Donitriptan Selectively Decreases Jugular Venous Oxygen Saturation in the Anesthetized Pig: Further Insights into Its Mechanism of Action Relevant to Headache Relief

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ABSTRACT

The effects of donitriptan on systemic arterial-jugular venous oxygen saturation difference were evaluated in pentobarbitone-anesthetized pigs. Oxygen and carbon dioxide partial pressures in systemic arterial and jugular venous blood as well as hemoglobin oxygen saturation were determined by conventional blood gas analysis. Vehicle (40% polyethylene glycol in saline, n = 9) or donitriptan (0.01, 0.04, 0.16, 0.63, 2.5, 10, and 40 μg/kg, n = 7) were cumulatively infused over 15 min/dose. The involvement of 5-hydroxytryptamine1B (5-HT1B) receptors was assessed in the presence of the 5-HT1B/1D receptor antagonist, GR 127935. Donitriptan decreased markedly and dose dependently jugular venous oxygen saturation [ED50 0.5 (0.3–1.1) μg/kg], in parallel with increases in carotid vascular resistance [ED50 0.9 (0.7–1.1) μg/kg]. Since arterial oxygen saturation and partial pressure remained unchanged, donitriptan significantly increased arteriovenous oxygen saturation difference from 0.63 μg/kg (maximal variation: 57 ± 18%, P < 0.05 compared with vehicle). Unexpectedly, donitriptan from 2.5 μg/kg induced marked and significant increases in carbon dioxide partial pressure (pVCO2) in venous blood (maximal increase 18.8 ± 5.7%; P < 0.05 compared with vehicle). Pretreatment with GR 127935 (0.63 mg/kg, n = 5) abolished the fall in venous oxygen saturation and the increase in carotid vascular resistance and reduced the increases in pVCO2 induced by donitriptan. The results demonstrate that donitriptan, via 5-HT1B receptor activation, decreases the oxygen saturation of venous blood draining the head, concomitantly with cranial vasoconstriction. Since donitriptan also increased pVCO2, an effect upon cerebral oxygen consumption and metabolism is suggested in addition to cranial vasoconstriction, which may be relevant to its headache-relieving effects.

Donitriptan is a unique high-efficacy agonist at 5-HT1B/1D receptors; it is currently being evaluated for efficacy in the acute relief of migraine headache in phase II clinical trials (Dukat, 2001; John et al., 1999, 2000). One of the key pharmacological actions of donitriptan is 5-HT1B receptor-mediated cranioselective vasoconstriction (Tom et al., 2002). Before the advent of the triptans, the nonselective 5-HT1B Receptor agonist ergotamine (Villalón et al., 1999) was also shown to elicit selective carotid vasoconstriction confined to cephalic AVAs (Johnston and Saxena, 1978). Moreover, increases in AVOSD due to decreases in jugular venous oxygen saturation and oxygen partial pressure (pO2) without affecting systemic arterial oxygen saturation or pO2 were also observed in this study (Johnston and Saxena, 1978). However, it is presently unknown whether the recently described triptan 5-HT1B/1D receptor agonist-induced increases in AVOSD are due to changes in systemic arterial or jugular venous oxygen saturation, or both.

The aim of the present investigation was therefore to elu-
cidate the mechanism of donitriptan-induced increases in AVOSD. The results indicate that donitriptan selectively decreases jugular venous pO2 and hemoglobin oxygen saturation while increasing jugular venous pCO2 concomitantly with carotid vasoconstriction. The results are discussed in light of established mechanisms of action of triptan 5-HT1B/1D receptor agonists in relation to migraine relief.

Materials and Methods

Animal Preparation. Twenty-seven male Landrace pigs (18–24 kg; M. Gaec, Sorèze, France) were premedicated with intramuscular administration of azaperone (3 mg/kg) after an overnight fast. General anesthesia was then induced with sodium pentobarbitone (25 mg/kg, i.v.; Sanofi, Montpellier, France). The animals were intubated, ventilated by positive pressure (Alpha 100; Minerve, Eternay, France), and anesthesia was maintained with a continuous infusion via the right saphenous vein of sodium pentobarbitone (6–18 mg/kg/h). Respiratory rate and tidal volume were carefully adjusted for maintaining blood gases within physiological limits (ABL 510; Radiometer, Copenhagen, Denmark). Body temperature was maintained constant between 37° and 38.5°C by a servo-controlled heating blanket.

A standard four-limb ECG in lead II was monitored throughout the experiments. Fluid-filled catheters were inserted into the descending thoracic aorta via the right femoral artery and left saphenous vein for continuously monitoring arterial pressure and drug administration, respectively. Blood was withdrawn through this arterial line, and the right external jugular vein was catheterized for venous blood sampling to obtain measurements of arterial and venous blood gases. Another catheter was introduced into the left ventricle via the left femoral artery to determine left ventricular pressure (LVP). Subsequently, left and right common carotid arteries were carefully cleaned of surrounding connective tissue; then blood flows in each artery were measured with pulsed Doppler flow probes (Crystal Biotech, Northborough, MA). The mean total carotid blood flow (TCBF) was calculated as the sum of left and right mean carotid blood flows.

A left lateral thoracotomy was performed in the fourth intercostal space, and the pericardium was opened. Aortic blood flow (ABF) was measured with an electromagnetic flow probe (SP 2202; Gould Instrument Systems, Inc., Cleveland, OH) placed around the thoracic aorta. The left anterior descending (LAD) coronary artery was isolated, and a pulsed Doppler flow probe was placed at its proximal level. Systemic and regional vascular resistances were determined as the ratio of mean arterial pressure to aortic blood flow or mean Doppler flows, except for LAD vascular resistance (LADVR) calculated by dividing coronary perfusion pressure (i.e., the difference between diastolic arterial pressure and left ventricular end-diastolic pressure) by LAD blood flow.

These parameters are the average of all successive determinations taken during a 30-s recording period. Analog phasic pressure and flow outputs were fed simultaneously to an amplifier-recorder (Gould) and to a personal computer equipped with an analog-to-digital converter board. Using Data flow software (Crystal Biotech), analog signals were digitized every 5 ms for high resolution and subsequently stored on optical disk.

An acceptable estimate of blood flow (Q) was calculated by the following equation: \( Q = 1.25 \cdot d^2 \cdot f_d \), where \( d \) is the vessel’s inside diameter in millimeters and \( f_d \) is the Doppler shift in kilohertz.

Several blood gas parameters were determined: The oxygen and carbon dioxide partial pressure values in arterial and venous blood, pAO2, pACO2, pVO2, and pVCO2, respectively, arterial and venous pH. The arterial and venous oxygen saturation was calculated by the following equation: \( \text{OS} = C_2 \cdot O_2 \cdot Hb \times 100 / C_2 \cdot O_2 \cdot Hb + C \cdot RHb \), where OS is the arterial or venous oxygen saturation, C2 O2 Hb is the concentration of oxyhemoglobin, and C RHb is the concentration of reduced hemoglobin.

The arteriovenous oxygen saturation difference (AVOSD) was calculated as oxygen saturation in systemic arterial blood (AOS) minus the jugular venous oxygen saturation (VOS). This difference is an index of cranial O2 extraction.

Experimental Protocol. Experiments were carried out in two separate groups of pigs: vehicle (a mixture of 40% polyethylene glycol 300 in sterile saline, 0.9%, \( n = 9 \)) and donitriptan (\( n = 7 \)). After completion of surgical procedures, a stabilization period of at least 30 min was observed.

Donitriptan was infused in cumulative fashion over the following incremental dose range: 0.01, 0.04, 0.16, 0.63, 2.5, 10, and 40 \( \mu g/kg \). Each dose of drug was infused over 15 min. Preliminary studies showed that 15-min/dose was more than sufficient to achieve steady-state responses. Similarly, seven 15-min cumulative administrations of vehicle were infused in the vehicle group.

An additional group was constituted to study the effects of donitriptan (\( n = 5 \)) in presence of GR 127935, a relatively selective 5-HT1B/1D receptor antagonist (Skingle et al., 1996). The effects of GR 127935 alone were evaluated in a further group (\( n = 6 \)). In all experiments, GR 127935 was infused over 2 h at 0.63 mg/kg (De Vries et al., 1996), starting 15 min before donitriptan administration.

Drugs. Azaperone was purchased from Janssen Pharmaceuticals (Antwerp, Belgium). Donitriptan [4-[4-[2-[3-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-[N-dol-5-yloxy]-acetyl]-piperazin-1-yl]-benzonitrile hydrochloride] and GR 127935 [N-[4-methoxy-3-[4-methyl-1-piperazinyl)phenyl]-2-[N-methyl-4-[5-methyl-1,2,4-oxadiazol-3-yl]-1,1-biphenyl]-4-carboxamide dihydrochloride] were synthesized by the Department of Analytical Chemistry and Division of Medicinal Chemistry IV at the Centre de Recherche Pierre Fabre (Perez and John, 1999). Donitriptan was dissolved in 40% polyethylene glycol 300 in sterile saline (0.9%), whereas GR 127935 was dissolved in sterile saline (0.9%). Drugs were weighed as base, taking into account the salt-to-base ratio.

Data and Statistical Analysis. Dose-response curves were fitted using an operational sigmoid model (Origin; OriginLab Corp., Northampton, MA) from relative maximal effects induced by agonists. From the results of these analyses, the geometric mean dose of agonist producing 50% of the maximal response (ED50) was calculated with 95% confidence intervals.

Parameters were measured at the end of baseline period and the end of each 15-min infusion period. All values were expressed as means ± S.E.M. One-factor analysis of variance (ANOVA) with repeated measurements followed by Dunnett’s test (Sigma Stat; SPSS Science, Inc., Chicago, IL) was used to assess significance among and between groups, and the unpaired Student’s t test as an additional posthoc test was used when appropriate (Sigma Stat).

Results

Effects of Donitriptan on Blood Gas Parameters. The effects of donitriptan on blood gases are presented in Table 1. The initial oxygen partial pressure values in arterial blood (pAO2) were comparable among both groups (\( P = \text{N.S.} \)). In vehicle-treated animals, pAO2 slightly but significantly decreased throughout the experiment reaching 114.2 ± 6.3 mm Hg by the end of experiments from an initial value of 122.5 ± 5.7 mm Hg (\( P < 0.05 \); Table 1). In donitriptan-treated animals, a comparably slight decrease in pAO2 occurred. The oxygen partial pressure in jugular venous blood (pVO2) was also determined in both groups. In the vehicle group, pVO2 remained unchanged throughout the experiments (\( P = \text{N.S.} \); Table 1). Donitriptan moderately but significantly decreased pVO2 only at 40 \( \mu g/kg \) compared with vehicle; the maximal decrease reached 31 ± 6% (\( P < 0.05 \)). The initial values of

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pACO₂ measured in the donitriptan-treated group were similar to those of the vehicle group. In both groups, pACO₂ values did not significantly change between the beginning and the end of the experiments. Baseline pVO₂ values did not significantly differ between vehicle and donitriptan groups. Vehicle was devoid of significant effects per se on pVO₂ as indicated in Table 1. On the other hand, donitriptan from 2.5 μg/kg induced marked and significant increases in pVO₂ (P < 0.05 compared with vehicle group; Table 1). This constitutes one of the major findings of the present study. It is interesting to note that no significant variations in pH were found in the arterial or venous blood analyses (Table 1).

Baseline AOS values were similar in the different treatment groups (P = 0.09). AOS was not significantly affected by vehicle or donitriptan (P = N.S.). In the vehicle group, baseline and end-experimental AOS values were 99.0 ± 0.4 and 98.6 ± 0.6%, respectively. The same time points in donitriptan-treated animals were 100.1 ± 0.1 and 96.3 ± 2.1% (P = N.S.; Table 1). These results are illustrated in Fig. 1, which represents the percentage changes from baseline values for AOS and VOS. In the vehicle group, VOS remained unchanged throughout the experiment (68.8 ± 3.5 and 68.0 ± 3.7%, initial and end-experiment values, respectively, P = N.S.; Table 1). In donitriptan-treated animals, VOS decreased dose dependently (geometric mean ED₉₀ value: 0.45 μg/kg and 95% confidence limits 0.27–1.06 μg/kg), leading to statistically significant differences versus vehicle group that occurred from 0.63 to 40 μg/kg (Fig. 1). VOS decreased by 32 ± 8 and 30 ± 9% at donitriptan 10 and 40 μg/kg, respectively (both P < 0.05 compared with vehicle group). AOS remained unchanged throughout the experiment. Consequently, decreases in pVO₂ determined the increases in AVOSD. Indeed, AVOSD significantly increased from 0.63 μg/kg (maximal variation: 57 ± 18%, P < 0.05 at 10 μg/kg compared with vehicle group; Fig. 2A). In vehicle-treated animals, AVOSD did not undergo significant changes (P = N.S.; Table 1).

**Effects of Donitriptan on Hemodynamic Parameters.** The effects of donitriptan on blood pressure, heart rate (HR), and blood flows are summarized in Table 2. Under baseline conditions, these cardiovascular parameters were not significantly different from those in the vehicle group, with the exception of TCBF, which was significantly higher in donitriptan than in controls (P < 0.05; Table 2).

In vehicle-treated animals, mean arterial pressure and LVP did not undergo notable changes throughout the experiments. As indicated in Table 2, HR gradually decreased with time in this group. Aortic and coronary blood flows tended to decrease with time, whereas TCBF remained constant throughout the experiments. Vascular resistances (SVR, TCVR, and LADVR) were not significantly affected by vehicle when compared with initial values; maximal changes in SVR,
TCVR, and LADV reached: 14 ± 10%, P = N.S.; –3 ± 6%, P = N.S.; and 18 ± 10%, P = N.S., respectively.

Donitriptan elicited no or weak increases in mean arterial pressure and LVP (Table 2). Similar small decreases in HR were obtained with donitriptan or vehicle. Donitriptan markedly decreased TCBF (maximal variation –50 ± 3%, P < 0.05, versus vehicle), whereas ABF and left anterior descending coronary artery blood flow were not significantly affected compared with vehicle (Table 2). The vascular selectivity of donitriptan was assessed by the measurement of relative vascular resistances. Donitriptan evoked dose-dependent increases in TCVR, leading to a 132 ± 10% maximal increase (at 40 μg/kg, P < 0.05 compared with vehicle; Fig. 2B) with a geometric mean ED₅₀ value of 0.9 μg/kg (95% confidence limits 0.72–1.12 μg/kg). It is interesting to note that donitriptan increased TCVR with a geometric mean ED₅₀ value of 0.9 μg/kg being not statistically significantly different from that calculated for decreasing VOS (0.45 μg/kg, P = 0.195).

These increases in TCVR were significantly greater than corresponding changes in SVR and LADV. Donitriptan produced no significant changes in LADV but significantly increased SVR from 0.16 μg/kg (maximal increase 58.3 ± 14.8% at 10 μg/kg, P < 0.05 versus vehicle group).

**Effects of GR 127935.** In an additional series of experiments, donitriptan was re-examined in animals pretreated by GR 127935 (0.63 mg/kg), a relatively selective 5-HT₁B/D receptor antagonist (Skingle et al., 1996). Under these conditions, baseline pAO₂, pVO₂, pACO₂, pVCO₂, AOS, VOS, and AVOSD values were similar in vehicle- and donitriptan-treated animals (data not shown). GR 127935 alone did not significantly modify these parameters. The maximal changes in AVOSD induced by GR 127935 alone were 22 ± 11% (P = 0.27 versus vehicle without GR 127935). In the presence of GR 127935, in vehicle- or donitriptan-treated animals a comparable, slight decrease in pAO₂ occurred (maximal variation, –7.1 ± 4.8 mm Hg and –5.1 ± 2.4 mm Hg, P = 0.68, respectively). In the same man-

**TABLE 2**

Effects of donitriptan (n = 7) and its vehicle (n = 9) on hemodynamic parameters in the anesthetized pig

Mean arterial pressure (MAP), HR, LVP, ABF, TCBF, and left anterior descending coronary artery blood flow (LADBF) were measured. Data are the changes (Δ) ± SEM in hemodynamic parameters following vehicle or donitriptan administration.

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<td>LVP (mm Hg)</td>
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<td>0 ± 7</td>
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<tr>
<td>LADBF (ml/min)</td>
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<td>Donitriptan (n = 7)</td>
<td>28.5 ± 3.2</td>
<td>0.1 ± 0.7</td>
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* P < 0.05 versus vehicle group by one-way ANOVA followed by Student’s t test.
ner, pVO₂ was moderately decreased but not significantly, and this tendency appeared in both groups. GR 127935 reduced the donitriptan-induced increase in pVCO₂ (P = N.S. versus vehicle, data not shown). AOS remained constant during the experiments in vehicle- and donitriptan-treated animals, maximal variations were −0.3 ± 0.3 and −0.5 ± 0.5%, respectively. The effects of GR 127935 on donitriptan-induced decreases in VOS were also studied. GR 127935 abolished the fall in VOS induced by donitriptan. The maximal changes in vehicle- and donitriptan-treated pigs were −19 ± 10 and −9 ± 3%, respectively (P = 0.38). Thus, in the presence of GR 127935, donitriptan-induced increases in AVOSD were abolished (maximal variation 29 ± 19 versus 22 ± 11% in vehicle group; Fig. 2A).

GR 127935 per se induced a significant increase in TCVR (maximal change: 24 ± 4%, P < 0.05 compared with vehicle; Fig. 2B). On the other hand, no significant effects of GR 127935 on the other parameters were noted (except for TCBF, maximal change −17 ± 3%, P < 0.05 compared with vehicle). The effects of donitriptan on TCBF were antagonized by GR 127935. Under these conditions, the maximal decrease in TCBF in the donitriptan group reached −20 ± 7%, (P = 0.60 compared with vehicle). Figure 2B shows that GR 127935 markedly antagonized the variations in TCVR induced by donitriptan 40 μg/kg, and maximal change was −24 ± 9% (P = 0.79 compared with vehicle).

Discussion

The mechanism of donitriptan-induced increases in AVOSD was investigated in the anesthetized farm pig. Donitriptan dose dependently increased AVOSD and decreased jugular venous hemoglobin oxygen saturation from 0.63 μg/kg i.v. without affecting systemic arterial oxygen saturation. Donitriptan-induced increases in AVOSD are therefore mediated by decreased jugular venous oxygen saturation. These effects were accompanied by decreases in jugular venous pO₂ and increases in pCO₂, demonstrating augmented cephalic oxygen consumption and metabolism. Donitriptan also concomitantly and dose dependently reduced carotid blood flow from 0.16 μl/kg. The 5-HT₁B receptor antagonist, GR 127935 (Skingle et al., 1996) significantly reduced both donitriptan-induced increases in AVOSD and carotid vascular resistance, indicating the likely involvement of 5-HT₁B receptors. The present results are in agreement with a previous study (John et al., 1999) and those of a recent study (Tom et al., 2002), which showed dose-dependent 5-HT₁B receptor-mediated decreases in carotid vascular conductance due to a highly selective reduction in cephalic arteriovenous anastomotic (AVA) blood flow. These latter effects were accompanied by an increase in AVOSD (Tom et al., 2002). Indeed, since constriction of cephalic AVAs is a model which has a predictive value for antimigraine activity (Tfelt-Hansen et al., 1999), donitriptan should be effective in the acute treatment of migraine.

Donitriptan-Induced Increases in AVOSD. Donitriptan dose dependently reduced jugular VOS and pVOS without significantly affecting systemic AOS or pAO₂. Consequently, the donitriptan-induced increases in AVOSD can be explained by the selective decreases in jugular VOS. The most plausible explanation for the selective decreases in jugular VOS and pVOS evoked by donitriptan is closure of cephalic AVAs, which underlies 5-HT₁B receptor-mediated cranial vasoconstriction in the present model (Tom et al., 2002). An unexpected finding in the present study, however, was that donitriptan also dose dependently and significantly increased jugular pVCO₂. Consequently, an additional effect of donitriptan in enhancing cerebral metabolism must also be considered. Augmented pVCO₂ concomitant with decreases in pVOS are hallmark increases of increased tissue metabolism (Dejours, 1963). Systemic AOS or pO₂ were not modified by donitriptan, thereby allowing effects on hemoglobin affinity for oxygen or on pulmonary blood oxygenation to be ruled out. Metabolic acidosis can also be excluded because no variations in arterial or venous pH or pACO₂ were detected. Donitriptan significantly decreased jugular venous pO₂ and hemoglobin oxygen saturation, indicating enhanced cephalic oxygen extraction. However, one of the main observations of the present study is the marked and dose-dependent increase in jugular venous pCO₂ in the absence of changes in arterial pCO₂, which were consistently and robustly elicited by donitriptan. This strongly suggests that, in addition to promoting cephalic oxygen extraction from arterial blood, as indicated by significant decreases in venous oxygen saturation and pO₂, donitriptan also enhances tissue metabolism, as indicated by significant increases in jugular venous pCO₂. It is noteworthy that physiological arteriovenous differences in pCO₂ are small (around 5–7 mm Hg; compared with a 50–60 mm Hg difference for pO₂), indicating a relatively low sensitivity of this parameter to changes in tissue metabolism. This is due to larger (around 17-fold) tissue reserves of dissolved CO₂ compared with O₂ (Farhi and Rahn, 1960) because of the greater water solubility of the former. A small but statistically significant increase in venous pCO₂ therefore reflects marked increases in tissue CO₂ reserve and metabolism (Dejours, 1963). Consequently, it cannot be excluded that donitriptan stimulates oxygen consumption and cerebral metabolism via 5-HT₁B receptor activation, in addition to 5-HT₁B receptor-mediated vasoconstriction of cranial AVAs. It was previously reported (Johnston and Saxena, 1978) that ergotamine evoked similar changes in blood gases to those presently described for donitriptan, in increasing jugular venous pO₂ and oxygen saturation, and with a notable propensity to increasing, albeit nonstatistically significantly, pVCO₂ (Johnston and Saxena, 1978).

Such effects have not been previously described for triptans, but since most members of this drug class are also selective 5-HT₁B receptor agonists (Goadby, 1998; De Vries et al., 1999b), similar, but possibly less efficacious, actions to those presently described for donitriptan can be expected (see below).

Enhancement of Tissue Metabolism by Donitriptan. The mechanism by which donitriptan enhances cerebral metabolism clearly deserves further study. On the basis of the present results and current knowledge in the field, we tentatively propose the following scheme of events: 5-HT₁B receptor agonists have been demonstrated on endothelial cells of human brain arteries and microvessels (Riad et al., 1998; Nilsson et al., 1999; Van den Broek et al., 2002b), but their precise function is unknown. Interestingly, endothelial cells are regulators of oxygen consumption via the cytochrome c oxidase oxygen sensor (Clementi et al., 1999), and 5-HT₁B receptor activation by sumatriptan and other triptans enhances cellular metabolic rate (Pauwels, 1998). Thus, by activating endothelial 5-HT₁B receptors in the cerebral microcirculation, donitriptan could enhance oxygen consumption and tissue metabolism. This could provide an additional


The current understanding of the chief mechanisms of triptan action in relieving migraine headache, based on 5-HT1B/1D receptor activation, comprises cranial vasostriction (De Vries et al., 1999a; Pauwels and John, 1999), peripheral (Moskowitz, 1992), and central (Hoskin et al., 1996) inhibition of trigeminal afferents thus preventing neurogenic plasma protein extravasation and sensory neuromediator release (Goadsby and Knight, 1997; Llimroth et al., 2001). However, the present data suggest that donitriptan-evoked enhancement of cerebral oxygen utilization and augmented tissue metabolism provides a further, important, and complementary mechanism to cephalic AVA closure. It will be of particular interest to see whether the currently available triptans, which are considered to be partial agonists at 5-HT1B/1D receptors (John et al., 1999; 2000), are as effective as donitriptan, a high-efficacy 5-HT1B/1D receptor agonist, in respectively reducing and augmenting jugular venous oxygen saturation and pCO2, and enhancing cerebral metabolism.

In summary, donitriptan elicited selective carotid vasoconstriction and increases in AVOSD with identical potency in anesthetized pigs. Both actions were inhibited by GR 127935, indicating mediation by 5-HT1B receptors. Increases in AVOSD were mediated by decreases in jugular venous oxygen saturation and pO2 and were unexpectedly accompanied by increases in pVCO2. The most plausible explanation for these effects, with the notable exception of increased pVCO2, resides in closure of cephalic AVAs by donitriptan. However, a concomitant and complementary 5-HT1B receptor-mediated increase in cerebral oxygen extraction and enhancement of tissue metabolism is proposed as a further mechanism of action of donitriptan, which may be relevant to its migraine-relieving efficacy.

References


