss) can be recommended for treatment of patients with chronic migraine and hypertension.

Keywords: migraine, chronic migraine, treatment of migraine, hypertension, candesartan, Ordiss

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Abbreviations: BP, blood pressure

Introduction

Episodic migraine and chronic migraine are very common in Russia. In particular, a large–scale epidemiological study demonstrated that the prevalence of migraine in the Russian Federation is 20.8%, and that of chronic headache is 10.5%.[1] Migraine is a chronic disease lasting many years and mostly affecting adaptation of young and middle–aged people of working age, thus leading to considerable economic burden. For instance, the financial loss associated with low productivity and disability of people suffering from episodic migraine in the Russian Federation is 460 billion rubles per year, and that from chronic headache is 590billion rubles per year.[2] Updated guidelines of Russian headache experts on the diagnosis and treatment of migraine were published in 2017.[3] According to these recommendations, the following agents may be used for the treatment of frequent episodic and chronic migraine:

i. Beta–blockers (metoprolol, propranolol), Level of Evidence A;

ii. Angiotensin II receptor antagonists (candesartan),

iii. Anti–epileptic drugs (valproic acid, topiramate), Level of Evidence A;

iv. Botulinum toxin type A (only in chronic migraine), Level of Evidence A;

v. Antidepressants (amitriptyline, venlafaxine), Level of Evidence B;

vi. Other medicinal products (naproxen, butterbur, bisoprolol, acetylsalicylic acid, gabapentin, magnesium sulphate, chamomile, riboflavin, coenzyme Q10 (idebenone), lisinopril, verapamil), Level of Evidence C.

Certain hopes have been pinned on the emergence of the new class of drugs for the treatment of migraine, which are currently being investigated in Phase III clinical studies and undergoing subsequent registration, i.e. monoclonal antibodies to calcitonin gene–related peptide or its receptor (fremenezumab, erenumab, eptinezumab, galcanezumab).

According to current guidelines, migraine should be treated for at least 12months.[3] Therefore, compliance with therapy is the main prerequisite for making it successful. Yet 40% of patients receiving beta–blockers, anticonvulsants, or antidepressants refuse to continue therapy within one month, 24% to 25% are still on treatment in 6months, and 13% to 16% take medication for 12months. The main reason to refuse therapy, particularly during the first few weeks, is

poor tolerability of these drugs (psychotropic effects, sedation, bradycardia). Therefore, good tolerability is one of the basic requirements for state–of–the–art migraine treatment options.

The need for treatment and prevention of migraine is due not only to the aforementioned economic factors, but also to the current conception of this disease and its prognosis. Several meta–analyses have demonstrated that migraine increases the risk of ischaemic stroke 1.6–to 2.04–fold.[4,5] The risk of stroke increases along with the frequency of migraine attacks: if the frequency exceeds 13 attacks per year, the risk of stroke increases 10times.[6]

Stroke has been shown to occur at a younger age and produce deeper damage in migraine sufferers, as compared with non–migraine patients. In particular, a study reported by Mawet J[7] compared the brain damage volume evaluated using diffusion weighted MRI (necrosis volume) and the damage volume assessed with perfusion MRI (volume of the penumbra, i. e. the area of ischaemic tissue) during the acute period of stroke. The study revealed that in 25% of patients with migraine this ratio was at a minimal level (0.8–1), whereas only in 7% of controls it was within the same range (0.8–1). Furthermore, reperfusion did not decrease this ratio in patients with migraine. Therefore, brain tissue is more susceptible to the effects of ischaemia in migraine patients. However, a study by Eikermann–Haerter K[8] demonstrated that mice on long–term topiramate or lamotrigine dosing had lower brain necrosis volumes than mice not given the drugs under the same experimental conditions of cerebral circulation impairment. This study led to a conclusion that neuronal hyperexcitability underlying migraine is responsible for poor survival of the nerve cell, whereas drugs that stabilize the neuronal membrane increase the likelihood of cell survival.

Damage to brain tissue develops in patients with migraine not only as a result of stroke. Asymptomatic ischaemic lesions are found on brain MRI in 8% of patients with migraine with aura and in 3% of patients with migraine without aura. These changes develop when migraine attacks occur once a month or more frequently; they are predominantly found in the frontal and parietal lobes, in the limbic system, and are independent of other cerebrovascular risk factors.[9,10] Besides, modern diagnostic tools have revealed thinning of the retinal nerve cell layer, which results in visual field loss.[11] The origin of these disturbances is actively discussed now: it is presumed that a role in the brain tissue damage developing in young patients with migraine is played by prothrombotic conditions, endothelial dysfunction, mitochondrial damage, and patent foramen ovale. In older patients suffering from chronic pain and resulting distress, the major risk factors of ischaemic stroke, i.e. hypertension, atherosclerosis, and diabetes mellitus, make their contribution.[12]

A population–based study conducted in the Netherlands demonstrated that patients with migraine tend to have elevated blood pressure levels (relative risk 1.76) and higher–than–normal cholesterol concentrations (relative risk 1.43), while their Framingham coronary heart disease risk score is increased twofold.[13] The large–scale population–based HUNT trial showed[14] that patients suffering from migraine are more likely than the general population to have certain risk factors, such as hypertension, increased body mass index, and hypercholesterolaemia, which increases their Framingham scores 10times. Essentially, the more frequent migraine attacks are the higher the Framingham score.[15]

The MIRACLE multicentre trial[16] investigated specific features of the comorbidity of migraine and hypertension. Arterial hypertension was observed in 19% of migraine patients, more frequently affecting patients over 45years of age. These patients typically had later migraine onset than non–hypertensive patients and earlier hypertension onset than non–migraine patients. The occurrence of cerebrovascular events was found to be 4.5% in the migraine plus hypertension group, 0.7% in migraine patients, and 3.1% in the hypertension group. The risk of transient ischaemic attack/stroke in patients with migraine and hypertension aged 40–49 years was 5times higher than in hypertensive patients of the same age. According to recently obtained epidemiological data, long–standing (over 9years), uncontrolled hypertension afflicts 41% of patients with migraine.[17]

In view of the above data, the use of candesartan in the treatment of migraine evokes special interest, particularly with regard to patients with cardiovascular risk factors, especially hypertension. The mechanism of action of candesartan is associated with selective, competitive binding to angiotensin II receptors, which interferes with the effects of angiotensin II, a key mediator of the renin–angiotensin system.[18] The drug was first tested in 1992, the first clinical studies that demonstrated the efficacy of candesartan in hypertension were conducted in 1994, and subsequent research revealed the effects of the drug in the treatment of stroke, heart failure, diabetic nephropathy, and diabetic retinopathy.[19] The SCOPE trial that included over 4,000 patients demonstrated the neuroprotective and anti–dementia effects of candesartan.[20] The action of candesartan, i. e. the anti–migraine effect, may be associated with the unique pharmacological properties of this drug. Candesartan has the greatest angiotensin II receptor binding potential, as well as the highest affinity, among the drugs of this class. Another pharmacological property of candesartan is a low pharmacokinetic variability, therefore dose titration, if required at all, may be done quickly.[21] The mechanism of action of candesartan in migraine is being studied; the role of angiotensin II receptors in the development of inflammation, neurogenesis, and pain control is being discussed.[19]

A double–blind placebo–controlled study conducted in patients with chronic migraine revealed[22] that candesartan at 16mg/day significantly decreased, as compared with placebo, the number of days with headache (13.6 vs 18.5days with headache on the average, $p=0.001$) and the number of days with migraine (9.0 vs 12.6days with migraine on the average, $p<0.001$). The use of candesartan helped reduce the severity of headache, the level of maladjustment, and the number of days off school/work. A triple–blind placebo–controlled trial compared the efficacy of candesartan (16mg), propranolol (160mg, extended–release), and placebo in patients with frequent episodic migraine.[23] Candesartan and propranolol were found to be superior to placebo in reducing the number of days with headache after treatment. Specifically, the number of days with migraine was 4.9 per month at baseline. After treatment, the number of days with migraine was 2.95 in the candesartan group, 2.91 in the propranolol group, and 3.53 in the placebo group ($p=0.02$ for each comparison versus placebo). The proportion of responders was 43% in the candesartan group (and 23% in the placebo group, $p=0.025$). Candesartan was well tolerated by the patients. Among adverse events that limited the use of candesartan in 7% of the patients, the most notable were general weakness and increased fatigue.

An indirect comparative meta–analysis of controlled studies revealed that candesartan has an efficacy comparable to that of the anticonvulsants topiramate and valproic acid.[24] A positive effect of

candesartan in combination with hydrochlorothiazide was found in migraine patients in whom a migraine attack was associated with the development of oedema.[25]

Patients and methods

The University Headache Clinic has accumulated experience in the use of candesartan (Ordiss) in patients with chronic migraine (diagnosed according to the International Classification of Headache Disorders III criteria, 2013) and hypertension (systolic blood pressure (BP) above 140mm Hg, diastolic BP above 90mm Hg).

Treatment was administered to 72 patients (9 men and 63 women, mean age 46.4±9.7years). Prior to treatment, the patients had a mean of 22.3±6.0days with headache per month and 16.9±5.4days with migraine per month. Sixty–five subjects (90.3%) met the criteria for medication–overuse headache (triptan overuse). The onset of migraine occurred at a mean age of 24.0±7.8years. Chronic migraine lasted for a mean of 10.2±9.7years. The mean age at the onset of hypertension was 42.1±8.4years. The onset of chronic migraine preceded the development of hypertension in 93% of the subjects.

Results and discussion

The mean systolic blood pressure was 155.3±10.1mm Hg, and the mean diastolic BP was 96.3±7.5mm Hg. Grade 1 hypertension was diagnosed in 86% of the patients (62 individuals), and grade 2 hypertension in 14% of them (10 subjects). Twelve patients (16.7%) had been on regular hypotensive medication (beta–blockers or ACE inhibitors), and 41 subjects (56.9%) had taken hypotensive agents only for BP elevations or from time to time. Nineteen patients (26.4%) had received no hypotensive therapy. Study subjects were administered candesartan 16mg/day (8mg twice daily, in the morning and in the evening). Patients kept a headache diary and recorded their blood pressure levels. Drug efficacy assessments were performed at 1month, at 3months, and at 6months. Two patients could not complete treatment due to general weakness. The efficacy of Ordiss in the treatment of migraine is presented in Figure 1. This figure shows that statistically significant reductions in the number of days with headache and the number of days with migraine were observed as soon as at one month of therapy. Subsequent months were also characterized by fewer days with cephalgia or migraine. This rapid effect may have been due to the fact that the dose of the drug did not have to be titrated. Study subjects started to report initial effects at 2weeks of therapy. There were 51(70%) responders, i. e. patients in whom the frequency of days with migraine had decreased by more than 50% by the third month of treatment. At the completion of the treatment course, medication–overuse headache had regressed in 56% of the patients. The drug was found to be most effective in patients with "pure" chronic migraine that was not accompanied by an exertion headache or severe anxiety–depressive or somatoform disorders.

Treatment with candesartan (Ordiss) also resulted in normalization of blood pressure in 92.8% of the subjects. Statistically significant differences were observed as soon as in the first month of therapy (Figure 2).

Ordiss was well tolerated by the patients. Two patients stopped treatment after experiencing general weakness and increased fatigue. Five subjects (6.9%) also reported general weakness and increased fatigue, but these events proved to be transient. The comparatively low cost of Ordiss therapy, as compared with treatment with other anti–migraine agents, should be mentioned.

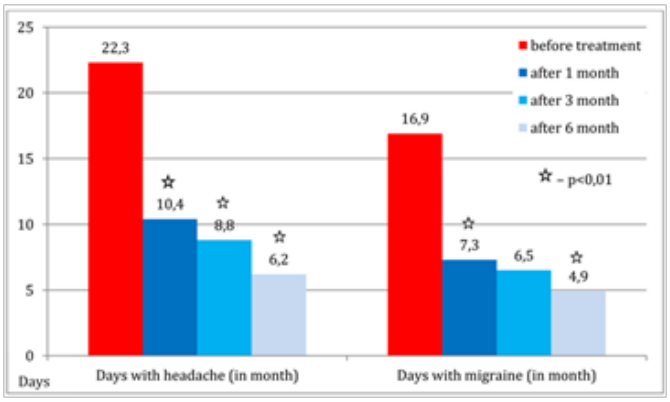

Figure 1 Efficacy of candesartan (Ordiss) in reducing the frequency of days with headache and days with migraine.

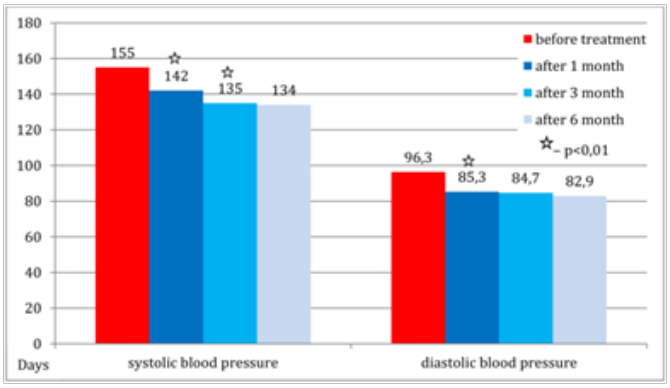

Figure 2 Efficacy of candesartan (Ordiss) in the treatment of hypertension.

Conclusion

Candesartan (Ordiss) can be recommended for patients with chronic migraine and concomitant hypertension. This clinical experience has a number of limitations (there was no placebo control); however, it reflects the real clinical practice. Efficacy studies have to be conducted for long–term candesartan therapy, including its use in the prevention of stroke, in patients with migraine. The presented clinical results also raise the problem of inadequate blood pressure control, self–administration of medication, and uncontrolled use of drugs relieving migraine attacks (triptans), which can also elevate blood pressure in patients with chronic migraine and hypertension.

Running head

Candesartan (Ordiss) can be recommended for treatment of patients with chronic migraine and hypertension.

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Conflict of interest

The author declares no conflict of interest.

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