Br. J. Pharmacol. (1993), **110**, 1445–1448

Effects of sumatriptan on the cerebral intraparenchymal microcirculation in the cat

[1]Masahiro Kobari, Yasuo Fukuuchi, Minoru Tomita, Norio Tanahashi, Shizuko Konno & Hidetaka Takeda

Department of Neurology, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan

1 Sumatriptan, a 5-hydroxytryptamine $(5\text{-HT})_1$-like receptor agonist, is effective against the headache of migraine. The effects of sumatriptan injected via the carotid artery on the cerebral microcirculation were studied in 10 anaesthetized cats.

2 The local cerebral blood volume (CBV), mean transit time of blood (MTT) and cerebral blood flow (CBF) in the parieto-temporal cortex were measured by a photoelectric method. CBV represents the cumulative dimensions of the cerebral microvessels.

3 Sumatriptan at 5 and 50 $\mu g\,kg^{-1}$ had no significant effects on the CBV, MTT, CBF, and mean arterial blood pressure (MABP); 500 $\mu g\,kg^{-1}$ of sumatriptan reduced the CBV, prolonged the MTT, and decreased the CBF (approximately -20%) without affecting the MABP. Sumatriptan, 5 $mg\,kg^{-1}$, elicited transient reductions in CBV and CBF, which were attributable to the rapid and marked falls of MABP seen with this dose.

4 Thus, while a high dose of sumatriptan (500 $\mu g\,kg^{-1}$) exhibits direct vasoconstrictor actions on the cerebral vessels, low doses of sumatriptan, within the therapeutic range, elicit no vasoconstriction. The data do not support a vasoconstrictor action of sumatriptan playing a primary role in reversing the headache of migraine.

Keywords: Cerebral blood flow; cerebral vessel; 5-hydroxytryptamine receptor; migraine; photoelectric method; sumatriptan

Introduction

Sumatriptan is a novel 5-hydroxytryptamine (5-HT) receptor agonist selective for the 5-HT_1-like receptors (Feniuk *et al.*, 1989; Humphrey *et al.*, 1990; Humphrey & Feniuk, 1991). When given orally (Goadsby *et al.*, 1991) or subcutaneously (Cady *et al.*, 1991; The Subcutaneous Sumatriptan International Study Group, 1991), it aborts the headache of migraine. The mechanisms involved, however, remain a matter of dispute in part because the pathogenesis of migraine itself is not yet fully understood. According to the widely held vascular hypothesis, the head pain of migraine arises from dilatation of previously contracted intra- and extracranial vessels, which are sensitive to pain (Kobari *et al.*, 1990). Sumatriptan may exert its therapeutic action by preventing the dilatation of, or by constricting, these vessels through the vascular 5-HT_1-like receptors (Humphrey *et al.*, 1990; Humphrey & Feniuk, 1991; Caekebeke *et al.*, 1992). *In vitro* studies have consistently demonstrated that sumatriptan constricts basilar arteries of dogs, primates (Connor *et al.*, 1989), and man (Parsons *et al.*, 1989). It also causes contraction of human dural arteries (Humphrey *et al.*, 1990; Jansen *et al.*, 1992), which are more likely to be involved in the generation of headache (Blau, 1978).

An alternative explanation has been put forward by Moskowitz (1992), who proposed that the headache of migraine is caused by activation of the 'trigeminovascular system', consisting of the cranial vessels and their trigeminal innervation. The antidromic transmission of impulses induces the release of vasoactive neuropeptides (Goadsby & Edvinsson, 1993), which may in turn elicit cerebral vasodilatation and plasma extravasation (Buzzi & Moskowitz, 1990), while the orthodromic conduction of potentials conveys the pain sensation to the central nervous system. Sumatriptan appears to suppress these mechanisms through activating neuronal inhibitory 5-HT_1-like receptors (Moskowitz, 1992).

The reported effects of sumatriptan on cerebral perfusion *in vivo* are far from conclusive. Sumatriptan reduced carotid blood flow measured with an electromagnetic flow probe in dogs and pigs (Feniuk *et al.*, 1989; den Boer *et al.*, 1991). However, sumatriptan did not affect the cerebral circulation measured by single photon emission computed tomography (SPECT) in healthy volunteers (Scott *et al.*, 1992) or in patients with migraine during headache (Friberg *et al.*, 1991). Friberg *et al.* (1991), employing transcranial Doppler flowmetry, found that sumatriptan improved the reduced blood flow velocity in the middle cerebral artery on the headache side, however, Diener *et al.* (1991) failed to detect similar changes.

One reason for such discrepancies may be the lack of appropriate methods for continuously monitoring the cerebral perfusion. Carotid blood flow measurements do not represent the cerebral circulation *per se*, and transcranial Doppler flowmetry provides only the blood flow velocity in the major cerebral arteries. SPECT does not permit quantitative determination of the cerebral blood flow (CBF). In addition, there have so far been no investigations examining the effects of sumatriptan on the cerebral intraparenchymal microvessels and circulation. Our photoelectric method (Tomita *et al.*, 1978; 1983) permits continuous, quantitative, and on-line measurements of the local cerebral blood volume (CBV), and intermittent estimations of the mean transit time of blood (MTT) and the CBF. The purpose of the present study was to elucidate the basic actions of sumatriptan injected into the carotid artery on the cerebral microcirculation by use of this new technique.

Methods

Ten adult cats of either sex weighing 2.1–2.7 kg were employed. The animals were anaesthetized by intraperitoneal injection of 50 $mg\,kg^{-1}$ α-chloralose and 500 $mg\,kg^{-1}$ urethane. The body temperature of the animals was maintained

[1] Author for correspondence.

at 37–37.5°C by a heated blanket. Endotracheal intubation was performed, and respiration was kept constant with a volume-controlled respirator for experimental animals (Harvard, model 662). A catheter was inserted into the left lingual artery, and used for injecting saline and drugs into the carotid artery. Another catheter was inserted into the left femoral artery, and used for monitoring the arterial blood pressure (BP). The mean arterial blood pressure (MABP) was calculated from the formula: MABP = (systolic pressure − diastolic pressure)/3 + diastolic pressure.

The head of each animal was fixed in a stereotaxic headholder. The local CBV was measured continuously with a photoelectric apparatus consisting of a micro-lamp, 1 mm in outer diameter (Hamai Electric), and a silicon photodiode (Sharp Electric) covered with a band pass filter (Tomita *et al.*, 1978; 1983). Through a small cranial hole made in the left parieto-temporal region, the micro-lamp was inserted into the brain tissue to approximately 5 mm below the surface. The photodiode was attached to the skull just above the inserted lamp. The photodiode continuously detected the intensity of transmitted light passing through a thin layer of cerebral cortex. Since the intensity of light depends largely on the content of haemoglobin, it can be calibrated to the amount of CBV if the tissue haematocrit is constant (Tomita *et al.*, 1978). To obtain tissue dilution curves from the same region, 0.2 ml of 0.9% saline was injected as a bolus into the left carotid artery via the lingual artery. The tissue dilution curves were drawn on the CBV recording. The MTT of blood through the brain tissue was estimated from the dilution curve employing the area-over-height method (Grodins, 1962; Zierler, 1962). The local CBF was calculated according to the Stewart-Hamilton equation, i.e. CBF = CBV/MTT (Grodins, 1962; Zierler, 1962; Tomita *et al.*, 1978).

In 10 animals each, 5 μg, 50 μg, 500 μg or 5 mg kg^{-1} of sumatriptan (Glaxo, UK) dissolved in 0.5 ml of saline was injected sequentially into the carotid artery via the lingual artery in approximately 10 s. The changes in CBV, MTT, CBF, and SABP were recorded for 15 min following the injection of sumatriptan. There was a 20 min interval between each dose.

The experimental protocols conformed to the guiding principles of the American Physiological Society. The data are presented as the mean ± s.e.mean. Statistical analysis was performed by Student's *t* test and Wilcoxon's signed-rank test.

Results

Figure 1 shows an example of recordings of CBV, tissue dilution curves (present on the CBV recording), and BP before and after intracarotid injection of either 500 μg kg^{-1} or 5 mg kg^{-1} of sumatriptan. After the injection of 500 μg kg^{-1}, both CBV and BP fell slightly. The MTT calculated from the dilution curves was slightly prolonged. Following the 5 mg kg^{-1} injection, the BP initially showed a marked reduction, but subsequently tended to recover. The CBV also exhibited a rapid decline, but then gradually increased to exceed the initial level.

There were no significant differences in the absolute values of MABP, CBV, MTT, and CBF prior to the injection of each dose of sumatriptan. Figure 2a summarizes the time course of MABP following intracarotid injection of 5 μg, 50 μg, 500 μg, or 5 mg kg^{-1} of sumatriptan. Following the administration of either 5 or 50 μg kg^{-1}, there were no significant changes in MABP. A small MABP reduction ($P<0.01$) was observed at 1 min after the injection of 500 μg kg^{-1}. Immediately after the injection of 5 mg kg^{-1}, there was a marked decline in MABP ($P<0.01$), which had returned to the initial level at 15 min.

The effects of sumatriptan on CBV are shown in Figure 2b. There were no significant alterations in CBV following the injection of either 5 or 50 μg kg^{-1}. Following the injection of 500 μg kg^{-1}, the CBV was decreased by approximately 10% ($P<0.05$) during the observation period. After the infusion of 5 mg kg^{-1}, the CBV initially exhibited a 12% reduction ($P<0.05$), but then showed an increase exceeding the initial level.

Figure 2c summarizes the effects of sumatriptan on MTT. There were no significant changes in MTT after the injection of either 5 or 50 μg kg^{-1}. Following the injection of 500 μg kg^{-1}, MTT was significantly prolonged ($P<0.05$) at 1 min. Immediately after the injection of 5 mg kg^{-1}, MTT was markedly prolonged ($P<0.05$), but returned to the initial level thereafter.

The time course of CBF following the intracarotid injection of sumatriptan is shown in Figure 2d. There were no significant changes in CBF after the injection of either 5 or 50 μg kg^{-1}. Following the injection of 500 μg kg^{-1}, the CBF was significantly decreased by approximately 20% ($P<0.05$). Immediately after the injection of 5 mg kg^{-1}, the CBF was markedly reduced ($P<0.05$), but then returned to the control level.

The Pa_{O_2}, Pa_{CO_2}, and pH values of the animals in the steady-state before the administration of the first dose of sumatriptan were 96.4 ± 4.9 mmHg, 29.6 ± 2.2 mmHg, and 7.336 ± 0.027, respectively. There were no statistically significant changes in Pa_{O_2}, Pa_{CO_2}, or pH after the injection of sumatriptan in any of the groups.

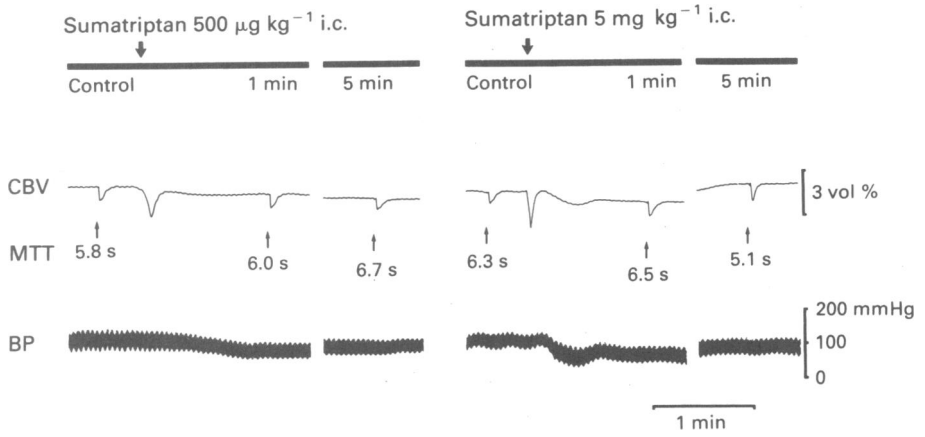

Figure 1 An example of recordings of cerebral blood volume (CBV) and blood pressure (BP) before and after intracarotid (i.c.) injection of sumatriptan. The small upward arrows, which indicate injections of 0.2 ml of saline, are followed by tissue dilution curves. The mean transit time of blood (MTT) estimated from the individual dilution curves is shown under the arrows.

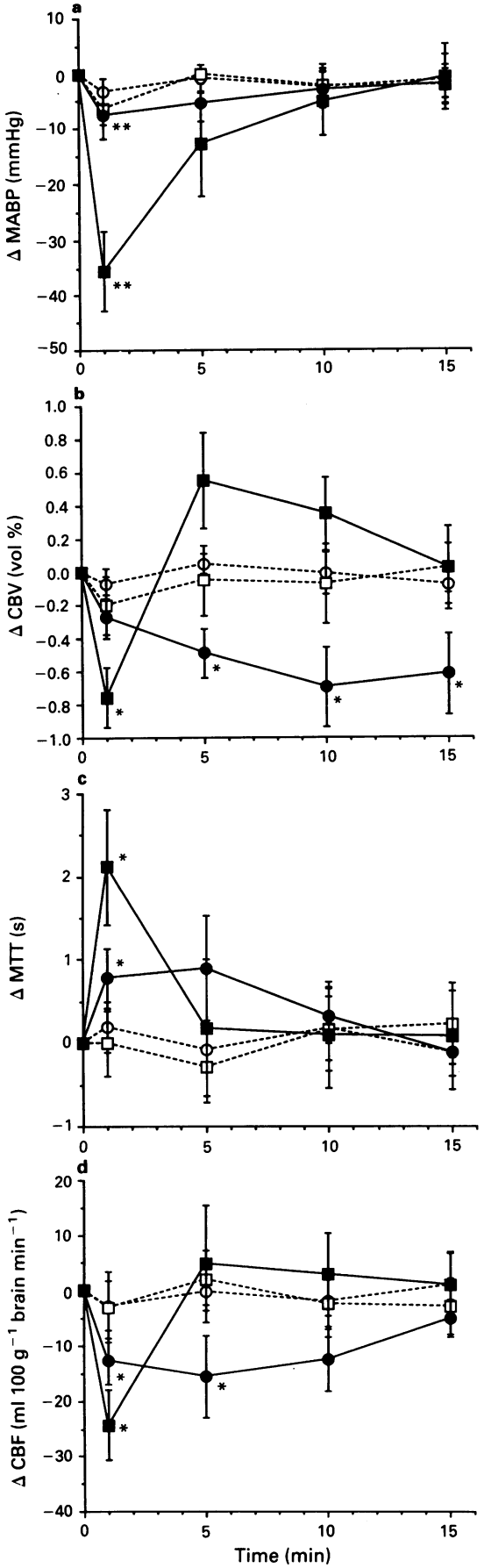

Figure 2 The changes in (a) mean arterial blood pressure (MABP), (b) cerebral blood volume (CBV), (c) mean transit time of blood (MTT) and (d) cerebral blood flow (CBF) following intracarotid injection of 5 μg (○), 50 μg (□), 500 μg (●), or 5 mg (■) kg^{-1} of sumatriptan. Values are mean ± s.e.mean ($n = 10$). *$P < 0.05$ and **$P < 0.01$ compared to the values at 0 min.

Discussion

Full details of the photoelectric method have been described elsewhere (Tomita *et al.*, 1978; 1983). CBV reflects the cumulative dimensions of the cortical microvessels. Insertion of the present micro-lamp into the brain tissue does not affect the cerebrovascular responses, such as the autoregulation or CO_2 reactivity of the CBF (Tomita *et al.*, 1978). The CBF values measured by the photoelectric and the hydrogen gas clearance methods were found to correlate well (Tomita *et al.*, 1988).

In the present study, low doses of sumatriptan (5 and 50 μg kg^{-1}) exerted no significant effects on the intraparenchymal circulation of the cortex, as evaluated from the CBV, MTT, and CBF. These results are consistent with those of Connor *et al.* (1992) who observed no significant changes in the diameter of feline pial arteries following intravenous infusion of 64 μg kg^{-1} of sumatriptan. The results are also in line with those of Scott *et al.* (1992) and Friberg *et al.* (1991) who found no changes in the regional CBF following intravenous injection of 2 mg (or approximately 30 μg kg^{-1} for an average person) of sumatriptan.

Sumatriptan, 500 μg kg^{-1}, was found to reduce the CBV, to prolong the MTT, and to decrease the CBF (by approximately 20%) without an associated change in MABP. A high dose of sumatriptan thus exerts a vasoconstrictor action on the intraparenchymal microvessels. Sumatriptan has been considered unlikely to cross the blood-brain barrier, since it induces contraction of the pial arteries when applied from the abluminal side, but not when applied from the luminal side (Connor *et al.*, 1992). However, our present results suggest that intravascular sumatriptan, albeit at a high concentration, may reach the smooth muscles of the microvessels, or that receptors are located in the intima. In either event, the 5-HT_1-like receptors appear to mediate the contractile responses to sumatriptan (Parsons, 1991; Humphrey & Feniuk, 1991).

A very high dose of sumatriptan (5 mg kg^{-1}) elicited transient reductions in CBV and CBF in the present study, which may be attributable to rapid and marked declines of MABP (Barzó *et al.*, 1993). It is possible that the marked falls in MABP may be due to cardiac depression elicited by a toxic dose of sumatriptan.

According to a dose-finding study on migraine patients (Perrin *et al.*, 1989), intravenous infusion of 64 μg kg^{-1} of sumatriptan was sufficient to relieve the headache in over 90% of the patients. In the present study, a vasoconstrictor action of sumatriptan was observed only after the administration of 500 μg kg^{-1}, which amounted to approximately eight times the above-cited therapeutic dosage. In contrast, a clinically effective dose of sumatriptan (50 μg kg^{-1}) did not influence the intraparenchymal circulation of the brain despite being given by the carotid route.

Our data suggest that vasoconstriction by sumatriptan may not be involved in aborting the pain of migraine. There is a possibility that sumatriptan may constrict the large intra- or extracranial vessels without affecting the intraparenchymal small vessels. However, from our experience, it seems very unlikely that the downstream intraparenchymal circulation is totally unaffected by the constriction of the large cerebral vessels. Further, the distribution, density, and subtypes of the 5-HT receptors in the cerebral vasculature differ among different species (Parsons, 1991). A problem thus remains as to whether or not the cerebrovascular responses observed in cats can be extrapolated to man. The present result does not exclude a possibility that sumatriptan may constrict the pathologically dilated vessels of migraine at doses lower than 500 μg kg^{-1}.

In conclusion, a high dose of sumatriptan given into the carotid artery decreased the local CBV and CBF through constriction of the intraparenchymal vessels. However, lower doses of sumatriptan, equivalent to those used in clinical practice, did not affect the cerebral vessels or perfusion. The

data do not support the vasoconstrictor action of sumatriptan playing a primary role in ameliorating the headache of migraine.

The authors are grateful to Glaxo Pharmaceuticals Inc., Tokyo, Japan, for providing sumatriptan.

References

BARZÓ, P., BARI, F., DÓCZI, T., JANCSÓ, G. & BODOSI, M. (1993). Significance of the rate of systemic changes in blood pressure on the short-term autoregulatory response in normotensive and spontaneously hypertensive rats. *Neurosurgery*, **32**, 611–618.

BLAU, J.N. (1978). Migraine: a vasomotor instability of the meningeal circulation. *Lancet*, **ii**, 1136–1139.

BUZZI, M.G. & MOSKOWITZ, M.A. (1990). The antimigraine drug, sumatriptan (GR43175), selectively blocks neurogenic plasma extravasation from blood vessels in dura mater. *Br. J. Pharmacol.*, **99**, 202–206.

CADY, R.K., WENDT, J.K., KIRCHNER, J.R., SARGENT, J.D., ROTHROCK, J.F. & SKAGGS, H. Jr. (1991). Treatment of acute migraine with subcutaneous sumatriptan. *J. Am. Med. Ass.*, **265**, 2831–2835.

CAEKEBEKE, J.F.V., FERRARI, M.D., ZWETSLOOT, C.P., JANSEN, J. & SAXENA, P.R. (1992). Antimigraine drug sumatriptan increases blood flow velocity in large cerebral arteries during migraine attacks. *Neurology*, **42**, 1522–1526.

CONNOR, H.E., FENIUK, W. & HUMPHREY, P.P.A. (1989). Characterization of 5-HT receptors mediating contraction of canine and primate basilar artery by use of GR43175, a selective 5-HT_1-like receptor agonist. *Br. J. Pharmacol.*, **96**, 379–387.

CONNOR, H.E., STUBBS, C.M., FENIUK, W. & HUMPHREY, P.P.A. (1992). Effect of sumatriptan, a selective 5-HT_1-like receptor agonist, on pial vessel diameter in anaesthetised cats. *J. Cereb. Blood Flow Metab.*, **12**, 514–519.

DEN BOER, M.O., VILLALÓN, C.M., HEILIGERS, J.P.C., HUMPHREY, P.P.A. & SAXENA, P.R. (1991). Role of 5-HT_1-like receptors in the reduction of porcine cranial arteriovenous anastomotic shunting by sumatriptan. *Br. J. Pharmacol.*, **102**, 323–330.

DIENER, H.-C., PETERS, C., RUDZIO, M., NOE, A., DICHGANS, J., HAUX, R., EHRMANN, R. & TFELT-HANSEN, P. (1991). Ergotamine, flunarizine and sumatriptan do not change cerebral blood flow velocity in normal subjects and migraineurs. *J. Neurol.*, **238**, 245–250.

FENIUK, W., HUMPHREY, P.P.A. & PERREN, M.J. (1989). The selective carotid arterial vasoconstrictor action of GR43175 in anaesthetized dogs. *Br. J. Pharmacol.*, **96**, 83–90.

FRIBERG, L., OLESEN, J., IVERSEN, H.K. & SPERLING, B. (1991). Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. *Lancet*, **338**, 13–17.

GOADSBY, P.J. & EDVINSSON, L. (1993). The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann. Neurol.*, **33**, 48–56.

GOADSBY, P.J., ZAGAMI, A.S., DONNAN, G.A., SYMINGTON, G., ANTHONY, M., BLADIN, P.F. & LANCE, J.W. (1991). Oral sumatriptan in acute migraine. *Lancet*, **338**, 782–783.

GRODINS, F.S. (1962). Basic concepts in the determination of vascular volumes by indicator-dilution methods. *Circ. Res.*, **10**, 429–446.

HUMPHREY, P.P.A. & FENIUK, W. (1991). Mode of action of the anti-migraine drug sumatriptan. *Trends Pharmacol. Sci.*, **12**, 444–446.

HUMPHREY, P.P.A., FENIUK, W., PERREN, M.J., BERESFORD, I.J.M., SKINGLE, M. & WHALLEY, E.T. (1990). Serotonin and migraine. *Ann. N.Y. Acad. Sci.*, **600**, 587–598.

JANSEN, I., EDVINSSON, L., MORTENSEN, A. & OLESEN, J. (1992). Sumatriptan is a potent vasoconstrictor of human dural arteries via a 5-HT_1-like receptor. *Cephalalgia*, **12**, 202–205.

KOBARI, M., MEYER, J.S. & ICHIJO, M. (1990). Cerebral hemodynamic changes during migraine and cluster headaches: pharmacological implications. *Headache Q. Curr. Treat. Res.*, **1**, 23–37.

MOSKOWITZ, M.A. (1992). Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. *Trends Pharmacol. Sci.*, **13**, 307–311.

PARSONS, A.A. (1991). 5-HT receptors in human and animal cerebrovasculature. *Trends Pharmacol. Sci.*, **12**, 310–315.

PARSONS, A.A., WHALLEY, E.T., FENIUK, W., CONNOR, H.E. & HUMPHREY, P.P.A. (1989). 5-HT_1-like receptors mediate 5-hydroxytryptamine-induced contraction of human isolated basilar artery. *Br. J. Pharmacol.*, **96**, 434–440.

PERRIN, V.L., FÄRKKILÄ, M., GOASGUEN, J., DOENICKE, A., BRAND, J. & TFELT-HANSEN, P. (1989). Overview of initial clinical studies with intravenous and oral GR43175 in acute migraine. *Cephalalgia*, **9**(Suppl 9), 63–72.

SCOTT, A.K., GRIMES, S., NG, K., CRITCHLEY, M., BRECKENRIDGE, A.M., THOMSON, C. & PILGRIM, A.J. (1992). Sumatriptan and cerebral perfusion in healthy volunteers. *Br. J. Clin. Pharmacol.*, **33**, 401–404.

THE SUBCUTANEOUS SUMATRIPTAN INTERNATIONAL STUDY GROUP (1991). Treatment of migraine attacks with sumatriptan. *N. Engl. J. Med.*, **325**, 316–321.

TOMITA, M., GOTOH, F., AMANO, T., TANAHASHI, N., KOBARI, M., SHINOHARA, T. & MIHARA, B. (1983). Transfer function through regional cerebral cortex evaluated by a photoelectric method. *Am. J. Physiol.*, **245**, H385–H398.

TOMITA, M., GOTOH, F., SATO, T., AMANO, T., TANAHASHI, N., TANAKA, K. & YAMAMOTO, M. (1978). Photoelectric method for estimating hemodynamic changes in regional cerebral tissue. *Am. J. Physiol.*, **235**, H56–H63.

TOMITA, M., GOTOH, F., TANAHASHI, N., KOBARI, M., TERAYAMA, Y., MIHARA, B., OHTA, K. & GERDSEN, I. (1988). Comparison between the photoelectric method and H_2 clearance method for measuring cerebrocortical blood flow in cats. *J. Cereb. Blood Flow Metab.*, **8**, 727–732.

ZIERLER, K.L. (1962). Circulation times and the theory of indicator-dilution methods for determining blood flow and volume. In *Handbook of Physiology*, Section 2: Circulation, Volume 1, pp. 585–615, Washington DC: American Physiology Society.

(Received June 14, 1993
Revised August 17, 1993
Accepted August 23, 1993)