Brief Rapid Communication

Effect of Subcutaneous Sumatriptan, a Selective $5HT_1$ Agonist, on the Systemic, Pulmonary, and Coronary Circulation

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Background. **Sumatriptan (GR43175) is a selective 5-hydroxytryptamine ($5HT_1$) receptor agonist effective in the acute treatment of migraine. Recent in vitro experiments suggest that it has vasoactive properties in vascular beds distinct from the cerebral circulation. The object of this study was to assess the vasoactive effects of the standard 6-mg subcutaneous dose of sumatriptan used in migraine on the systemic and pulmonary circulations and the coronary artery vasculature.**

Methods and Results. **Ten patients undergoing diagnostic coronary arteriography were studied with digital subtraction angiography and invasive hemodynamic monitoring. After subcutaneous injection of sumatriptan, there was no significant change in heart rate or ECG morphology. There was a significant rise in the systemic (20%, $p<0.05$ by ANOVA) and pulmonary arterial (40%, $p<0.05$ by ANOVA) pressures. There was no change in cardiac output, but there was a significant increase in total systemic (27%, $p<0.05$) and total pulmonary vascular resistance (40%, $p<0.05$). Sumatriptan caused a significant reduction ($p<0.001$ by ANOVA) in mean absolute coronary artery diameter, from 4.36±1.60 mm at baseline to 3.67±1.49 mm (16%) at 10 minutes and to 3.63±1.49 mm (17%) at 30 minutes after injection. There were no clinical sequelae.**

Conclusions. **Sumatriptan, a $5HT_1$ receptor agonist administered by the subcutaneous route, causes a vasopressor response in the systemic and pulmonary arterial circulations and coronary artery vasoconstriction. (*Circulation* 1993;87:401–405)**

KEY WORDS • **sumatriptan** • **5-hydroxytryptamine** • **serotonin** • **coronary circulation**

Sumatriptan, GR43175 (3-[2-(dimethylamino)ethyl]-*N*-methyl-1*H*-indole-5-methane sulfonamide), is a selective 5-hydroxytryptamine ($5HT_1$) receptor agonist effective in the acute treatment of migraine,[1,2] possibly by reversal of intracranial arterial dilatation.[3] The $5HT_1$ receptor may be further subdivided into $5HT_1$ a–d subtypes. There is some evidence that sumatriptan is a selective $5HT_1$d receptor agonist.[4–6] In isolated vascular preparations, it has been shown to cause selective constriction of rabbit,[7] dog, and primate basilar arteries[8] and dog saphenous vein.[9] In anesthetized intact animals, it caused selective vasoconstriction of feline and canine carotid arterial circulations, with no effect on extracranial vascular beds.[10,11]

Human isolated basilar artery rings constricted in response to sumatriptan,[12] as did normal and atherosclerotic human epicardial coronary artery rings from explanted hearts.[13,14] In early clinical trials, transient increases in systolic and diastolic arterial blood pressures were seen after administration of sumatriptan, but this was not a consistent finding in all subjects.[1,2] Femoral arterial vasoconstriction has been demonstrated noninvasively in humans after sumatriptan.[15] These studies suggested that sumatriptan causes vasoconstriction of various vascular beds in humans and that in humans, $5HT_1$ receptors may not be confined to the cranial circulation, unlike other species.

The object of this study was therefore to determine the effects on central hemodynamics and coronary vascular tone of sumatriptan given in the standard 6-mg subcutaneous dose used in migraine.

Methods

Patient Group

Ten patients, six men and four women (mean age, 49±11 years), were studied during coronary arteriography being performed for diagnostic purposes. All vasoactive therapy other than sublingual glyceryl trinitrate was discontinued 24 hours before the study.

Exclusion criteria included women of childbearing potential, myocardial infarction within 3 months, unstable angina, cardiac arrhythmias, and hypertension (diastolic blood pressure ≥95 mm Hg). Because this drug had the potential to cause vasoconstriction, patients found to have coronary artery stenosis of ≥50% during diagnostic angiography were not entered.

The study was approved by the Ethics Committee of Stobhill General Hospital. Each patient was issued an appropriate information sheet, and written informed consent was obtained.

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Central Hemodynamic Monitoring

Routine left ventricular angiography and selective coronary arteriography were performed by the conventional Judkins technique.

After the diagnostic procedure, the Judkins catheter was retained in the aorta to measure systemic arterial systolic and diastolic blood pressures. A 7F balloon flotation catheter was positioned in the pulmonary artery and used to measure pulmonary artery systolic, diastolic, and occluded wedge pressures. Hard copies of systemic and pulmonary arterial pressure tracings were obtained at baseline and at 5-minute intervals until repeated measurements were within 5% to confirm reproducibility. Thereafter, the pressures were measured at 5-minute intervals for a total of 40 minutes after injection of sumatriptan. Heart rate was measured from a continuously monitored ECG, and hard-copy ECGs were obtained at 5-minute intervals. Cardiac output was measured by the thermodilution technique, a mean value of at least three measurements at each time point. The total systemic vascular resistance and the total pulmonary vascular resistance were calculated at baseline, 10 minutes, and 30 minutes after injection.

Drug Administration

After baseline measurements, sumatriptan (6 mg s.c.) was injected into the deltoid region of the right arm. Blood sampling to determine sumatriptan concentration was performed at 10 and 30 minutes after injection.

Quantitative Coronary Angiography

Seven left and three right coronary arteries were studied. After visualization of the coronary artery system in the standard views, a projection was chosen that allowed simultaneous visualization of the coronary artery system and the diagnostic 7F catheter that was used as the reference of measurement. Serial angiograms were obtained with a Siemens angioscope C arm. The x-ray tube–to–patient distance was fixed to maintain identical magnification and to avoid parallax error. Nonionic contrast medium (4–7 ml) (Niopam, Merck Products) was injected by hand into the coronary artery under study. Hard-copy end-diastolic frames were processed from the third or fourth cardiac cycles for analysis of coronary artery dimensions with a 512×512 matrix in mask mode using a Siemens on-line Digitron II software DSA system at baseline and at 10 and 30 minutes after injection. Several corresponding segments were identified along the length of the artery on each of the hard-copy films. Two blinded observers used digital calipers (Summagraphics digitizer) to measure coronary artery diameter at these corresponding segments. The external diameter of the catheter (7F; nominal value, 2.33 mm) was measured to convert the coronary artery diameter to an absolute value. The mean absolute coronary diameter was calculated for each time point.

Reproducibility Study

The reproducibility of the methodology to measure coronary artery dimensions was assessed in eight more patients (five men, three women; mean age, 60.5±5.6 years) undergoing diagnostic coronary arteriography.

TABLE 1. Baseline and Maximum Hemodynamic Measurements at 5 Minutes After Subcutaneous Injection of Sumatriptan

	Arterial pressure (mm Hg)		Increase (%)
	Baseline	Maximum	
SBP	136±20.8	162.9±43.3	20
DBP	78.4±8.5	89.3±13.9	16
PASP	28.7±9.1	41.2±13.2	40
PADP	13.5±6.3	18.6±7.5	33
PAWP	8.7±6.0	15.6±4.6	90

SBP, DBP, systemic arterial systolic and diastolic blood pressures; PASP, PADP, PAWP, pulmonary arterial systolic, diastolic, and occluded wedge pressures. Values are mean±SEM.

Statistics

Repeated-measures ANOVA with Bonferroni multiple comparisons was used to determine the effect of sumatriptan on central hemodynamics and absolute coronary artery diameters. The results are expressed as mean±SD in the text but graphically as mean±SEM. Significant differences ($p<0.05$) are highlighted with an asterisk in the figures.

Results

Central Hemodynamics

There were no significant changes in heart rate after placebo or sumatriptan infusion. There were no changes in the standard ECG intervals (PR, QRS, QT, and QT_c). Sumatriptan caused a significant increase in systemic arterial systolic and diastolic pressures and pulmonary artery systolic, diastolic, and occluded wedge pressures within 5 minutes of subcutaneous administration, which persisted until at least 20 minutes after injection (Table 1 and Figure 1). No significant changes in cardiac output were measured at 10 and 30 minutes after injection; however, there was a significant rise in total systemic and total pulmonary vascular resistance at 10 minutes (Figures 2a and 2b and Table 2).

Coronary Artery Diameters

Reproducibility study. The mean intraobserver and interobserver differences in measurements of coronary artery diameter were 0.02 mm (95% CI, −0.02 to +0.07) and 0.05 mm (95% CI, +0.02 to +0.09), respectively.

Effect of sumatriptan. Sumatriptan caused a significant reduction ($p<0.001$ by ANOVA) in mean absolute coronary artery diameter, from 4.36±1.60 to 3.67±1.49 mm (16%), which was apparent at 10 minutes and sustained for 30 minutes to 3.63±1.49 mm (17%) (Figure 2c).

There were no clinical symptoms suggestive of angina or ECG evidence of myocardial ischemia associated with these changes. There was no relation between the age of the patient and the vascular effect of sumatriptan in this study.

Plasma Sumatriptan Concentrations

The mean plasma sumatriptan concentration was 123.5±49.1 ng/ml measured at 10 minutes and 71.4±23.4 ng/ml measured at 30 minutes.

Discussion

These results show a vasopressor response in the systemic and pulmonary circulation after subcutaneous

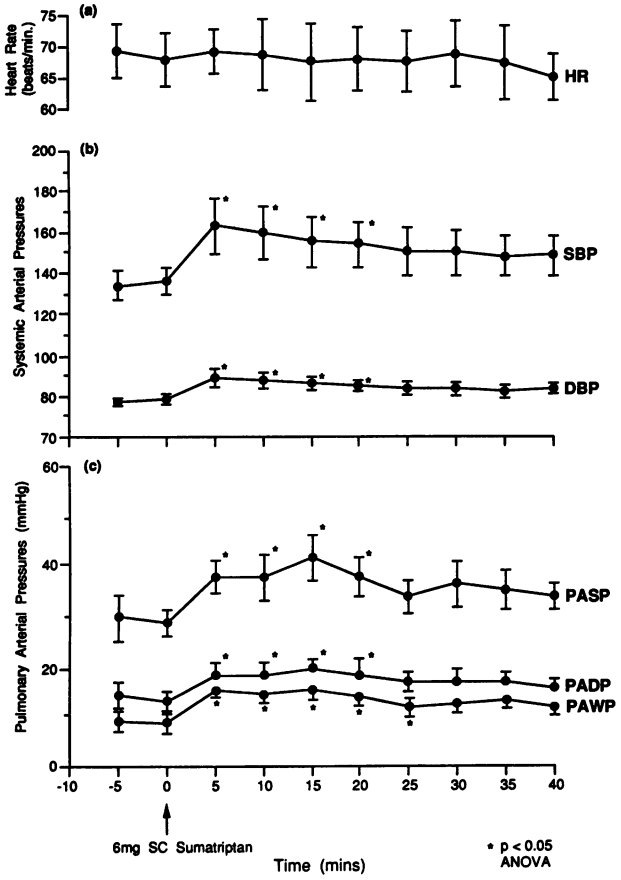

FIGURE 1. *Graphs showing heart rate and systemic and pulmonary arterial pressures after 6 mg subcutaneous sumatriptan. HR, heart rate; SBP, DBP, systemic arterial systolic and diastolic blood pressures; PASP, PADP, PAWP, pulmonary arterial systolic, diastolic, and occluded wedge pressures; SC, subcutaneous. Values are mean±SEM.*

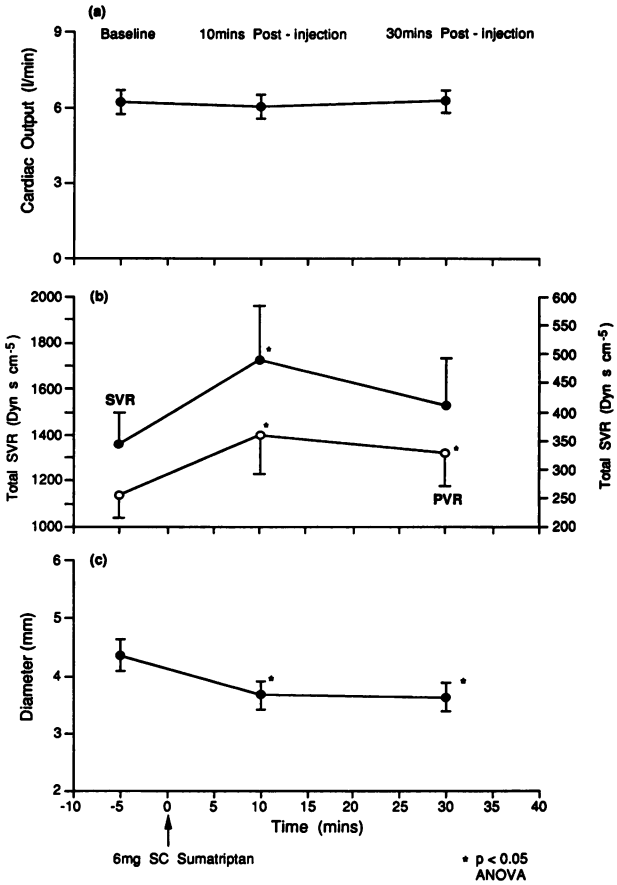

FIGURE 2. *Graphs showing changes in cardiac output, total systemic vascular resistance (SVR), total pulmonary vascular resistance (PVR), and coronary artery diameter after injection of 6 mg sumatriptan. Values are mean±SEM.*

injection of sumatriptan. This response was transient, the maximum rise occurring within 5 minutes of subcutaneous injection and arterial pressures returning to preinjection levels within 25 minutes. The rise in total systemic and total pulmonary vascular resistance, without a change in heart rate or cardiac output, implies that the observed pressure response is attributable to a direct vasoconstrictor effect.

Because there is no evidence to suggest a chronotropic or inotropic effect with serotonergic agonists, we would not expect a change in left ventricular end diastolic or left atrial pressures, but these were not measured in this study.

Therefore, we postulate that the change in pulmonary artery wedge pressure may be due to pulmonary venoconstriction rather than a consequence of an increase in left atrial pressure, although further studies, including the measurement of left ventricular end-diastolic pressure, are required to confirm this.

The presence of $5HT_1$ receptors and their subtypes varies markedly between species and between different vascular beds within the same species.[16] We have demonstrated that the $5HT_1$ receptor subtype mediating the effects of sumatriptan does exist in vascular beds distinct from the cranial circulation in humans.

We demonstrated a vasoconstrictor effect of sumatriptan on epicardial coronary arteries by serial quantitative digital subtraction angiography. The observed 16% reduction in coronary artery diameter was not accompanied by clinical symptoms or ECG evidence of myocardial ischemia. The rise in systemic arterial diastolic pressure will lead to an increase in coronary artery perfusion pressure. This may offset the reduction in coronary artery blood flow caused by the reduction in coronary artery diameter. Further experiments that measure coronary artery blood flow directly are required to confirm this.

In vitro, the vasoconstrictive effects of serotonin in normal and atherosclerotic coronary artery rings have been shown to be predominantly $5HT_2$-receptor mediated.[13,14] However, a small ketanserin-resistant contraction was produced by sumatriptan and therefore attributed to $5HT_1$ receptor activation. Although the magnitude of this $5HT_1$-mediated contraction is small compared with the $5HT_2$ response, it could become functionally significant in vivo in the presence of severe coronary artery stenosis. The development of selective $5HT_1$ antagonists may be of therapeutic value.

The plasma levels of sumatriptan obtained at 10 and 30 minutes in this study were 123.5±49.1 and 71.4±23.4 ng/ml, respectively, and were consistent with levels

TABLE 2. Changes in Cardiac Output, Total Systemic Vascular Resistance, and Total Pulmonary Vascular Resistance Measured at Baseline and 10 and 30 Minutes After Injection

	Baseline	10 Minutes	Increase (%)	30 Minutes	Increase (%)
CO (l/min)	6.25±1.4	6.04±1.4	...	6.27±1.3	...
TSVR (dyne · sec · cm^{-5})	1,360±139	1,728±229	27	1,530±200	12
TPVR (dyne · sec · cm^{-5})	256±39.4	360±67.2	40	328±58.4	28

CO, cardiac output; TSVR, total systemic vascular resistance; TPVR, total pulmonary vascular resistance. Values are mean±SEM.

obtained from previous studies of normal volunteers using the same dose and route of administration (Glaxo Group Research).

Data from the two time points showed no obvious concentration–effect relation; further studies are required to determine whether one exists.

It has been suggested that the presence of functional endothelium may determine the net effect of serotonergic agonists.[17–21] In vivo, normal human epicardial coronary arteries studied angiographically dilated in response to serotonin.[22] This was attributed to activation of $5HT_1$ receptors situated on the endothelial surface, which are thought to cause release of endothelium-derived relaxing factors.[23,24] Diseased atherosclerotic coronary arteries constrict in response to serotonin by activation of $5HT_2$ receptors situated on the smooth muscle cell.[25] Therefore, it was postulated that the loss of functional endothelium in diseased arteries results in a loss of $5HT_1$-receptor–mediated vasodilatation.

This study demonstrated $5HT_1$-mediated vasoconstriction in the coronary circulation in vivo. Although we did not study the effects of $5HT_2$ antagonists such as ketanserin or ritanserin, there is no evidence in the existing literature to suggest that sumatriptan has $5HT_2$ activity. We have confirmed the results of previous in vitro experiments, suggesting the presence of a $5HT_1$ receptor subtype that can mediate vasoconstriction. The effects of $5HT_1$ agonists, therefore, will depend on which receptor subtypes they activate and the relative abundance of each receptor subtype within a particular vascular bed.

In summary, vasoconstrictor effects were seen in the pulmonary, systemic, and coronary circulations after administration of sumatriptan. These changes were not associated with clinical symptoms of angina or objective evidence of myocardial ischemia. In clinical studies with subcutaneous sumatriptan, approximately 0.3% of patients experienced a sensation of pressure or heaviness in the chest.[26] None of these patients were shown to have ECG evidence of myocardial ischemia. However, there have been case reports of sumatriptan causing chest pain with associated ST elevation in the ECG.[26,27] The patients had a previous history of chest pain but no exercise-induced evidence of myocardial ischemia. Although symptom-limited exercise tests were performed, neither patient had coronary angiography or an ergonovine provocation test to exclude underlying coronary artery disease and variant angina, respectively. Further clinical observations are required to determine whether the effects of sumatriptan are of clinical relevance in the presence of coronary artery disease. Our study may have implications in the administration of this therapy to patients who have migraine and concurrent cardiovascular disease.

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