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Rizatriptan does not change cerebral blood flow velocity during migraine attacks

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Abstract

Rizatriptan represents a major advance in the treatment of migraine attack: inhibition of peripheral trigeminal nerve and constriction of intracranial extracerebral blood vessels have been proposed as its main antimigraine mechanisms of action. Although many studies may suggest that rizatriptan causes highly selective vasoconstriction within intracranial extracerebral vessels (i.e., meningeal arteries), no literature data are available to date on possible cerebral hemodynamic changes in humans after treatment with rizatriptan. The aim of this study was to evaluate the effect of rizatriptan on cerebral blood flow velocity performing transcranial Doppler during spontaneous attacks of migraine without aura. Fourteen patients suffering from migraine without aura were monitored to evaluate mean flow velocity changes on both middle cerebral arteries during migraine attack 30 min before and 120 min after oral administration of rizatriptan 10 mg. Monitoring was repeated for 30 min during the pain-free period. All patients turned out to be drug responders and no significant mean flow velocity changes were observed between the pain-free period and pre-treatment phase; besides no significant difference in mean flow velocity value have been detected between the periods after the drug administration during the attack versus both pre-treatment period and pain-free phase. These findings indicate that the antimigraine action of rizatriptan is not associated with clear intracranial cerebral hemodynamic changes and may support its cerebrovascular safety.

Keywords: Migraine; Rizatriptan; Transcranial Doppler

1. Introduction

An important contribution to the symptomatic treatment of migraine has been brought about by serotonin $(5HT)_{1B/1D}$ receptor agonists of the first- and second-generation, known as triptans [9,15]. Such drugs show a certain selectivity towards both the vasoconstrictor $5HT_{1B}$ receptors situated in the smooth muscle of meningeal blood vessels and the prejunctional $5HT_{1D}$ receptors involved in the neurogenic inflammation and central cerebral transmission of pain [16,19].

Because of the potential vasoconstricting action of triptans also in cerebral and coronary arteries [25] as documented in vitro, the contraindication for the use of such molecular entities in patients with cardiovascular and cerebrovascular risk factors still stands [13,24].

A haemodynamic effect of first the generation triptan, sumatriptan, has been documented by means of transcranial Doppler (TCD) studies; blood flow velocity (BFV) changes, indicating vasoconstriction in the main cerebral arteries of patients during migraine attack treated with sumatriptan have been detected by most studies [1,3,10,14,26], however Diener et al. [11] failed to find any change in BFV in middle cerebral artery after sumatriptan administration, both in migraine-attack period and headache-free period.

The high efficacy profile of sumatriptan as well as some of its shortcomings (low oral bioavailability, high headache recurrence and chest symptoms) have prompted the devel-

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opment of several second-generation triptans, including rizatriptan (RZT).

In animal models, RZT induces vasoconstriction of isolated dural and cerebral arteries [21,23] and inhibits the release of sensory neuropeptides from perivascular trigeminal nerves to prevent neurogenic vasodilation and extravasation in the dura mater [28]. In humans, vasoconstrictor and neural effects, central and peripheral, have been proposed as mechanisms by which RZT relieves headache [16].

Even if, according to findings from several studies, rizatriptan may be expected to cause highly selective vasoconstriction within intracranial extracerebral vessels (i.e., meningeal arteries), no literature data are available to date on possible cerebral hemodynamic changes in humans after rizatriptan treatment.

The aim of this study was to evaluate the effect of RZT on cerebral BFV performing TCD monitoring during spontaneous attack of migraine without aura.

2. Material and methods

Fourteen patients (10 women and 4 men, mean age 40.6 ± 12.2 years, range 25–58 years) with migraine without aura diagnosed according to International Headache Society criteria [17] were evaluated at the Headache Center of the Neuroscience Department, Pisa University.

The criteria of inclusion were an attack frequency of less than four attacks per month and pain habitually moderate or severe at the attack onset according to the last 3 months headache diary, illness duration longer than 12 months, absence of pharmacological prophylaxis and absence of other vasoactive drugs in the last 3 months, no history of internal medicine or neuropsychiatric pathologies, normal findings on cranial CT scan and/or MRI, absence of carotid stenosis documented by Duplex scanner, and absence of cerebrovascular and cardiovascular risk factors. All patients were naive to triptans and gave their informed consent before being admitted to the study. Drug antimigraine efficacy was evaluated by use of the pain relief criterion that is defined as a decrease from an initially moderate or severe headache to a mild or no headache 2 h after treatment.

A TCD (DWL Multidop X4-TCD 7, FRG) device using a head metallic support fixed on both transtemporal windows was employed for simultaneous and bilateral monitoring of the mean flow velocity (MFV) in the left and right middle cerebral arteries (MCA). MFV was calculated as diastolic velocity + one-third (systolic velocity − diastolic velocity). Monitoring was started as soon as possible after the migraine onset with an average latency of 50.7 ± 15.1 min. Non-invasive arterial blood pressure, cardiac and respiratory frequencies and PO_2 changes using digital oximetry were also monitored.

All patients underwent TCD monitoring in two different sessions: during the spontaneous attack period and during the pain-free period. During the spontaneous attack period, the recording lasted 150 min and included five periods of 30 min each: a pre-treatment period (P_0) and four periods after administration of RZT 10 mg given orally (P_1 = 0–30 min, P_2 = 31–60 min, P_3 = 61–90 min and P_4 = 91–120 min). In all cases, pain has to be moderate or severe at the migraine attack onset (i.e., pre-treatment period). Monitoring was then repeated for 30 min during the pain-free period (i.e., intercritical period, $P_{\text{int.}}$) at least seven days from the last attack. In each of these periods, MFV relative to 30 intervals lasting 60 s was considered and the average value was calculated. Such MFV values detected during each period after treatment (P_1, P_2, P_3 and P_4) were compared to average values found during P_0 and $P_{\text{int.}}$ periods.

Statistical analysis was performed using non-parametric Wilcoxon's test. The level of statistical significance was $p < 0.05$. In single patients, only variations greater than 15% between MFV values obtained at different post-treatment periods and those obtained at P_0 and $P_{\text{int.}}$ were considered significant according to Diener et al. [11].

3. Results

After treatment with RZT, all patients were found to be responders, i.e., they showed significant antimigraine drug-related benefit according to the above-mentioned pain relief criterion. Two patients reported drowsiness as a side effect, however, without producing interference in their normal daily activities.

No differences were detected in MFV values between the left and right MCA during the entire monitoring period (Table 1). MFV values recorded in the right and left MCA during pre-treatment period (P_0) and pain-free period ($P_{\text{int.}}$), indeed, did not significantly differ. Moreover with regard to treatment phase MFV values detected in the right and left MCA during the migraine attack in the different periods after administration of RZT (P_1, P_2, P_3 and P_4) showed no significant differences when compared to the pre-treatment period (P_0) even if during the later periods (P_3 and P_4), a trend towards reaching statistical significance ($p = 0.05$) was

Table 1
Mean flow velocity ± S.D. (cm/s) comparison between right and left middle cerebral artery (MCA) during pain-free period and migraine attack, before and after rizatriptan (RZT) administration

	MCA		
	Right	Left	p
Pain-free period			
$P_{\text{int.}}$: 0–30 min	62.5 ± 6.9	62.4 ± 12.2	0.24
Migraine attack before RZT			
P_0: 0–30 min	61.6 ± 7.7	64.5 ± 12.2	0.19
Migraine attack after RZT			
P_1: 0–30 min	61.1 ± 7.7	64.7 ± 11.4	0.25
P_2: 31–60 min	60.2 ± 6.0	63.3 ± 10.9	0.26
P_3: 61–90 min	62.4 ± 8.8	62.8 ± 10.6	0.48
P_4: 91–120 min	64.7 ± 8.6	62.7 ± 9.3	0.34