The effect of i.v. sumatriptan, a selective 5-HT$_1$-receptor agonist on central haemodynamics and the coronary circulation

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1 Sumatriptan (GR43175) is a selective 5-HT$_1$-receptor agonist effective in the acute treatment of migraine. Vasoactive properties in other vascular beds have been suggested by recent *in vitro* studies.

2 Its effects on coronary artery dimensions and central haemodynamics were assessed in 10 patients undergoing diagnostic coronary arteriography using digital subtraction angiography and invasive haemodynamic monitoring.

3 Following a 10 min i.v. infusion of sumatriptan to a total dose of 48 μg kg^{-1} there was a significant increase ($P < 0.05$) in systemic and pulmonary arterial pressures. There was a significant reduction in coronary artery diameter from 4.3 ± 1.6 mm to 3.6 ± 1.6 mm 12.9 ± 6.9% ($P < 0.001$). There was no significant change in heart rate or ECG morphology.

4 Sumatriptan, a 5-HT$_1$-receptor agonist, causes a vasopressor response in the systemic and pulmonary arterial circulations and coronary artery vasoconstriction; in this study there were no clinical sequelae.

Keywords   sumatriptan   5-HT$_1$-receptor   haemodynamics   coronary circulation

Introduction

Sumatriptan, GR43175 (3-[2-(dimethylamino)ethyl]-*N*-methyl-1H-indole-5-methanesulphonamide), is a selective 5-HT$_1$-receptor agonist, effective in the acute treatment of migraine (Brion *et al.*, 1989; International Subcutaneous Sumatriptan Trial 1991) possibly by reversing cerebral arterial dilatation (Friberg *et al.*, 1991). In isolated vascular preparations it has been shown to cause selective constriction of rabbit (Parsons *et al.*, 1989), dog and primate basilar arteries (Connor *et al.*, 1989a) and dog saphenous vein (Humphrey *et al.*, 1988). In intact animals selective vasoconstriction of arteriovenous anastomoses in the carotid circulation has been demonstrated in anaesthetised cats (Perren *et al.*, 1989). Similarly, it caused selective vasoconstriction within the canine carotid arterial circulation, with no alteration in the systemic arterial pressure or the vascular resistance of the coronary or vertebral circulation (Feniuk *et al.*, 1989).

Human isolated basilar artery rings constricted in response to sumatriptan (Parsons *et al.*, 1989), as did normal and atherosclerotic human epicardial coronary artery rings obtained from explanted hearts (Chester *et al.*, 1990; Connor *et al.*, 1989b).

In early clinical studies transient increases in systolic and diastolic blood pressure were seen with intravenous sumatriptan, but this was not a consistent finding in all subjects (Brion *et al.*, 1989; International Subcutaneous Sumatriptan Trial 1991).

These studies suggest that sumatriptan in humans causes vasoconstriction of various vascular beds and that 5-HT$_1$-receptors may not be confined to the cranial circulation as in most animals. To investigate this possibility we studied the effects of sumatriptan on the systemic, pulmonary and coronary circulations *in vivo*.

Methods

Ten patients, six males, four females, mean age 52.9 ± 9.8 years (age range 18–65 years) were studied during coronary arteriography being performed for diagnostic purposes. Exclusion criteria included women of childbearing potential, myocardial infarction within 3 months, unstable angina, cardiac arrhythmias requiring drug therapy and hypertension (diastolic blood pressure ≥95 mm Hg). As this drug had the potential to cause coronary vasoconstriction, patients found to have coronary artery

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stenosis of $\geq 50\%$ during diagnostic angiography were not entered. All vasoactive therapy other than sublingual GTN was discontinued 24 h prior to the study. The study was approved by the Ethics Committee of Stobhill General Hospital. Each patient was issued with an appropriate information sheet, and written informed consent was obtained. Cardiac catheterisation was performed in the joint investigation laboratory based at the Royal Infirmary, Glasgow.

Patients were fasted prior to cardiac catheterisation. Routine left ventricular angiography and selective coronary arteriography were performed using a 7F pigtail and the 7:4 left and right Judkins' catheters (Cordis Limited) introduced through a 7F femoral arterial sheath using the Seldinger technique. Following the diagnostic procedure, a Judkins' catheter was retained in the aorta for coronary artery injections, and to measure the aortic systolic and diastolic pressures. The mean systemic arterial pressure was derived electronically.

A 7F balloon flotation catheter (Ecosse Medical Limited) was passed through a venous sheath in the right femoral vein and positioned in the pulmonary artery. The systolic, diastolic and mean pressures were obtained. The systemic and pulmonary artery pressures were recorded at baseline and at 5 min intervals throughout the study. Hard copy arterial tracings were obtained on a Mingograph 64 recorder. Heart rate was measured from a continuously monitored electrocardiogram, and a hard copy 6 lead electrocardiogram was recorded at 5 min intervals during the study. Placebo infusion was given for 10 min through an intravenous cannula positioned in the right antecubital vein, followed by an infusion of sumatriptan over 10 min to a total dose of 48 μg kg^{-1}. Central haemodynamics and 6 lead electrocardiograms were recorded for a further 10 min following cessation of the infusion. Any side-effects or adverse events were noted. The study protocol is represented diagrammatically in Table 1.

Quantitative coronary angiography

Following visualisation of the coronary artery system in standard views, a projection was chosen which allowed simultaneous visualisation of the coronary artery system and diagnostic 7F catheter which was used as a reference of measurement. Serial angiograms were obtained using a Siemens Angioskop C arm. The X-ray tube to patient distance was fixed to maintain identical magnification and avoid parallax error. Four to seven mls of non-ionic contrast medium (Niopam, Merck Products) was injected into the coronary artery under study. Seven left and

three right coronary arteries were studied. Hard copy end diastolic frames were processed from the third or fourth cardiac cycles for analysis of the coronary artery diameters with a 512 matrix in mask mode using a Siemens on-line Digitron 2 software DSA system. Digital calipers were used to measure the coronary artery diameters on at least three identified points along the length of the artery. In the 10 subjects, a total of 42 identified points were measured at each time point. The external diameter of the catheter (7F nominal value = 2.33 mm) was measured to convert the coronary artery diameter to an absolute value. Measurements were made blindly by two investigators with no prior knowledge of the injection sequence. The absolute diameters on the hard copy angiograms were measured at baseline, post placebo and post sumatriptan infusion. The diameters measured post placebo and post sumatriptan were then expressed as a percentage of the control pre-study value.

To assess the reproducibility of the coronary arteriographic measurements, the effect of placebo infusion on coronary artery dimensions was assessed in a further eight patients (five males, three females, mean age 60.5 $\pm$ 5.6 years, age range 49–67) undergoing diagnostic coronary angiography. Serial measurements were performed on four left and four right coronary arteries. Hard copy angiograms were obtained at baseline and following placebo infusion given for 10 min followed by a second placebo infusion for a further 10 min. The absolute coronary artery diameters were measured after each placebo infusion and percentage change from baseline calculated for each infusion.

Sumatriptan drug concentrations

Blood sampling was performed at the end of the sumatriptan infusion to determine peak concentration measured by h.p.l.c. (Glaxo Group Research).

Statistics

All results, unless indicated, are expressed as a mean $\pm$ s.d. and where appropriate, 95% confidence intervals (CI) are shown. Significant changes ($P < 0.05$) are highlighted with an asterisk. Analysis of variance with Bonferoni multiple comparisons was used to determine the effect of sumatriptan infusions on central haemodynamics and absolute coronary artery diameters. A paired Student's t-test was used to compare percentage change in coronary artery diameter, following placebo and sumatriptan infusion.

Table 1   Study protocol

Time (min)	−5	0	5	10	15	20	25	30	35	40
Infusion				Placebo			Sumatriptan			
ECG	*	*	*	*	*	*	*	*	*	*
Digital subtraction angiography	*				*			*		
Central haemodynamics	*	*	*	*	*	*	*	*	*	*

Results

Electrocardiography

There were no significant changes in heart rate (Figure 1) following placebo or sumatriptan infusion. There were no changes in standard electrocardiographic intervals and no changes in ECG morphology as assessed from the hard copies of six lead ECGs taken at 5 min intervals throughout the study.

Systemic arterial pressures (Figure 1)

Systolic arterial pressures (SAP) increased significantly with sumatriptan infusion rising from 135.9 ± 15.9 mm Hg to 159.2 ± 23.4 mm Hg (17.2%) at the end of the infusion and was still significantly different from baseline values 10 min post-cessation. Similarly, diastolic arterial pressure (DAP) increased from 77.7 ± 6.7 mm Hg to 86.9 ± 12.9 mm Hg (11.8%) at the end of the infusion. The mean arterial pressure (MAP) shows a similar time course, rising from 99.5 ± 10.3 mm Hg to 115.9 ± 22.6 mm Hg (16.5%) at the end of the infusion. By 10 min post cessation of the infusion, DBP and MAP had fallen and were not significantly different from the pre-drug control value.

Pulmonary artery pressures (Figure 2)

The pulmonary artery systolic pressure (PASP) increased with sumatriptan infusion from 24.6 ± 7.1 mm Hg to 37.4 ± 11.8 mm Hg, (52.6%). Although returning towards baseline by 10 min following the cessation of infusion, the PASP was still significantly different from pre-drug values. The pulmonary artery diastolic pressure (PADP) increased from 11.1 ± 6.2 mm Hg to 19.6 ± 9.9 mm Hg (76.6%) at the end of the infusion. The mean pulmonary artery pressure (MPAP) rose from 16.2 ± 6.2 mm Hg to 25.6 ± 11.2 mm Hg (58%) at the end of the infusion. The DAP and MPAP 10 min post cessation of the infusion had fallen and were not significantly different from pre-drug baseline.

Coronary artery dimensions

Reproducibility study The results of mean percentage change in coronary artery diameter for each subject after two placebo infusions are shown in Table 2. As shown, consecutive placebo infusions caused no significant change in coronary artery diameter ($P > 0.05$).

The mean difference for intra-observer measurements was 0.02 mm (95% CI −0.02 to +0.07) and inter-
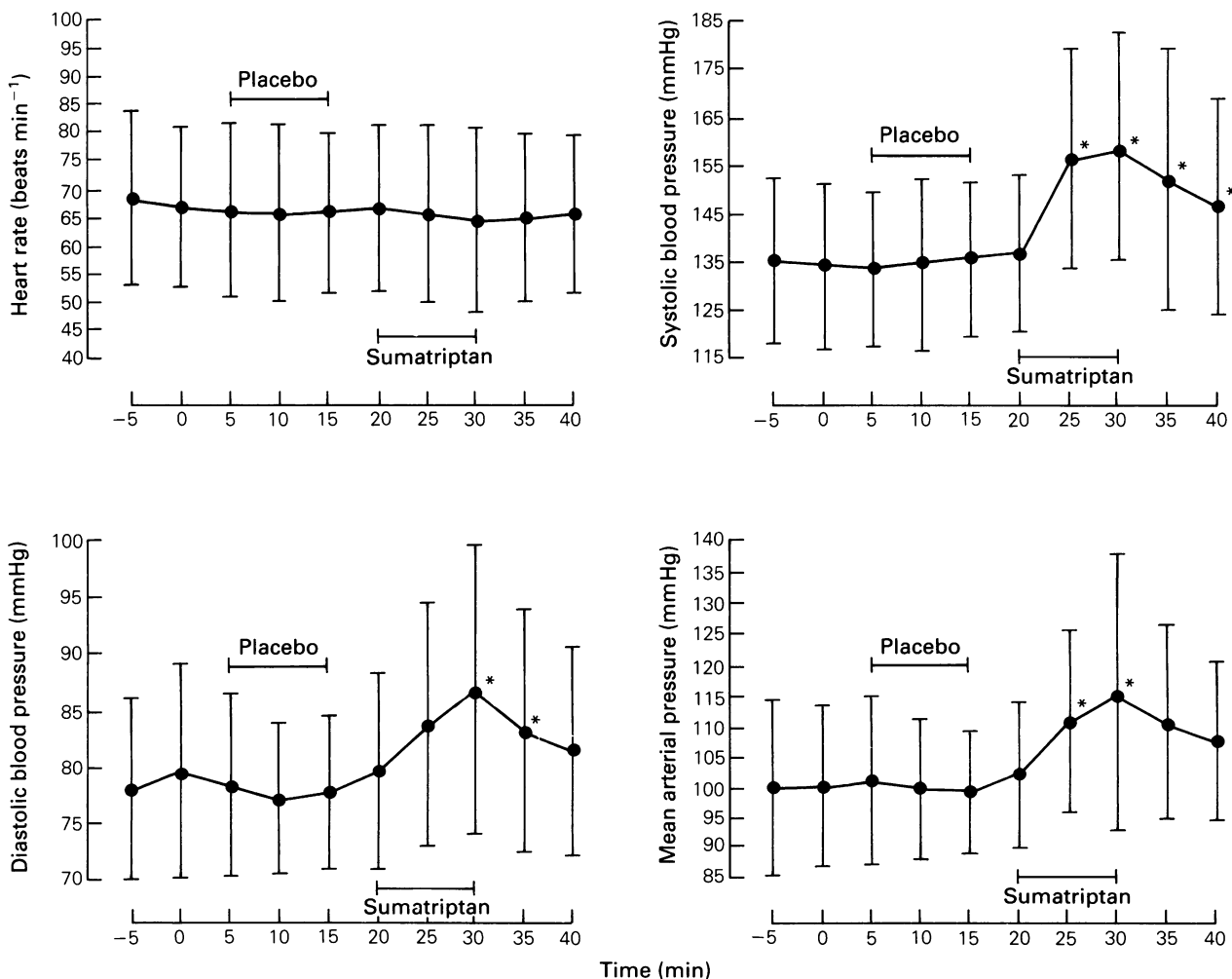
Figure 1 Changes in heart rate and systemic arterial pressures following placebo and sumatriptan infusion.
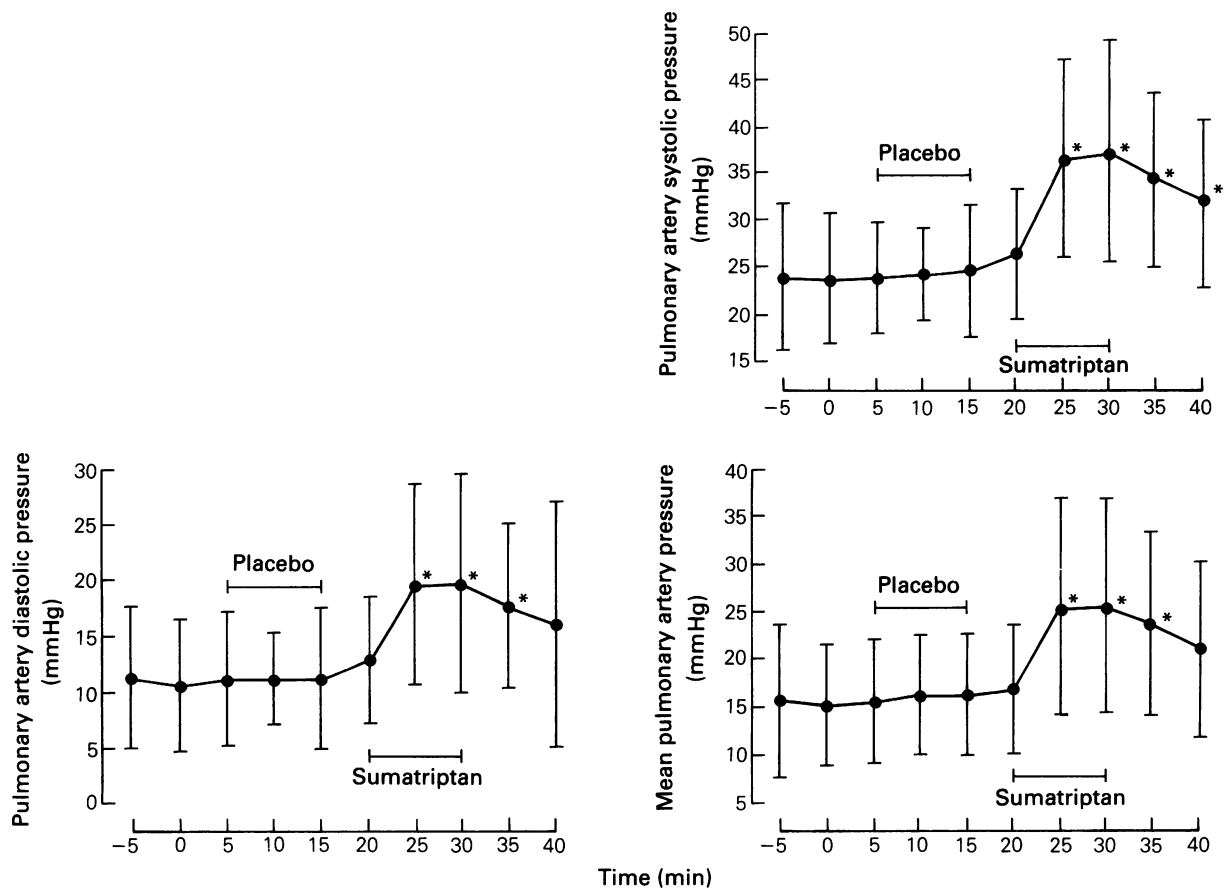
Figure 2   The changes in pulmonary arterial pressures following placebo and sumatriptan infusion.

Table 2   The mean percentage change in coronary artery luminal diameters following two placebo infusions for each individual subject

Subject	% change	
	Placebo 1	Placebo 2
	%	%
1	−1.4	2.3
2	1.9	8.1
3	2.6	3.5
4	6.6	−1.4
5	−7.8	7.3
6	1.7	−4.6
7	−3.4	−7.3
8	0.8	0.6
Mean	0.12	1.06
s.d.	4.34	5.4
Confidence intervals	(−3.5% to +3.7%)	(−3.4% to +5.6%)

Table 3   The mean percentage change in coronary artery luminal diameter following placebo and sumatriptan infusion for each individual subject

Subject	% change	
	Placebo 1	Sumatriptan
	%	%
1	−4.2	−16.0
2	13.5	−20.7
3	−2.3	−8.8
4	−9.1	−6.0
5	−4.3	0.6
6	0.6	−16.0
7	6.3	−10.6
8	3.2	−17.4
9	−3.3	−21.3
10	−3.8	−12.5
Mean	−0.3	−12.9
s.d.	6.5	6.9
Confidence intervals	(−5.0 to +4.3)	(−7.9 to −17.8)

observer measurements 0.05 mm (95% CI +0.02 to 0.09).

The mean percentage change in coronary artery diameter following placebo and sumatriptan infusion are shown for each subject in Table 3. Following placebo, there was no significant change in the mean value ($P > 0.05$). The mean percentage reduction in coronary artery diameter was 12.9 ± 6.9% (95% CI +7.9 to + 17.8%). Following sumatriptan, the absolute coronary artery diameter fell from 4.3 mm ± 1.6 mm to 3.6 mm ± 1.6 mm ($P < 0.001$). The mean absolute reduction in coronary artery diameter was 0.60 ± 0.38 mm (95% CI +0.44 to +0.68).

Plasma sumatriptan concentrations

The mean peak plasma sumatriptan concentration in 10 subjects measured at the end of the infusion was 156 ± 48 ng ml^{-1} (range 94–223 ng ml^{-1}).

Discussion

This study is the first detailed study of the haemodynamic changes in man following intravenous administration of

sumatriptan. The results demonstrate a vasopressor response in both pulmonary and systemic arterial circulations. These changes occurred within 5 min of administration of sumatriptan, but were short-lived, and returned towards baseline some 10 min post cessation of the infusion. This study confirms the reports of an increase in systemic arterial blood pressure in a small number of patients measured non-invasively in the early clinical trials (Brion *et al.*, 1989; International Subcutaneous Sumatriptan Trial 1991). However, our study suggests that the vasopressor responses observed in the systemic circulation is a consistent finding and does not represent an idiosyncratic reaction to sumatriptan administration.

Sumatriptan mediates its vasoactivity through 5-HT$_1$-receptors which may be further sub-divided into 5-HT$_1$a–d. There is evidence that sumatriptan activates 5-HT$_1$d receptors (Peroutka & McArthy, 1989; Schoeffter & Hoyer, 1989a, b). These vasoconstrictor properties may be antagonised by methiothepin, a non-selective 5-HT$_1$/5-HT$_2$-receptor antagonist, but not by ketanserin, a selective 5-HT$_2$-receptor antagonist (Humphrey *et al.*, 1988). The presence of 5-HT$_1$ receptors and their subtypes varies markedly between species and between different vascular beds in the same species (Van Zwieten *et al.*, 1990) which perhaps explains the selective effects of sumatriptan and other 5-HT$_1$-receptor agonists. In this study the relative percentage increase in mean pulmonary artery pressure is greater than the change in systemic arterial pressure by a factor of 3. This may suggest that the density of the 5-HT$_1$ receptor subtype activated by sumatriptan is greater in the pulmonary than systemic arterial circulation. Further studies are necessary to elicit the role of 5-HT$_1$ stimulation in the development and maintenance of pulmonary hypertension in disease states, and these observations may also indicate potential pharmacological therapy using 5-HT$_1$-receptor antagonists.

There was no significant change in heart rate in response to sumatriptan infusion. This finding is in keeping with previous evidence that sumatriptan or other 5-HT$_1$ receptor agonists lack positive chronotropic effects. The cardiac output was not measured in this study, but as there is no evidence to suggest that 5-HT receptors have a positive inotropic effect we postulate that the increase in vascular pressures is secondary to increased vascular tone, rather than to increased cardiac contractility.

Our study demonstrated a vasoconstrictor effect of sumatriptan on the epicardial coronary arteries observed by serial coronary arteriography. The change in diameter of 12.9 ± 6.9% was not accompanied by clinical symptoms nor ECG evidence of myocardial ischaemia. It is however the first observation of 5-HT$_1$ receptor mediated vasoconstrictor response in the coronary circulation *in vivo*. *In vitro*, the contractile effects of serotonin on normal human epicardial coronary artery rings were shown to be predominantly 5-HT$_2$ mediated (Connor *et al.*, 1989b). However, a reduced residual contraction, resistant to ketanserin was also demonstrated and was attributed to 5-HT$_1$ receptors. Contractile response to 5-HT$_2$ receptor activation was significantly reduced in atherosclerotic coronary artery rings compared to normals. Sumatriptan caused selective vasoconstriction of normal coronary artery rings but the

force of contraction was only 30% of that elicited by serotonin. However, in atherosclerotic coronary artery rings this selective 5-HT$_1$ receptor mediated contraction with sumatriptan was preserved in comparison to normals. Although the magnitude of the 5-HT$_1$ mediated effect was small compared with 5-HT$_2$ it may become functionally significant in the presence of a sub-total coronary artery stenosis. The development of selective 5-HT$_1$ receptor antagonists capable of blocking this response in human coronary arteries may be of value in the treatment of patients with unstable angina or in the very early phase of acute myocardial infarction. In these acute ischaemic syndromes, serotonin, released from aggregating platelets, may cause 5-HT$_1$ mediated vasoconstriction, resulting in a significant reduction in coronary artery flow, and therefore predisposing to further platelet aggregation and thrombus formation. *In vivo* studies suggested that the presence of functional endothelium may determine the net effect of serotonergic agonists (Vanhoutte & Shimokawa, 1989; Chu & Cobb, 1987; Cocks & Angus, 1983; Connor & Feniuk, 1989; Brum *et al.*, 1984). In contrast to *in vitro* studies, normal human coronary arteries studied angiographically dilated in response to serotonin; this effect is potentiated by ketanserin, and thus attributed to 5-HT$_1$ receptor activation. Diseased atherosclerotic coronary arteries however showed vasoconstriction in response to serotonin (Golino *et al.*, 1991). It was postulated that the loss of functional endothelium in diseased arteries prevents a 5-HT$_1$ receptor mediated vasodilatation and thus this response was attributed to 5-HT$_2$ receptors. In the coronary circulation, 5-HT$_1$ receptors which mediate vasodilatation by release of endothelium relaxing factors (EDRF) (Angus, 1989; Vanhoutte, 1990) have been demonstrated on the endothelial surface. 5-HT$_2$-receptors are situated on the surface of coronary artery smooth muscle cells and cause vasoconstriction (Vanhoutte, 1990). The present study has demonstrated 5-HT$_1$-like mediated vasoconstriction in the coronary circulation *in vivo* and suggests the presence of a 5-HT$_1$ subreceptor which can mediate this anomalous response.

The patients in our study were being investigated for chest pain, but patients with unstable clinical symptoms were excluded, as were patients with significant obstructive coronary artery stenotic lesions. None had unstable angina nor previously documented variant angina. In this latter condition, serotonin has been shown to cause marked vasoconstriction in the presence of pre-existing coronary artery stenosis (McFadden *et al.*, 1991). It was suggested that this was a 5-HT$_2$ response, although ketanserin was not administered to confirm this. So far there are no clinical observations of the effects of sumatriptan in patients with unstable angina. In addition, in view of our patients' normal or near normal coronary artery anatomy, further studies would be required to elicit the effects of sumatriptan on obstructive coronary artery lesions.

It should be emphasised that sumatriptan was administered intravenously in the present study in order to limit pharmacological problems of absorption and variable duration of action. The peak plasma levels achieved (mean 156 ± 48 ng ml^{-1}, range 94–223 ng ml^{-1}) were higher than those peak concentrations found after the standard 6 mg subcutaneous dose in the clinical treat-

ment of patients with migraine (mean 72.4 ng ml^{-1}, range 54.9–108.4 ng ml^{-1} (Glaxo Group Research)).

In summary, short-lived vasoconstrictive effects were seen in pulmonary, systemic and coronary circulations following sumatriptan administration possibly mediated by stimulation of 5-HT_1-like receptors. These changes were brief and not associated with clinical symptoms nor objective evidence of myocardial ischaemia. The clinical experience of sumatriptan extends to several thousand patients, and no significant clinical sequelae have been reported with its usage. However, further clinical observations are required to determine whether responses we observed have clinical relevance, as this study may have implications in the treatment of patients with migraine who have concurrent cardiovascular disease.

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