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Cranial vascular effects of zolmitriptan, a centrally active 5-HT$_{1B/1D}$ receptor partial agonist for the acute treatment of migraine

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Abstract

The anti-migraine drug zolmitriptan is a novel 5-HT$_{1B/1D}$ receptor partial agonist which, unlike sumatriptan, has been shown to cross the intact blood–brain barrier. In this study we examined whether or not the ability to access the cerebro-vascular intima affects the way in which a centrally-active 5-HT$_{1B/1D}$ receptor agonist influences cranial haemodynamics. The effects of zolmitriptan on carotid arterial blood flow distribution were studied in anaesthetised cats using radiolabelled microspheres. Zolmitriptan (10–1000 μg kg^{-1} i.v.) selectively reduced arteriovenous–anastomotic (AVA) conductance producing a maximum decrease of 92.5 $\pm$ 2.3%. The drug also produced a modest reduction in extra-cerebral conductance (23.9 $\pm$ 6.5% maximum reduction at 30 μg kg^{-1}, i.v.), but was without effect on cerebral conductance. Using laser doppler flowmetry in anaesthetised cats, zolmitriptan (1–30 μg kg^{-1}, i.v.) produced dose-dependent decreases in ear microvascular conductance (15 $\pm$ 5 to 60 $\pm$ 6%) which mirrored decreases in carotid arterial conductance (12 $\pm$ 11 to 61 $\pm$ 5%). By contrast, zolmitriptan at doses up to 1000 μg kg^{-1} was without effect on cerebral microvascular conductance. Although zolmitriptan crosses the blood–brain barrier and can therefore access the cerebro-vascular intima, this study suggests that this property does not adversely affect cerebrovascular function.

Keywords: Zolmitriptan; Sumatriptan; Cranial blood flow distribution; Migraine; 5-HT$_{1B/1D}$ receptor agonist

1. Introduction

Zolmitriptan ((*S*)-4[[3-[2-dimethylamino)ethyl]-1*H*-indol-5yl]methyl]-2-oxazolidinone) is a new 5-HT$_{1B/1D}$ receptor partial agonist (Martin, 1994; Martin et al., 1997) that has recently been approved for use in the acute treatment of migraine and related vascular headaches. Clinical studies to date have shown that the orally administered drug is safe (Earl, 1996; Geraud, 1996) and highly effective at terminating the headache and associated symptoms of a migraine attack (Klein, 1995; Ferrari, 1996), with preliminary evidence for efficacy in pre-emptive treatment in some patients (Dowson, 1996; Proietti-Cecchini et al., 1997). Activation of the trigemino-vascular system is believed to be a key step in the initiation of migraine headache (see Moskowitz, 1984; Goadsby et al., 1991). The process involves an early release of sensory neuroptides (substance P, calcitonin gene-related peptide) from trigeminal sensory afferents innervating meningeal and large cerebral vessels to produce a 'nocifensor' response comprising cranial vessel dilation, endothelial fenestration and sensitisation of nociceptors leading ultimately to the perception of throbbing pain (see Goadsby et al., 1991; Buzzi and Moskowitz, 1992).

Like other drugs in this class, i.e., the ergots, sumatriptan and the other 'triptans' currently in development, zolmitriptan acts at '5-HT$_{1B}$-like' receptors to inhibit trigemino-vascular activation peripherally. Hence, each of these drugs produces constriction of cranial blood vessels in vitro and inhibits plasma protein extravasation into the dura during trigeminal stimulation (Markowitz et al., 1988; Moskowitz, 1992; Martin, 1994; Martin et al., 1997).

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However, unlike sumatriptan, zolmitriptan inhibits trigeminal activation *centrally* as well as peripherally, hence the drug accesses inhibitory 5-$HT_{1B/1D}$ receptors in the trigeminal nucleus caudalis which are not normally accessible to sumatriptan (Kaube et al., 1993; Goadsby and Edvinsson, 1994; Goadsby and Hoskin, 1996; Goadsby and Knight, 1997). To determine whether or not this central action of zolmitriptan also influences the craniovascular actions of the drug in vivo, we have examined its effects on the distribution of carotid arterial blood flow in anaesthetised cats and dogs. In addition, we have determined cerebral blood flow effects following systemic administration. The results are discussed in terms of data reported previously for sumatriptan and the ergots.

2. Materials and methods

All in vivo studies were conducted in accordance with the United Kingdom Home Office guidelines and the United Kingdom Animal (Scientific Procedures) Act 1986. Cats and dogs were used in this study to explore any species differences with respect to the pharmacology of 5-$HT_{1B/1D}$ receptors.

2.1. Anaesthetised cat: microsphere studies

Mongrel cats (male, 3–4 kg; Campbell Farms) were initially anaesthetised with isoflurane/O_2 mixture by inhalation. A polythene cannula (Portex; Hythe, Kent) was inserted into the left femoral vein and anaesthesia completed by intravenous administration of α-chloralose (60 mg kg^{-1}; BDH, Poole, Dorset) with pentobarbitone sodium (20 mg kg^{-1}; Sagatal; Rhone-Poulenc-Rorer, Dagenham, Essex). Further polythene cannulae were inserted into the abdominal aorta via the right femoral artery, to measure blood pressure and heart rate, and into the left femoral artery for blood sampling. Finally, a polythene cannula was inserted into the left lingual artery for the subsequent retrograde injection of microspheres (16 μm diameter) into the carotid arterial circulation to measure blood flows (Spierings and Saxena, 1980). The microspheres were radio-labeled with one of the γ-emitting isotopes (Ce^{141}, Ru^{103}, Sn^{113}, Sc^{46}, Nb^{95}; New England Nuclear, New England, USA). A tracheotomy was also performed and artificial ventilation maintained via a respiration pump (room air at 15 ml kg^{-1}, 30–35 breaths min^{-1}). The effectiveness of this ventilation was monitored regularly by analysis of arterial blood samples (ABL-3; Radiometer, Crawley, W. Sussex) to ensure that blood gases were maintained within acceptable limits (Green, 1979). An ultrasonic blood flow probe (Transonic Systems, NY, USA) was then placed on the left common carotid artery (via a neck incision) to measure carotid blood flow. Blood pressure, heart rate and carotid arterial blood flow were continuously recorded on a polygraph (Gould; Hainault, Essex). At the end of the surgical preparation each animal was allowed to stabilise for 30 min prior to commencing the experimental protocol.

The first injection of microspheres containing approximately 4×10^6 microspheres labeled with Ce^{141} (~10 μCi) was made following post-surgical stabilisation of animals, to allow the measurement of resting cranial blood flows and conductances. The animals were then challenged at 20 min intervals with ascending intravenous bolus doses of zolmitriptan (0–30 μg kg^{-1}, as 0.1 ml kg^{-1}) or repeated intravenous bolus injections of saline (0.1 ml kg^{-1}). Fifteen minutes after each dose, an intra-arterial injection of microspheres labeled with one of the remaining isotopes (Ru^{103}, Sn^{113}, Sc^{46} or Nb^{95}) was made. At the end of the experimental protocol, the animals were euthanised with intravenous pentobarbitone and the intracranial and all of the tissues of the head, together with the lungs, heart and kidneys, removed for subsequent measurement of radioactivity (Packard gamma counter equipped with software enabling correction of radioactive spill-over). Blood flow to each tissue was calculated from the following equation:

$$\frac{\text{Tissue radioactivity}}{\text{Total radioactivity injected}} \times \text{carotid bloodflow}\,(\text{ml}\,\text{min}^{-1})$$

which makes the assumption that the total radioactivity collected represents the total radioactivity injected.

2.2. Anaesthetised cat: laser doppler studies

Mongrel cats (male, 3–4 kg; Campbell Farms) were anaesthetised and instrumented as described above with the exception that pentobarbitone was not used and the dose of α-chloralose was 80 mg kg^{-1}. The head of each animal was positioned on a stereotaxic frame (Kopf, CA, USA) and immobilised using ear bars and a nose/mouth clamp. A skin incision was made on the top of the skull and using a small dental drill, a skull window (1–1.5 cm diameter) was carefully cut to allow access to the left parietal cortical region of the brain. The cut portion of skull was carefully removed without damaging the underlying dura, and any bleeding was stopped with bone wax. A laser doppler flow probe (Moor Instruments; Exmoor, Devon) was then carefully positioned on the dura to allow measurement of cerebral micro-vascular blood flow (as red blood cell flux through the dural, pial and cortical surface micro-vasculature). A second laser doppler flow probe was positioned on one of the ears to allow measurement of extra-cerebral micro-vascular blood flow (as red blood cell flux through cutaneous ear micro-vasculature). Each animal was then allowed to stabilise for at least 30 min prior to commencing the experimental protocol. Blood pressure, heart rate, carotid arterial blood flow and ear and cerebral microvascular flux were recorded continuously via a poly-

graph (Grass Instruments, MA, USA or Gould) and a data-acquisition system (Mi2; Modular Instruments, USA). Zolmitriptan (0.1–100 μg kg^{-1}, in saline as 0.1 ml kg^{-1}) in an ascending series of doses, or saline alone (0.1 ml kg^{-1}), was administered by intravenous bolus injection. Subsequent doses were administered only when the response to the preceding dose had stabilised, resulting in a 10–20 min separation between each dose.

2.3. Anaesthetised dog-carotid arterial blood flow studies

Beagle dogs (male, 12–17 kg; Campbell Farms) were anaesthetised with intravenous pentobarbitone sodium (30 mg kg^{-1}; Sagatal; Rhone-Poulenc-Rorer) and a polythene cannula (Portex) inserted into the upper abdominal aorta (via a femoral artery), to measure blood pressure and heart rate. A second cannula was inserted into a femoral vein for drug administration. A tracheotomy was also performed and artificial ventilation maintained via a Palmer respiration pump (room air at 20 ml kg^{-1}, 18 breaths min^{-1}). The effectiveness of this ventilation was regularly monitored by analysis of arterial blood samples (ABL-3; Radiometer) to ensure that blood gases were maintained within acceptable limits (Green, 1979). An ultrasonic blood flow probe (Transonic Systems) was then placed on the left common carotid artery (via a neck incision) to measure carotid blood flow. The chest was opened via a left thoracotomy at rib space 5 to expose the heart, which was then supported by a partial pericardial cradle. A polythene cannula was inserted into the left atrium to allow systemic administration of zolmitriptan without first passage through the pulmonary circulation. Each animal was then allowed to stabilise for at least 30 min prior to commencing the experimental studies. Blood pressure, heart rate, and carotid arterial blood flow were recorded continuously on a polygraph (Grass Instruments or Gould).

2.4. Drugs

Zolmitriptan ((*S*)-4[[3-[2-dimethylamino)ethyl]-1*H*-indol-5yl]methyl]-2-oxazolidinone) was synthesized in the Medicinal Chemistry Laboratories of the Wellcome Research Laboratories at Beckenham, by Dr. A.D. Robertson. Doses of zolmitriptan were calculated as the free base, dissolved in acidified water, and diluted with physiological (0.9% w/v) saline.

2.5. Analysis of data

Dose–response curves to zolmitriptan were constructed by measuring the haemodynamic responses to systemic administration of ascending doses, each higher dose was given when the response to the preceding dose has stabilised. In blood flow studies using microspheres, doses were administered at specific time points. Changes in local vascular responses to drugs were assessed in terms of vascular conductance in order to account of any systemic blood pressure changes. Vascular conductance was derived for each animal by dividing the blood flow by the mean arterial blood pressure.

Where appropriate, data are presented as the arithmetic mean ± S.E.M. ED_{50} values (the dose of zolmitriptan to elicit a 50% maximum response) are presented as geometric means with 95% confidence limits. The analytical treatment of data presented in this paper utilised parametric and non-parametric tests (Student's *t*-test and Willcoxon test, respectively) to assess the significance of the effects of zolmitriptan. The analysis of multiple doses was first conducted using a One-way ANOVA, followed by a Student's *t*-test. A value of $P < 0.05$ was taken to be statistically significant.

3. Results

3.1. Effects of zolmitriptan on carotid arterial blood flow and conductance

In anaesthetised cats ($n = 4$) and dogs ($n = 5$) intravenous bolus administration of 0.1–30 (cat) or 0.1–100 (dog) μg kg^{-1} of zolmitriptan caused little or no change in systemic blood pressure (baseline values = 144 ± 10 and 106 ± 7 mm Hg, respectively) or heart rate (baseline values = 179 ± 7 and 203 ± 16 bpm, respectively). Only at the highest dose studied was there a small but significant reduction in heart rate (20 and 22 bpm, respectively; $P < 0.05$). Using ultra-sound flowmetry, the administration of 0.1–30 μg kg^{-1} zolmitriptan caused significant, dose-related and sustained reductions in carotid arterial blood flow and conductance (Fig. 1). The baseline carotid conductances in cats and dogs were 0.25 ± 0.01 ml min^{-1} mm Hg^{-1} and 1.52 ± 0.14 ml min^{-1} mm Hg^{-1}, respectively. No further reductions were achieved with the administration of higher doses. The ED_{50} (95% confidence

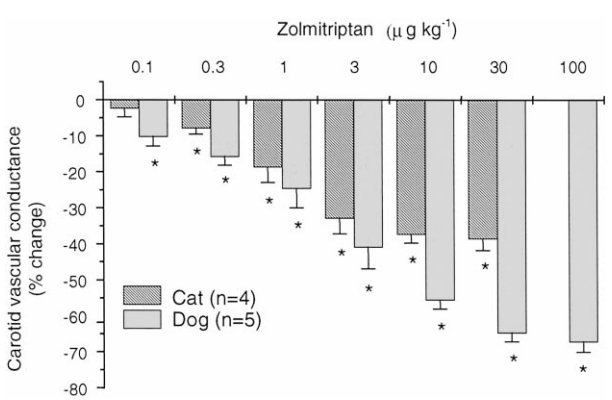

Fig. 1. Effects of zolmitriptan on carotid arterial conductance in anaesthetised cats (0–30 μg kg^{-1}, i.v.) and dogs (0.1–100 μg kg^{-1}, intra-left atrium). Blood flow was measured using ultra-sound flowmetry and conductance calculated by dividing blood flow by the mean arterial blood pressure. * Indicates significant change ($P < 0.05$) from baseline.

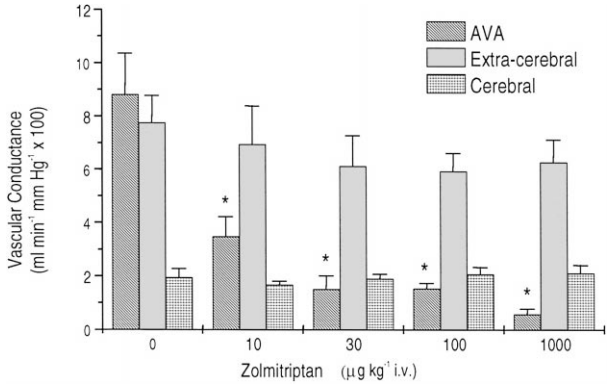

Fig. 2. Effects of intravenous zolmitriptan (10–1000 μg kg^{-1}) on AVA, extra-cerebral and cerebral vascular conductance in anaesthetised cats ($n = 5$). Blood flow to these regions was measured using radio-labeled microspheres, and conductance derived by dividing blood flow by mean arterial blood pressure. * Indicates significant difference ($P < 0.05$) when compared with control (0) value.

limits) for zolmitriptan on carotid arterial conductance in cats and dogs was 1.02 (0.70–1.49) and 2.28 (1.16–4.48) μg kg^{-1}, respectively. The maximum reduction in carotid arterial conductance achieved by zolmitriptan was 39 ± 3% and 67 ± 3%, respectively (Fig. 1).

3.2. Effects of zolmitriptan on cranial and arteriovenous–anastomotic (AVA) blood flow and conductance

These studies were performed in cats. Initial studies showed that after close-arterial injection of radio-labeled microspheres (16 μm diameter) into the left carotid arterial bloodflow, 98.6 ± 0.3% of the administered radioactivity was found in the left side of the head and in the lungs. Previous studies have shown that entrapment of 16 μm diameter microspheres in the lungs provides a good index

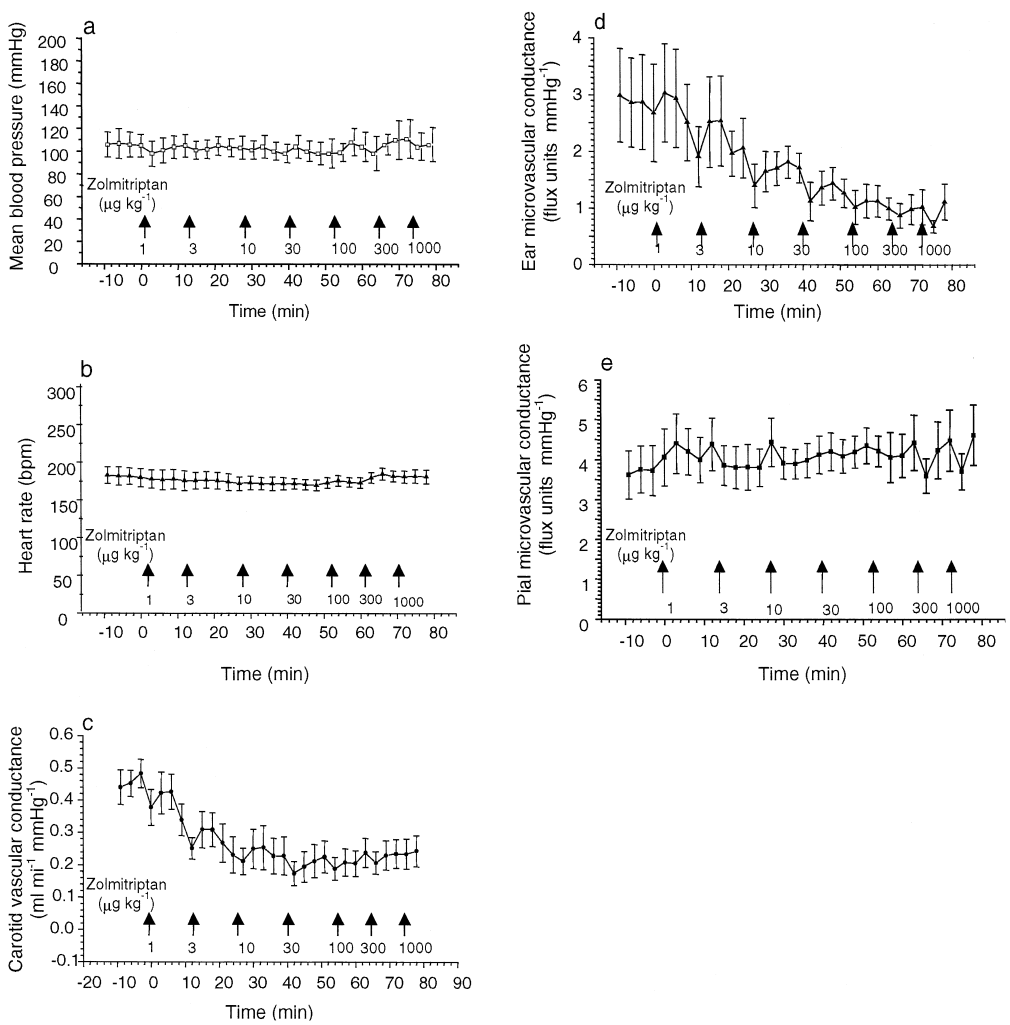

Fig. 3. Effects of intravenous zolmitriptan (1–1000 μg kg^{-1}) on (a) mean blood pressure, (b) heart rate, (c) carotid vascular conductance, (d) ear microvascular conductance and (e) pial microvascular conductance in anaesthetised cats ($n = 4$). Carotid blood flow was measured using ultrasound flowmetry while ear and pial blood flows were measured using laser doppler flowmetry. Conductances were calculated by dividing blood flow by mean arterial blood pressure.

of blood flow through cerebrovascular arteriovenous–anastomoses (see Saxena and Verdouw, 1982). The remaining radioactivity was found in the contralateral side of the head with a barely detectable amount ($< 0.01\%$) in the heart and kidneys. Prior to drug administration, $51.4 \pm 2.4\%$ of carotid arterial blood flow (23.6 ± 1.1 ml min^{-1}) passed through arteriovenous anastomoses, while $34.0 \pm 1.4\%$ and $13.4 \pm 1.0\%$ was distributed to extracerebral and cerebral tissues, respectively. A time–course study using animals ($n = 5$) which received saline injection on five occasions at intervals of 20 min, showed that blood flow through arteriovenous anastomoses, as well as the cerebral and extracerebral vascular beds, remained stable for the duration of the experiment (data not shown).

Intravenous injection of zolmitriptan (10–1000 μg kg^{-1}) in anaesthetised cats ($n = 5$) had no consistent effect upon either blood pressure or heart rate (baseline values = 140 ± 5 mm Hg and 208 ± 16 bpm, respectively), except at the 1000 μg kg^{-1} where there was a significant reduction in heart rate only ($-20 \pm 2\%$). By contrast, zolmitriptan at all doses significantly altered the distribution of radio-labeled microspheres within the cranial vascular beds arising from the carotid arterial blood flow (Fig. 2). These changes were primarily a consequence of a dose-related reduction in AVA blood flow and conductance ($94 \pm 2\%$ and $92 \pm 2\%$ reduction at 1000 μg kg^{-1}, respectively). Zolmitriptan caused a modest reduction in extra-cerebral blood flow and conductance (up to 32 ± 2 and $24 \pm 6\%$ reduction at 30 μg kg^{-1}, respectively), but was without effect on cerebral blood flow and conductance (Fig. 2).

3.3. Effects of zolmitriptan on cerebral and extra-cerebral microvascular blood flow and conductance

Intravenous injection of zolmitriptan (1–1000 μg kg^{-1}) in anaesthetised cats ($n = 4$) caused no significant changes in systemic blood pressure (baseline mean blood pressure 106 ± 11 mm Hg), or heart rate (baseline heart rate = 183 ± 11 bpm) in these animals (Fig. 3). By contrast, zolmitriptan (1 to 30 μg kg^{-1}) caused a significant dose-related reduction in carotid arterial blood flow and conductance (-12 ± 11 to $-61 \pm 5\%$), which was accompanied by an equivalent reduction in ear microvascular conductance (-15 ± 5 to $-60 \pm 6\%$). The estimated ED_{50} for these vascular responses to zolmitriptan was 2–3 μg kg^{-1}. However, zolmitriptan at doses up to 1000 μg kg^{-1} caused no reduction in cerebral microvascular conductance (Fig. 3).

4. Discussion

In normal, anaesthetised animals, the 'amphibaric' nature of cardiovascular responses to intravenous 5-HT has been documented from the earliest studies of Page and colleagues (see Page and McCubbin, 1953). Studies in our laboratory (Cambridge et al., 1995) and elsewhere (e.g., Mylecharane and Phillips, 1989) have confirmed that bolus injections of 5-HT produce vasodilatation or vasoconstriction depending on the vascular bed and the magnitude of sympathetic involvement in the maintenance of vascular tone. In contrast to 5-HT, the vascular effects of zolmitriptan are almost exclusively confined to the carotid vasculature. Since sumatriptan produces an essentially similar cardiovascular profile in anaesthetised cats and dogs (Feniuk et al., 1989; Perren et al., 1989; Cambridge et al., 1995), this probably reflects a highly regional distribution of '5-HT$_{1B}$-like' receptors mediating vasoconstriction. This is reinforced by the fact that zolmitriptan is 3–5 times more potent than sumatriptan at '5-HT$_{1B}$-like' receptors in a variety of isolated blood vessels (Martin, 1994; Martin et al., 1997; cf. Connor et al., 1989; Parsons et al., 1989) and a similar difference in potency is evident in the ability of these two drugs to constrict cranial arteriovenous anastomoses in vivo.

Although both sumatriptan and zolmitriptan are highly effective acute treatments for migraine, the precise mechanism of action of these drugs remains a topic of considerable debate (Humphrey and Goadsby, 1994; Martin, 1996). Constriction of arteriovenous anastomoses, and cerebral vessels that are believed to be inflamed and distended during an attack, coupled with inhibition of neuropeptide release from perivascular sensory nerves, appear to be important attributes of the 5-HT$_{1B/1D}$ receptor agonist drugs as well as the ergots (see Humphrey and Feniuk, 1991; Moskowitz, 1992; Humphrey and Goadsby, 1994). However, sumatriptan is completely ineffective when given pre-emptively either to cluster headache patients (Monstad et al., 1995) or to migraine with aura patients just prior to development of the headache (Bates et al., 1994). In the latter case, drug (6 mg) was administered by sub-cutaneous injection 20–30 min before the onset of the headache such that plasma concentrations available at the time of the headache would be expected to exceed those required for cranio-vascular constriction (see Caekebeke et al., 1992). It has been argued (Kaube et al., 1993; Martin, 1994) that this intriguing result reflects the inability of sumatriptan to penetrate the blood–brain barrier and access key central components of the trigemino-vascular system. Zolmitriptan, on the other hand, is less hydrophilic and inhibits trigeminal neuroactivation within the brainstem after systemic administration (Goadsby and Edvinsson, 1994; Goadsby and Hoskin, 1996; Goadsby and Knight, 1997). While this property is expected to confer therapeutic advantage on zolmitriptan, it raises the possibility that the increased lipophilicity with respect to sumatriptan ($\log_{10} D = -1.0$ vs. -1.3—unpublished data) might lead to important differences in the cerebro-vascular actions of these two drugs.

Clinical studies to determine the effects of sumatriptan on cerebral blood flow velocity and distribution have

provided equivocal results. Two early studies using doppler flowmetry suggested that sumatriptan constricts the middle cerebral artery during a migraine attack (Friberg et al., 1991; Caekebeke et al., 1992). However, a third investigation failed to confirm this finding (Zwetsloot et al., 1993) and subsequent studies employing positron emission tomography and single photon emission computed tomography, have provided no evidence that sumatriptan modifies cerebral blood flow distribution (Ferrari et al., 1995; Diener and May, 1996). Pre-clinical studies, on the other hand, have provided unambiguous evidence that although sumatriptan potently constricts cerebral blood vessels in vitro (Connor et al., 1989; Parsons et al., 1989), it has little or no effect on cerebral blood flow (Goadsby and Edvinsson, 1993) or pial artery diameter (Connor et al., 1992) when administered intravenously to anaesthetised cats. Therefore, sumatriptan may not reduce blood flow as the modest arterial vasoconstriction is not flow limiting. Nevertheless, when applied topically to pial arteries in this species, the drug causes significant reductions in vessel diameter (up to 19% at 1 μM) consistent with data obtained using isolated vessels (Connor et al., 1992). This was interpreted to mean that the absence of small cerebral blood vessel responses following the systemic administration of sumatriptan reflects an inability to penetrate the cerebrovascular intima. Perhaps relevant to this, Den Boer et al. (1992) also demonstrated that sumatriptan has no effect upon the arteriovenous anastomoses of the dura mater in anaesthetised pigs.

Although zolmitriptan, like sumatriptan, contracts isolated cerebral arteries from various species (Martin et al., 1997), there is no evidence that the greater lipophilicity of this new drug has an important effect on cerebral blood flow in vivo. As determined by the radiolabelled microsphere technique in anaesthetised cats, the component of cerebral blood flow derived from the carotid artery was not affected by zolmitriptan. This result is consistent with a report by Goadsby and Edvinsson (1994) describing the use of laser doppler flowmetry to show that although zolmitriptan inhibits trigeminal-evoked increases in pial arterial blood flow (presumably by inhibiting evoked neuropeptide release), the drug has no effect on resting cerebral blood flow. However, with respect to other haemodynamic variables, the drug produces similar responses to those reported for sumatriptan. In both anaesthetised cats and dogs the intravenous administration of low doses of zolmitriptan causes a significant dose-related reduction in carotid arterial blood flow and conductance with an ED_{50} of 1–3 μg kg^{-1}. This carotid vascular activity of zolmitriptan is achieved in the absence of any important changes in systemic haemodynamics (blood pressure or heart rate). In the cat, using radio-labeled microspheres, the carotid vascular response to zolmitriptan is mirrored by a dose-related constriction of the cerebrovascular arteriovenous anastomoses and a modest reduction in total extracerebral vascular conductance. The latter is evident in the ear microvasculature using laser doppler flowmetry, where the effects of zolmitriptan are very similar to those seen in the carotid vascular beds. By contrast, the use of radiolabeled microspheres showed that even at high doses zolmitriptan causes no reduction in total cerebral vascular conductance. This lack of effect of zolmitriptan upon the cerebral vasculature was confirmed in separate experiments using laser doppler flowmetry.

Thus, it would appear that in spite of its ability to cross the blood–brain barrier, zolmitriptan has little or no effect on the vascular tone of the small cerebral blood vessels in vivo. This is the case even at doses which clearly produce maximal constriction of the cranial arteriovenous anastomoses, and of some extra-cerebral vascular beds, such as in the ears. Conceivably, the absence of cerebral vasoconstriction following systemic administration of either sumatriptan or zolmitriptan reflects the remarkable ability of the cerebral vasculature to autoregulate in the face of a reduction in the blood flow through the cranial arteriovenous anastomoses. In this regard it is worth noting that unlike the carotid vasculature, where these drugs produce persistent decreases in blood flow, in the ear microvasculature there was evidence of recovery from the constrictor response to zolmitriptan. This might suggest that even in the extra-cerebral vascular beds there are some reflex or autoregulatory mechanisms able to counteract 5-$HT_{1B/1D}$ receptor-mediated constrictor responses. This could involve the release of the endogenous vasodilator nitric oxide, in response to changes in endothelial shear-stress, or through the activation of endothelial 5-HT receptors, as in the dog kidney (Cambridge et al., 1995).

In conclusion, these studies show that the novel 5-$HT_{1B/1D}$ receptor partial agonist zolmitriptan causes a selective vasoconstriction of the carotid arterial vascular beds in experimental animals, which is primarily a consequence of the constriction of cranial arteriovenous anastomoses. In this respect it is some 2–3 times more potent in these beds than sumatriptan. Zolmitriptan can also effect a modest reduction in extra-cerebral blood flow and conductance. However, the drug has very little effect upon cerebral blood flow or conductance. These data therefore confirm that zolmitriptan selectively influences cranial haemodynamics in a manner consistent with an anti-migraine action and that the ability of this drug to cross the blood–brain barrier does not adversely affect cerebral blood flow.

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