Eur J Clin Pharmacol (2005) 61: 733–742
DOI 10.1007/s00228-005-0988-4

PHARMACODYNAMICS

**Christopher M. H. Newman · Ian Starkey · Nigel Buller
Ricardo Seabra-Gomes · Simon Kirby
Jayasena Hettiarachchi · David Cumberland
William S. Hillis**

Effects of sumatriptan and eletriptan on diseased epicardial coronary arteries

Received: 27 June 2005 / Accepted: 29 July 2005 / Published online: 8 September 2005

Abstract *Background*: Triptans are contraindicated in patients with known or suspected coronary artery disease (CAD); however, few studies have evaluated triptans in patients with obstructive CAD to quantify the vasoconstrictive effect on diseased coronary vessels. *Methods*: Patients undergoing percutaneous transluminal coronary angioplasty for symptomatic single-vessel CAD were randomised to one of three parallel cohorts to receive (1) 6 mg intravenously (IV) infused eletriptan plus subcutaneous (SC) placebo, (2) IV infused placebo plus 6 mg SC sumatriptan or (3) IV infused placebo plus SC placebo, as simultaneous administrations in a double-blind manner. Serial arteriograms, hemodynamic indices, electrocardiography and triptan plasma concentrations were obtained. *Results*: Fifteen minutes after triptan challenge, median (95% confidence interval) changes in coronary artery diameter (CADM) at the focal point of the stenosed segment were: dilation of 2.6% (−5.0, 11.4), eletriptan 6 mg IV ($n=18$); constriction of 6.8% (−12.6, 0.4), sumatriptan 6 mg SC ($n=17$), and constriction of 4.5% (−7.0, 7.9), placebo ($n=10$). One patient had angiographic evidence of a new thrombus at the stenosis site, necessitating termination of study infusion and successful stenting of the lesion. There was no correlation between effects on CADM and triptan concentration, or between hemodynamic or electrocardiograph changes and the presence ($n=13$) or absence ($n=33$) of chest pain. *Conclusions*: Triptans had very little effect on diseased epicardial coronary arteries in a small group of angina sufferers with established CAD. Results should be interpreted cautiously since there may be instances where even modest triptan-associated epicardial constriction is sufficient to precipitate myocardial ischemia in patients with severe obstructive CAD.

Keywords Triptan · Coronary artery disease · Eletriptan · Sumatriptan

C. M. H. Newman (✉)
Division of Clinical Sciences (North), Cardiovascular Research Unit, University of Sheffield, Sheffield, S5 7AU, UK
E-mail: c.newman@sheffield.ac.uk
Tel.: +44-114-2714456
Fax: +44-114-2619587

I. Starkey
Department of Cardiology, Western General Hospital, Edinburgh, UK

N. Buller
Department of Cardiology, Queen Elizabeth Hospital, Birmingham, UK

R. Seabra-Gomes
Department of Cardiology, Hospital Santa Cruz, Carnaxide, Portugal

S. Kirby
Pfizer Inc., Sandwich, UK

J. Hettiarachchi
Pfizer Inc., New York, NY, USA

D. Cumberland
Department of Cardiology, Northern General Hospital, Sheffield, UK

W. S. Hillis
Western Infirmary, Glasgow, UK

Introduction

The selective 5-$HT_{1B/1D}$ agonists known as triptans have provided a major advance in the treatment of patients with migraine, based on their receptor-mediated ability to counteract the abnormal vasodilation of cerebral vessels seen in this condition [1, 2].

Triptans as a class appear to be generally well tolerated, with minimal differences between drugs with respect to the incidence of adverse events [3]. Soon after the introduction of sumatriptan, reports began to appear of angina-like chest symptoms [4, 5]. Data from large post-marketing surveys [5–7] suggested that the vast majority of triptan-related chest symptoms were

noncardiac in origin. Furthermore, direct in vivo challenge studies in patients with normal or minimally diseased coronary arteries have shown that triptan administration results in only a relatively modest reduction in epicardial coronary artery diameter (CADM) – insufficient in itself to affect coronary flow – and a modest increase in systemic and pulmonary vascular resistance [8–11]. These findings have recently been confirmed by a large prescription database analysis which showed that triptan therapy is not associated with an increased risk of cardiovascular or cerebrovascular morbidity or mortality [12].

Nevertheless, isolated cases of chest pain of cardiac origin, ischemia and myocardial infarction have been reported following the use of sumatriptan [13–16]. As a result, triptans have class labelling that contraindicates their use in patients with known or suspected coronary artery disease (CAD). Despite the reassuring results obtained in patients with normal or minimally diseased coronary arteries, it is possible that similar or exaggerated vasoconstrictor effects of triptans in patients with undiagnosed obstructive CAD may be sufficient to cause myocardial ischemia and, consequently, explain some of the reports of triptan-related chest pain that have occurred in previously asymptomatic individuals.

In cardiovascular disease, the endothelium loses its normal homeostatic regulatory function, thereby resulting in heightened vasoreactivity [17]. The extent to which triptans, which act primarily via 5-$HT_{1B/1D}$ receptors, may be associated with exaggerated vasoconstrictor effects in coronary arteries with diseased endothelia has never been systematically studied in vivo.

Serotonin and related agonists (such as the triptans) act on the coronary endothelium through 5-HT_2 receptors and also via some 5-HT_1 receptor subtypes [18–20]. The known coronary 5-HT_1 vasoconstrictive effects appear to be predominantly due to agonist activity at the 5-HT_{1B} receptors, with a minor contribution from 5-HT_{1D} receptors [21–28]. These preclinical data appear to confirm the enhanced selectivity of triptans for cerebral rather than coronary vasoconstriction [9, 10, 29, 30].

Preclinical data suggest that there are substantial differences among triptans with respect to their coronary contractile potential at therapeutic plasma concentrations. For both eletriptan and sumatriptan, the maximum mean plasma concentration (C_{max}) at therapeutic doses is more than tenfold lower than the concentration needed to elicit 50% maximal effect on coronary arteries (EC_{50}). Based on in vitro studies [31], eletriptan and sumatriptan appear to have the lowest C_{max}/EC_{50} ratio for coronary artery constriction among available triptans.

The study reported here was designed to test the relative coronary vasoconstrictive potential of eletriptan and sumatriptan in an at-risk sample of patients with obstructive CAD. A placebo challenge group was included to provide a reference for the nonspecific vasoconstrictive effect of the test procedures. The study was conducted in patients scheduled to undergo percutaneous revascularisation for relief of angina because these circumstances allowed the coronary vasoconstrictor effects of these triptans to be assessed in a defined population under controlled experimental conditions. Furthermore, any occurrences of triptan-associated chest pain could be directly correlated with detailed assessments of epicardial coronary vasoconstriction, intracoronary (IC) pressure and myocardial ischemia.

Methods

Patients

This double-blind, randomised, placebo-controlled, double-dummy, single-dose, parallel-group study was conducted in patients scheduled to undergo percutaneous transluminal coronary angioplasty (PTCA) for symptomatic single-vessel CAD. The local research ethics committees of the five participating institutions approved the study. Written informed consent was obtained on two separate occasions, the first after initial screening and the second on the day of the scheduled PTCA. In each case, study risks and procedures had been fully explained, and the patient had time alone with partners or other family members to review the subject information sheet.

Patients were entered into the study if they were aged ≥18 years; women were included if they were confirmed to be of nonchild-bearing potential (i.e. 2 years post-menopausal, surgically sterilised or using medically approved contraception with a negative urinary pregnancy test at screening). Patients with angina pectoris could be included unless they had a history of transmural myocardial infarction within the last 3 months or in the territory supplied by the vessel of the stenosis to be dilated.

Patients with Braunwald classes 1A, 1C, 2A, 2C or 3A–C symptoms of angina were excluded, as were those patients with cardiac arrhythmias who required drug therapy. Other exclusion criteria included cardiogenic shock, a left ventricular ejection fraction of $<30\%$, diastolic blood pressureof ≥95 mmHg at initial screening or significant valvular disease that required surgical intervention. Patients were also excluded if they had any contraindication to emergency coronary artery bypass surgery or if they had undergone a coronary revascularisation procedure within the last 30 days. The presence of any clinically significant active systemic, renal, hepatic, gastrointestinal, urological, endocrine, metabolic or psychiatric disease was also reason for exclusion.

Inclusion criteria on the study day (i.e. the day of PTCA) included coronary arteriographic confirmation of the presence of single-vessel disease with a $>50\%$ diameter stenosis requiring revascularisation with a native vessel diameter ≥3 mm, and with a lesion length <23 mm and associated with thrombolysis in myocardial infarction grade III flow prior to PTCA.

Angiographic exclusion criteria included intended angioplasty of an aorto-ostial lesion, ostial left anterior descending or circumflex vessel stenoses, lesions with evidence of thrombus or a total occlusion.

Study procedures

Patients were scheduled for PTCA within 30 days of recruitment into the study during an initial screening visit. Anti-anginal medications were tapered prior to PTCA, with beta-blocker usage discontinued at least 48 h prior to the study day and other vasoactive therapy discontinued at least 24 h prior. If required, sublingual nitrate was administered up to 1 h before the start of the PTCA.

Upon arrival in the catheter laboratory, patients were prepared for PTCA from the right femoral artery in the standard manner, with the exception that continuous 3-lead ECG monitoring was performed using radiolucent ECG pads and leads (Philips Medical Systems, Eindhoven, the Netherlands), which allowed the recording of 12-lead ECGs throughout the procedure. Following visual confirmation of angiographic entry criteria and systemic heparinisation, the target vessel was instrumented with a Radi pressure wire (Radi Medical Systems, Uppsala, Sweden) with the transducer element placed distal to the target stenosis. Baseline study angiograms were performed at 25 frames per second, 5 min apart, on two occasions using two orthogonal views of the right coronary artery and three views of the left coronary artery as appropriate. An independent core laboratory (Cardialysis, Rotterdam, the Netherlands), blinded to treatment randomisation, performed the quantitative coronary arteriography (QCA).

Patients were randomised to one of three parallel cohorts to receive (1) 6 mg intravenously (IV) infused eletriptan plus subcutaneous (SC) placebo, (2) IV infused placebo plus 6 mg SC sumatriptan or (3) IV infused placebo plus SC placebo, as simultaneous administrations in a double-blind manner (Fig. 1). The 30-min study period was followed by a single injection of 200 μg glyceryl trinitrate (GTN).

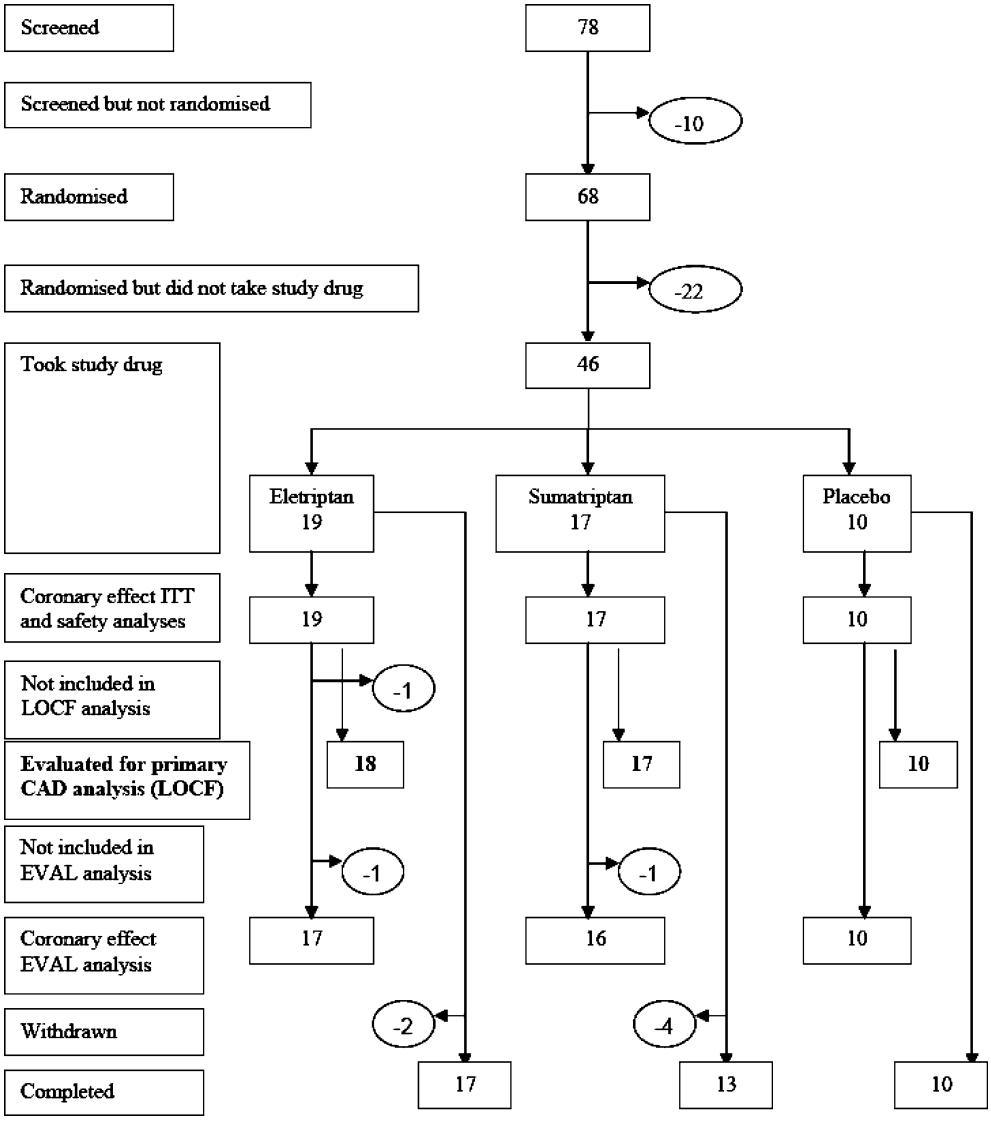

Fig. 1 Patient enrollment, treatment randomisation and study procedures

Figure 2 shows the time course of measurements carried out. Aortic pressure, heart rate and a 12-lead ECG were recorded at baseline, 5, 10, 15, 20, 25, 30 and 32 min (i.e. 2 min after IC GTN) after administration of the study medication. Simultaneous recordings of central aortic and distal IC pressure were made at baseline, 15, 30 and 32 min. Study arteriograms were repeated at 5, 15, 30 and 32 min. All of these measurements were repeated in the event that the patient developed chest pain or other symptoms during the study period. The study infusion was stopped and/or IC GTN was administered if patients developed ECG evidence of ischemia, >25% focal or diffuse vasoconstriction (by visual determination) in association with chest pain or ECG changes or exhibited >50% focal or diffuse vasoconstriction (by visual determination) that was asymptomatic.

Following the completion of the study period, planned PTCA of the target lesion was performed. Patients were contacted between 3 and 7 days after their procedure to evaluate any post-study adverse events.

Eletriptan/sumatriptan assays

Blood samples were collected at the start and at the end of the infusion, and at 30 min after the start of infusion. Samples were centrifuged in heparinised tubes at room temperature for 10 min at 1500 *g*, and the plasma was stored upright in screw-capped polypropylene tubes at −20°C until the assay was performed. Eletriptan levels were measured by high-performance liquid chromatography (HPLC) with ultraviolet detection by Clinical Innovations (Warwickshire, UK). The assay had a coefficient of variation that ranged from 3.2 to 9.7% for eletriptan concentrations in the range of 3–200 ng/ml. Sumatriptan levels were measured by HPLC by Clinical Innovations, followed by tandem mass spectrometric detection. The assay had a coefficient of variation that ranged from 6 to 11.5% for sumatriptan concentrations in the range of 3–80 ng/ml.

Data analysis

The pre-specified primary analysis was based on the percentage change in coronary CADM at the focal point of the stenosed segment at 15 min post-dose, based on QCA analysis of data points. This time point was expected to coincide with the peak drug concentration and, therefore, maximum coronary artery changes. The comparison of interest was between eletriptan 6 mg IV and sumatriptan 6 mg SC, which was reflected in a 2:2:1 randomisation protocol for sumatriptan, eletriptan, and placebo, respectively. Balanced randomisation was achieved by the use of permuted blocks of five.

Fig. 2 Time course of measurements carried out

	Time (min)										
	–10	–5	*	0	5	10	15	20	25	30	32
Confirmatory angiography[1]	■										
Insert pressure wire	■										
QCA		■	■				■[2]			■	■
IV infusion				■	■	■	■				
SC injection				■							
Intracoronary pressure			■				■[2]			■	■
Systemic BP			■				■[2]	■	■	■	■
12-lead ECG and heart rate			■				■[2]	■	■	■	■
Plasma samples for drug assay			■				■[2]			■	
GTN administration										■[3]	

*Immediately prior to drug administration
[1]Carried out immediately prior to insertion of pressure wire
[2]Carried out immediately prior to turning off infusion
[3]Carried out immediately after the 30-minute measurements

The Wilcoxon-Mann-Whitney test was used to compare the data for sumatriptan and eletriptan, and a corresponding nonparametric 95% confidence interval (CI) was calculated. Data from the placebo group were included to put the results into context with the two triptans. The mean percentage changes for the sumatriptan and eletriptan groups were assumed to be a reduction of 13 and 6%, respectively [8]. If a common standard deviation for the two groups was assumed to be 6.9% [8], then the sample size required to give an 80% power to detect a difference at the 5% (2-tailed) level was at least 17 patients in each active treatment group.

Two patient populations were evaluated. The "evaluable" group comprised all patients who received study medication and reached the primary endpoint of 15 min post-administration without requiring IC GTN or termination of the study infusion. Since this could theoretically exclude patients who developed important coronary vasoconstriction before the 15-min time point, the primary analysis was carried out on an intention-to-treat (ITT) cohort. This cohort comprised all patients who received study medication, including those patients who terminated before the 15-min time point, carrying forward for analysis the last measurement of CADM where measurements at 15 min after administration of the study drug were not available (last-observation-carried-forward). As there were no significant differences between the results from the "evaluable" and ITT groups, the data presented in this paper refer to the ITT cohort. Secondary analyses included the IC pressure ratio (defined as mean aortic pressure/mean distal coronary pressure), heart rate, systemic blood pressure and 12-lead ECGs.

Results

Seventy-eight patients were screened, 46 of whom were randomised and received study medication. Of these, 19 received eletriptan 6 mg IV (15 males, four females; 37–72 years; mean height/weight, 172 cm/84 kg); 17 patients received sumatriptan 6 mg SC (eight males; nine females; 45–74 years; mean height/weight, 168 cm/77 kg); ten patients received a placebo (nine males, one female; 41–68 years; mean height/weight, 172 cm/72 kg).

All study patients were receiving at least one concomitant medication at screening, with the following classes being the most common among patients in the eletriptan, sumatriptan, and placebo groups, respectively: nonsteroidal anti-inflammatory drugs, $n = 17$, 15, 8; statins, $n = 15$, 14, 8; beta-blockers, $n = 13$, 11, 6; vasodilators, $n = 11$, 14, 5; anticoagulants and/or antiplatelet drugs, $n = 11$, 10, 7; angiotensin-converting enzyme inhibitors, $n = 4$, 5, 0.

Of the 46 patients who received study medication, six patients discontinued during the study period due to adverse events (chest pain); these comprised two patients on eletriptan and four patients on sumatriptan.

Plasma triptan concentrations

The mean (± standard error, SE) plasma eletriptan concentration was 102 (2.41) ng/ml at 15 min after infusion start, and 38 (1.42) ng/ml at 30 min. At 15 min, this was similar to the maximum mean plasma concentration (C_{max}) achieved by an 80 mg oral dose of eletriptan during a migraine attack [32].

The mean plasma concentration (±SE) for sumatriptan was 62 (1.76) ng/ml at 15 min after the start of the infusion, and 49 (2.49) ng/ml at 30 min. The mean value at 15 min was similar to the C_{max} achieved by a 100 mg oral dose of sumatriptan during a migraine attack [33].

Systemic blood pressure and heart rate

Small increases in mean systemic blood pressure during the procedure were observed in all three treatment groups, with the largest difference observed in the SC sumatriptan/IV placebo group; however, no changes in heart rate were observed in any treatment group.

Epicardial coronary artery diameter

Analysis of the primary study endpoint showed that the median CADM changes at 15 min post-dose were minimal following both IV eletriptan and SC sumatriptan. A median 2.6% (nonparametric 95% CI: −5.0 to 11.4) dilatation was observed after IV eletriptan compared with a median 6.8% (nonparametric 95% CI: −2.6 to 0.4) constriction after SC sumatriptan; this difference was not considered to be significant ($p = 0.062$). The small magnitude of any effects of either triptan in this patient cohort as a whole was further shown by the observation that there was a median 4.5% (nonparametric 95% CI: −7.0 to 7.9) constriction in CADM at the 15-min time point in the placebo group.

Given the known variability in vasoconstrictor reactivity of epicardial vessels between patients, it was considered prudent to evaluate the range of individual vasoconstrictor responses within patients. Figure 3 shows the maximal reduction in CADM at the focal point of the lesion (Fig. 3a), proximal to the lesion (Fig. 3b) and distal to the lesion (Fig. 3c) at any time point, in individual patients receiving eletriptan, sumatriptan or a placebo. (Note: where only increases in CADM were observed in an individual patient, the minimum increase in CADM over baseline is plotted.) For eletriptan, sumatriptan and the placebo, respectively, the median maximum percentage reduction in focal CADM was very similar, −4.4% (nonparametric 95% CI: −8.4 to 2.1) versus −7.3% (nonparametric 95% CI: −13.7 to −3.8) versus −4.5% (nonparametric 95% CI: −11.7 to 2.0). In each treatment group however, there were clear outliers, ranging from a >40% CADM increase in an IV eletriptan-treated patient to a 35%

CADM reduction in an SC sumatriptan-treated patient. CADM changes in the placebo group showed similarly wide variations, from more than an 8% dilation to a 22% constriction (Fig. 3). Figure 4 indicates that no obvious correlation exists between the plasma triptan concentrations and effects on CADM.

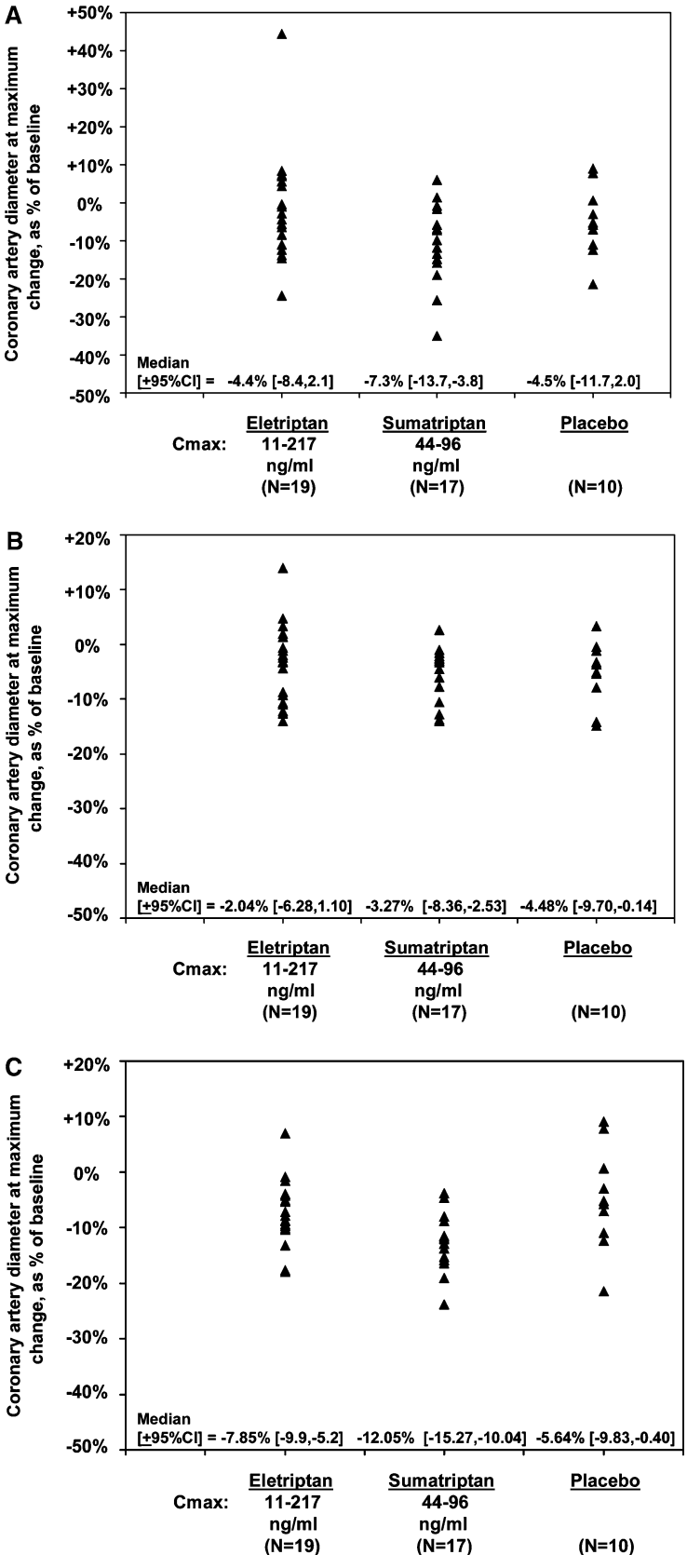

Fig. 3 **a** Maximal percentage change from baseline in CADM: at the focal point of the lesion for sumatriptan 6 mg SC versus eletriptan 6 mg IV. **b** Maximal percentage change from baseline in CADM: proximal to lesion for sumatriptan 6 mg SC versus eletriptan 6 mg IV. **c** Maximal percentage change from baseline in CADM: distal to lesion for sumatriptan 6 mg SC versus eletriptan 6 mg IV

Intracoronary pressure

Median baseline IC pressure ratios across the target stenosis in the absence of maximal distal vasodilatation with adenosine were 0.75, 0.87 and 0.83 in the eletriptan, sumatriptan, and placebo groups, respectively. No appreciable reductions were seen in any group during the study period (Table 1), suggesting that there were no major increases in the resistance to flow of these stenoses. Administration of GTN similarly had little effect, which suggests little vasodilator tone within the target stenosis.

Chest pain and evidence of myocardial ischemia

Despite the minor effects of the triptans on CADM in the study population, 13 (28%) patients complained of chest pain during the study period: four (21%) patients after receiving eletriptan, eight (47%) patients after sumatriptan and one (10%) patient after the placebo. Of these, two eletriptan patients and four sumatriptan patients withdrew from the trial prior to completion of the 30-min post-dose period.

Detailed analysis of the hemodynamic and ECG recordings was carried out for each of these 13 patients. Of the four patients in the eletriptan group who reported chest pain, two exhibited ECG changes consistent with myocardial ischemia. One of these patients had angiographic evidence of new thrombus at the stenosis site, which necessitated premature termination of the study infusion and progression to successful stenting of the target lesion. The second patient showed evidence of myocardial ischemia which was at least partly due to severe anxiety and associated tachycardia (140 bpm). The maximal CADM reduction at the focal point of the target stenosis in this patient was 14.5%, and the IC pressure ratio fell from 0.84 at baseline to 0.68 during chest pain, suggesting a potential contribution of epicardial coronary vasoconstriction to the observed myocardial ischemia.

Of the eight sumatriptan-treated patients who reported chest pain, four developed ST-T wave ECG changes consistent with myocardial ischemia. Of these, three patients showed evidence of epicardial vessel constriction in one or more segments, accompanied by a reduced IC pressure ratio. The fourth patient showed evidence of coronary vasoconstriction at the target

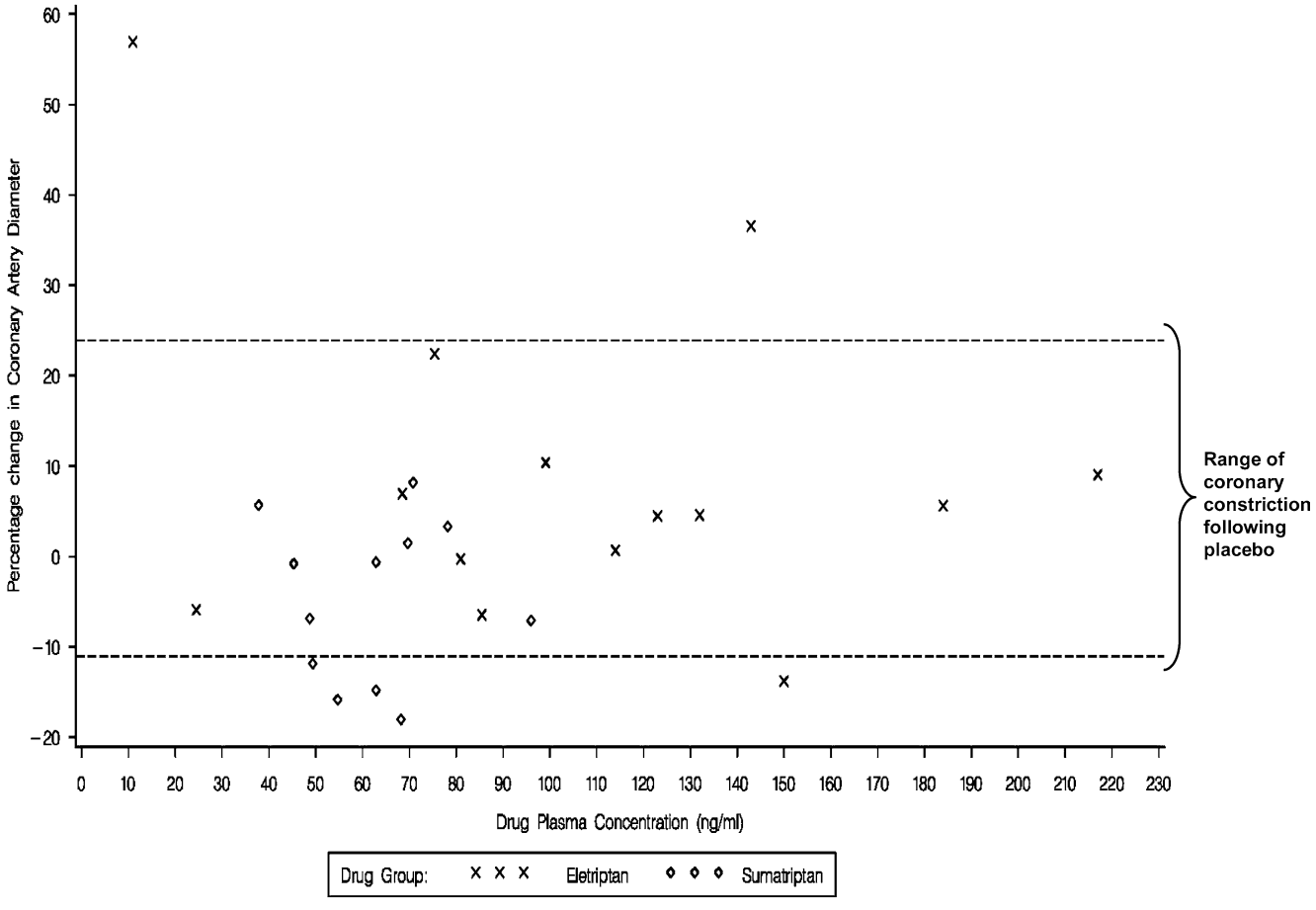

Fig. 4 Scatter plot that shows the lack of correlation between maximum eletriptan/sumatriptan plasma concentration and maximum change in CADM at the focal point of stenosis

Table 1 Median IC pressure ratio[a] and median percentage change

Time (min)	Eletriptan 6 mg IV ($n = 17$–19)[b]	Sumatriptan 6 mg SC ($n = 11$–17)[b]	Placebo ($n = 10$)
0	0.75	0.87	0.83
+15	0.72 (−2.63%)	0.85 (−4.33%)	0.82 (−1.56%)
+30	0.70 (+0.80%)	0.86 (−0.46%)	0.80 (−1.21%)
+32	0.83 (+4.65%)	0.87 (−0.44%)	0.85 (−1.08%)
Mean maximum change (95% CI)	0.03 (−0.07, 0.12)	−0.10 (−0.22, 0.02)	−0.06 (−0.17, 0.06)

[a]Ratio equals mean arterial distal/proximal IC pressure
[b]The number of subjects measured at each time point varied

lesion and both proximally and distally, but a paradoxically increased IC pressure ratio, which may reflect a technical fault in the baseline IC pressure readings.

The single placebo-treated patient who developed chest pain showed no evidence of epicardial coronary vasoconstriction or ECG changes indicative of myocardial ischemia, but interestingly, showed a reduction in IC pressure ratio from 0.83 to a minimum of 0.45. In all patients, IC GTN reversed both the epicardial vasoconstriction and returned the IC pressure ratio to baseline values.

Overall, five of the 12 patients with chest pain (excluding the subject with an IC thrombus) had ECG evidence of myocardial ischemia as well as evidence of epicardial vasoconstriction that was ordinarily associated with a reduced IC pressure ratio. Conversely, the remaining seven patients had no ECG changes and no appreciable CADM reductions.

These data were also compared with those obtained in patients who did not report chest pain. Thus, five of the 13 patients with chest pain (38%) had focal CADM reductions post-dose of $>10\%$ (eletriptan $n = 2$; sumatriptan, $n = 3$). Among the patients with no chest pain, seven (21%) had focal CADM reductions post-dose of $>10\%$. Conversely, the proportion of patients reporting chest pain was similar in those with $>10\%$ CADM constriction (5 of 12; 42%) compared with those who had $\leq 10\%$ CADM constriction (7 of 24; 29%). These results indicate that triptan-associated chest pain is not consistently correlated with the extent of epicardial vessel constriction, although in some patients who reported this symptom, it may be associated with myocardial ischemia, a supposition supported by the ECG changes.

Discussion

Consistent with the findings of Goldstein et al. [11] and Elkind et al. [34], the systemic triptan doses used in this study yielded plasma concentrations that were comparable to the C_{max} of an oral 80 mg eletriptan dose [32] and a 100 mg oral dose of sumatriptan [33] during a migraine attack. It is important to note, however, that IV dosing of triptans is not an approved route of administration, and the pharmacodynamic effect of such IV challenge may differ significantly from oral administration.

Overall, the results of this study suggest that epicardial vessels in patients with established CAD are no more reactive to a single, systemic triptan challenge than angiographically normal or minimally diseased vessels, despite data in the literature suggesting otherwise [17]. The modest vasoconstrictive changes seen after IV eletriptan and SC sumatriptan in these patients are consistent with results from previous studies of patients without CAD [8–10, 35]. These previous studies also detail the hemodynamic changes seen with triptans, including increased systemic vascular resistance and pulmonary vascular resistance, but without a change in contractility.

One of the important features of the current study was to determine whether triptan-associated chest pain was attributable to myocardial ischemia secondary to coronary vasoconstriction. Of the 13 patients with chest pain, five exhibited clear evidence of myocardial ischemia following systemic triptan administration. It is not possible with such small numbers to conclude with any certainty that myocardial ischemia was directly caused by either triptan; particularly since the development of coronary hyper-reactivity following guidewire insertion is well recognised. Additionally, in contrast to the usual clinical setting, coronary vasodilators were not permitted during the study.

We may conclude that the majority of triptan-associated chest pain was not attributable to myocardial ischemia, since seven of the remaining eight patients with chest pain had received either IV eletriptan or SC sumatriptan, but showed no hemodynamic or ECG evidence of myocardial ischemia. This is consistent with previous studies that have cast doubt on the relationship between triptan-associated chest pain and myocardial ischemia in the vast majority of cases [5–7, 36].

The present study has a number of limitations. First, our sample size calculations overestimated the expected vasoconstrictor effects of both triptans. Furthermore, we anticipated a smaller variation in CADM in the placebo group (based on studies where pressure wires were not used) and, hence, did not include the placebo as a formal matched group for statistical analysis. However, the

placebo served as a means of assessing nonspecific effects of the angiography procedure. As a consequence, we cannot formally conclude that either triptan had any effect on CADM over and above the variation seen in the placebo group. We included the use of a pressure wire in the protocol to collect as much data as possible in this highly selected patient cohort undergoing a complex interventional study. While the results of the IC pressure analysis largely support the CADM findings, they must be interpreted with caution given the lack of comparable data from other studies. Also, IC pressure measurements are generally performed after maximal distal vasodilatation using adenosine, which was clearly not possible in this study of coronary vasoreactivity.

Finally, it should be emphasised that the current study was conducted in a small and carefully monitored group of patients with known CAD undergoing an invasive angiographic procedure. The results should not be directly applied to clinical situations in which triptans are contraindicated for reasons of safety. Moreover, none of the triptans is indicated for IV use since the pharmacodynamic effect of this administration route may exaggerate the known vasoconstrictive properties of this drug's class.

The current IV challenge data provide preliminary information suggesting that eletriptan, even when administered IV, may cause relatively modest changes in epicardial coronary arteries in patients with severe obstructive CAD. The magnitude of the changes is in the same range as has been reported in a sample of patients with normal coronary arteries using a similar IV challenge procedure [11].

Acknowledgements This study was supported by a grant from Pfizer Inc. Chris Newman conceptualised the study, assisted in trial design, conducted the trial, analysed the trial results and co-wrote the manuscript. Ian Starkey conducted the trial and assisted in analysing the trial results. Nigel Buller conducted the trial and assisted in analysing the trial results. Ricardo Seabra-Gomes conducted the trial and assisted in analysing the trial results. Simon Kirby assisted in trial design and analysed the trial results. Jayasena Hettiarachchi conceptualised the study, obtained funding, assisted in trial design, analysed the trial results and co-wrote the manuscript. David Cumberland conceptualised the study, assisted in trial design, conducted the trial, analysed the trial results and co-wrote the manuscript. William Hillis conceptualised the study, assisted in trial design, conducted the trial, analysed the trial results and co-wrote the manuscript. The authors would like to acknowledge the editorial assistance of Dr. Edward Schweizer and Thomson Gardiner-Caldwell London in the preparation of this manuscript.

References

1. Goadsby PJ (2000) The pharmacology of headache. Prog Neurobiol 62:509–525
2. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine—current understanding and treatment. N Engl J Med 346:257–270
3. Fox AW (2000) Comparative tolerability of oral 5-HT1B/1D agonists. Headache 40:521–527
4. Hillis WS, MacIntyre PD (1993) Sumatriptan and chest pain. Lancet 341:1564–1565
5. Ottervanger JP, van Witsen TB, Valkenburg HA, Grobbee DE, Stricker BH (1994) Adverse reactions attributed to sumatriptan. A postmarketing study in general practice. Eur J Clin Pharmacol 47:305–309
6. Visser WH, Jaspers NM, de Vriend RH, Ferrari MD (1996) Chest symptoms after sumatriptan: a two-year clinical practice review in 735 consecutive migraine patients. Cephalalgia 16:554–559
7. Ottervanger JP, Valkenburg HA, Grobbee DE, Stricker BH (1997) Characteristics and determinants of sumatriptan-associated chest pain. Arch Neurol 54:1387–1392
8. MacIntyre PD, Bhargava B, Hogg KJ, Gemmill JD, Hillis WS (1992) The effect of i.v. sumatriptan, a selective 5-HT1-receptor agonist on central haemodynamics and the coronary circulation. Br J Clin Pharmacol 34:541–546
9. MacIntyre PD, Bhargava B, Hogg KJ, Gemmill JD, Hillis WS (1993) Effect of subcutaneous sumatriptan, a selective 5HT1 agonist, on the systemic, pulmonary, and coronary circulation. Circulation 87:401–405
10. Hood S, Birnie D, Hillis S (1997) The haemodynamic effects of subcutaneous sumatriptan, a 5HT1-receptor agonist. Br J Clin Pharmacol 43:327–328
11. Goldstein J, Massey K, Kirby S et al (2004) Effect of high-dose intravenous eletriptan on coronary artery diameter. Cephalalgia 24:515–521
12. Hall GC, Brown MM, Mo J, MacRae KD (2004) Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. Neurology 62:563–568
13. Stricker BH, Ottervanger JP (1993) Heart infarct following administration of sumatriptan (Imigran). Ned Tijdschr Geneeskd 137:141
14. Ottervanger JP, Paalman HJ, Boxma GL, Stricker BH (1993) Transmural myocardial infarction with sumatriptan. Lancet 341:861–862
15. Mueller L, Gallagher RM, Ciervo CA (1996) Vasospasm-induced myocardial infarction with sumatriptan. Headache 36:329–331
16. Ottervanger JP, Wilson JH, Stricker BH (1997) Drug-induced chest pain and myocardial infarction. Reports to a national centre and review of the literature. Eur J Clin Pharmacol 53:105–110
17. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA (2003) The clinical implications of endothelial dysfunction. J Am Coll Cardiol 42:1149–1160
18. Connor HE, Feniuk W, Humphrey PP (1989) 5-Hydroxytryptamine contracts human coronary arteries predominantly via 5-HT2 receptor activation. Eur J Pharmacol 161:91–94
19. Bax WA, Heuven-Nolsen D, Bos E, Simoons ML, Saxena PR (1992) 5-Hydroxytryptamine-induced contractions of the human isolated saphenous vein: involvement of 5-HT2 and 5-HT1D-like receptors, and a comparison with grafted veins. Naunyn Schmiedebergs Arch Pharmacol 345:500–508
20. Bax WA, Renzenbrink GJ, Van Heuven-Nolsen D, Thijssen EJ, Bos E, Saxena PR (1993) 5-HT receptors mediating contractions of the isolated human coronary artery. Eur J Pharmacol 239:203–210
21. Nilsson T, Longmore J, Shaw D et al (1999) Characterisation of 5-HT receptors in human coronary arteries by molecular and pharmacological techniques. Eur J Pharmacol 372:49–56
22. Kaumann AJ, Frenken M, Posival H, Brown AM (1994) Variable participation of 5-HT1-like receptors and 5-HT2 receptors in serotonin-induced contraction of human isolated coronary arteries. 5-HT1-like receptors resemble cloned 5-HT1D beta receptors. Circulation 90:1141–1153
23. Ishida T, Kawashima S, Hirata Ki et al (2001) Serotonin-induced hypercontraction through 5-hydroxytryptamine 1B receptors in atherosclerotic rabbit coronary arteries. Circulation 103:1289–1295
24. Longmore J, Maguire JJ, MacLeod A, Street L, Schofield WN, Hill RG (2000) Comparison of the vasoconstrictor effects of the selective 5-HT1D-receptor agonist L-775,606 with the mixed 5-

HT1B/1D-receptor agonist sumatriptan and 5-HT in human isolated coronary artery. Br J Clin Pharmacol 49:126–131
25. Carel I, Ghaleh B, Edouard A et al (2001) Comparative effects of frovatriptan and sumatriptan on coronary and internal carotid vascular haemodynamics in conscious dogs. Br J Pharmacol 132:1071–1083
26. Hamel E, Fan E, Linville D, Ting V, Villemure JG, Chia LS (1993) Expression of mRNA for the serotonin 5-hydroxytryptamine1D beta receptor subtype in human and bovine cerebral arteries. Mol Pharmacol 44:242–246
27. Sgard F, Faure C, Graham D (1996) Evidence for 5-HT1D beta but not 5-HT1D alpha receptor subtype expression in canine large coronary arteries and saphenous vein. Cardiovasc Res 31:793–799
28. Bouchelet I, Case B, Olivier A, Hamel E (2000) No contractile effect for 5-HT1D and 5-HT1F receptor agonists in human and bovine cerebral arteries: similarity with human coronary artery. Br J Pharmacol 129:501–508
29. Muir DF, McCann GP, Swan L, Clark AL, Hillis WS (1999) Hemodynamic and coronary effects of intravenous eletriptan, a 5HT1B/1D-receptor agonist. Clin Pharmacol Ther 66:85–90
30. Hood S, Birnie D, Swan L et al (1999) Effects of subcutaneous naratriptan on systemic and pulmonary haemodynamics and coronary artery diameter in humans. J Cardiovasc Pharmacol 34:89–94
31. Maassen-van den Brink A, van den Broek RW, de Vries R, Bogers AJ, Avezaat CJ, Saxena PR (2000) Craniovascular selectivity of eletriptan and sumatriptan in human isolated blood vessels. Neurology 55:1524–1530
32. Relpax product website. Available at http://www.pfizer.com/download/uspi_relpax.pdf. Accessed April 2005.
33. Imitrex product website. Available at http://us.gsk.com/products/assets/us_imitrex_tablets.pdf. Accessed April 2005.
34. Elkind AH, Satin LZ, Nil A, Keywood C (2004) Frovatriptan use in migraineurs with or at high risk of coronary artery disease. Headache 44:403–410
35. Gnecchi-Ruscone T, Bernard X, Pierre P et al (2000) Effect of naratriptan on myocardial blood flow and coronary vasodilator reserve in migraineurs. Neurology 55:95–99
36. Dahlof CG, Mathew N (1998) Cardiovascular safety of 5HT1B/1D agonists – is there a cause for concern? Cephalalgia 18:539–545