Acute and chronic effects of flosequinan on resting and exercise haemodynamics in congestive heart failure

P. THOMAS, D. J. O'GORMAN & D. J. SHERIDAN

Academic Cardiology Unit, St Mary's Hospital Medical School, London W2

- 1 The acute and chronic (8 weeks) haemodynamic responses to oral flosequinan have been investigated in 12 male patients of mean age 58.9 years with congestive heart failure of N.Y.H.A. classes II and III.
- 2 Flosequinan 125 mg orally significantly reduced right atrial pressure, pulmonary artery pressure and pulmonary wedge pressure prior to and following 8 weeks chronic treatment (125 mg daily). A significant decrease in systemic pressure and an increase in heart rate were also observed with acute flosequinan prior to chronic treatment. A reduction in systemic vascular resistance and an increase in cardiac index reached significance in response to flosequinan 125 mg orally following 8 weeks of therapy.
- 3 In the erect position, flosequinan reduced pulmonary wedge pressure and tended to reduce systemic vascular resistance, without decreasing mean arterial pressure.
- 4 Following chronic treatment, there was a trend towards a reduction in pulmonary wedge pressure and an increase in cardiac index, otherwise resting and exercise haemodynamics were unchanged.
- 5 The response to flosequinan was similar at week 1 and after 8 weeks of treatment for all of the haemodynamic parameters.
- 6 Flosequinan increased bicycle exercise times and attenuated exercise-induced increases in pulmonary arterial and systemic pressures. There was a trend towards an increase in treadmill exercise time.
- 7 Sublingual glyceryl trinitrate (0.5 mg) and oral flosequinan (125 mg) had similar effects on right atrial pressure, pulmonary arterial and pulmonary wedge pressures at 5 min and 2 h respectively post-dosing. A small additive effect on pulmonary arterial and wedge pressures was observed.

Keywords vasodilator flosequinan congestive heart failure

Introduction

Significant improvements have been seen in recent years in the treatment of heart failure, with improved survival and quality of life [1]. These benefits have been observed in particular since the introduction of angiotensin-converting-enzyme (ACE) inhibitors [2, 8]. Despite these advances up to 40% of patients optimally treated may die within 4 years [2] and the use of ACE inhibitors may be limited by renal dysfunction, hyperkalaemia and other side effects. For these reasons further extensive trials of treatment for heart failure are planned or underway [9] using new or combined treatments.

Flosequinan (7-fluoro-1-methyl-3-methyl-sulphonyl-4-quinolone) is a vasodilator which is active in both veins and arteries [10, 11]. It has a hypotensive action

[11, 12] and, in patients with congestive heart failure, it has been shown to decrease resting preload and afterload while improving cardiac performance [13–15]. In patients with congestive heart failure following acute myocardial infarction, the peak haemodynamic effect was observed at 1–2 h post dose [16] with persistent effects over the 4 h post-dose study period. Further acute haemodynamic studies in patients with heart failure have shown significant resting haemodynamic effects up to 24 h post dose [14, 15]. In non-invasive studies of patients with chronic congestive heart failure, flosequinan has been shown to improve exercise tolerance after 4 [15] and 8 weeks treatment [17]. No studies to date have reported its effects on pulmonary and systemic haemodynamics during exercise,

in patients with cardiac failure and it is unclear whether its haemodynamic effects are maintained with chronic treatment.

In the present study we investigated resting and exercise haemodynamic responses to acute oral flosequinan prior to and following chronic (8 weeks) treatment in patients with stable heart failure. Symptomatic responses and exercise tolerance were also assessed following chronic treatment. We also investigated its haemodynamic interaction with glyceryl trinitrate.

Methods

Patients

Twelve male patients of mean age 58.9 years (range 20–68 years) were recruited to the study. The clinical details are shown in Table 1. All had chronic congestive heart failure of at least 2 months' duration, eight were New York Heart Association (NYHA) class II and four were NYHA class III. Nine had ischaemic heart disease and three had dilated cardiomyopathy. One patient was in controlled atrial fibrillation. Eleven patients were receiving diuretics: up to 80 mg frusemide and 10 mg amiloride daily; and four patients were receiving digoxin. These drugs were continued unchanged throughout the study. None of the patients had been receiving vasodilators prior to the study. All patients gave informed written consent and the study was approved by the local Ethics Committee.

Exercise testing

Treadmill exercise tests were carried out using a modified Bruce protocol in 3 min stages: Stage I (1.7 mph, 0% gradient); Stage II (1.7 mph, 5% gradient); Stage III (1.7 mph, 10% gradient); Stage IV (2.5 mph, 12% gradient) and Stage V (3.4 mph, 14% gradient). Cycling exercise was commenced at 40 rev min⁻¹ at an initial workload of 25W for 3 min, increasing by 25W every 3 min until maximal symptom-limited exercise was achieved, haemodynamic measurements were recorded during the last minute of each 3 min stage. All patients underwent

training for the treadmill and bicycle exercise testing on at least two occasions in the week prior to the study until consecutive exercise capacities were within 5% of each other. All exercise tests were performed to maximal symptom-limited exercise prior to and following chronic treatment.

Haemodynamic assessment

Patients were admitted to hospital 24 h prior to haemodynamic measurements and received their usual therapy including digoxin and diuretics on the morning of the study days. At 09.00 h a thermodilution Swan-Ganz catheter was inserted under local anaesthesia into the left subclavian vein and advanced to the pulmonary circulation for measurement of pulmonary pressures and cardiac output. Right atrial pressure was obtained from the proximal port of the catheter. Heart rate was obtained from a simultaneous electrocardiogram and systemic arterial pressure was indirectly measured from the right arm using a mercury-column sphygmomanometer: the diastolic pressure was taken at Korotkoff phase V. The mean arterial pressure was calculated as the diastolic pressure plus one-third (systolic pressure–diastolic pressure). Cardiac output was measured by the thermodilution technique, using 10 ml boluses of cooled 5% dextrose solution, injected by hand in triplicate.

Study protocol

The protocol consisted of two periods: (1) an initial run-in period of 1 week during which patients received placebo in a single-blind manner; (2) an 8 week study period of open design (Figure 1). All patients underwent routine clinical assessment prior to the study. Chest radiographs were obtained prior to the study and at the end of the 8 week phase.

The treadmill exercise test was performed on day 0. A Swan Ganz catheter was positioned on the morning of day 1. Following catheter insertion a period of at least 2 h was allowed for stabilization. Haemodynamic parameters were then recorded supine and after 5 min erect both prior to and following glyceryl trinitrate (GTN) (0.5 mg sublingually). A further period of 30 min was allowed for haemodynamic parameters to return to

Table 1 Clinical details of the 12 patients studied

Patient	Age (years)	Diagnosis	Duration of CHF (months)	NYHA Class	Rhythm	Treatment
1	68	IHD	3	III	SR	Digoxin 0.125 mg, frusemide 80 mg, amiloride 10 mg
2	20	DCM	6	II	SR	Digoxin 0.25 mg, frusemide 40 mg, amiloride 5 mg
3	67	IHD	12	II	SR	—
4	53	IHD	12	III	SR	Frusemide 80 mg, amiloride 10 mg
5	43	DCM	2	II	SR	Digoxin 0.25 mg, frusemide 40 mg, amiloride 5 mg
6	65	IHD	3	III	SR	Frusemide 40 mg, amiloride 5 mg
7	63	DCM	10	II	SR	Frusemide 40 mg, amiloride 5 mg
8	65	IHD	60	II	SR	Frusemide 40 mg, amiloride 5 mg
9	67	IHD	8	II	SR	Frusemide 40 mg, amiloride 5 mg
10	66	IHD	3	II	SR	Digoxin 0.25 mg, frusemide 40 mg, amiloride 5 mg
11	68	IHD	3	II	AF	Frusemide 80 mg, amiloride 10 mg
12	62	IHD	60	III	SR	Frusemide 40 mg, amiloride 5 mg

Abbreviations: SR, sinus rhythm; AF, atrial fibrillation; IHD, ischaemic heart disease; DCM, dilated cardiomyopathy.

Haemodynamic assessment	
Day 1	Day 2
Supine/Erect	Supine/Erect
Post GTN	Flosequinan 125 mg
30 min recovery	1 h post dose
Bicycle exercise	2 h post dose
	Post GTN
	30 min recovery
	Bicycle exercise
	4 h post dose
	8 h post dose
	24 h post dose

Figure 1 Study protocol: Protocol for the study of the acute and chronic haemodynamic effects of flosequinan in patients with congestive heart failure.

baseline and measurements were then recorded as the patient sat erect on a bicycle ergometer. Haemodynamic measurements were repeated during the last minute of each 3 min stage of the exercise protocol. All subjects completed at least 6 min of the bicycle exercise protocol. The catheter was then left *in situ* overnight and the following morning baseline measurements were again obtained supine and after 5 min erect. Flosequinan, 125 mg orally, was then given and supine haemodynamic measurements were recorded at 1, 2, 4, 8 and 24 h post-dose. At 2 h post dose measurements were also recorded after 5 min erect, and both supine and erect measurements were obtained after GTN 0.5 mg sublingually, as on day 1. Following 30 min rest a maximal symptom-limited bicycle exercise test was performed as on day 1. The Swan-Ganz catheter was removed following the 24 h post dose recording. Flosequinan 125 mg daily was then continued for the 8 week open period.

Regular outpatient follow-up was undertaken and following 8 weeks oral therapy, the patient was readmitted and the above protocol was repeated. On day 1 oral flosequinan was omitted prior to haemodynamic measurements to allow baseline parameters to be recorded at least 24 h post drug administration.

Data analysis

Results are expressed as means $\pm$ standard error of the mean (s.e. mean). A paired *t*-test was performed for

parameters measured on two occasions only. The maximal change in haemodynamic parameters measured during week 1 and week 8 were compared using a paired *t*-test. Haemodynamic data were analysed using analysis of variance for repeated measures, means for each time period were compared with baseline values using time after dosing as a contrast variable. Analysis of variance for repeated measures using two contrast variables, phase (week 1 or week 8) and time after dosing, was used to assess a difference in haemodynamic response between week 1 and week 8. Comparison of the responses to flosequinan and GTN were assessed using four values for the treatment variable (baseline, GTN, flosequinan and the combination) in a repeated measures model. Three contrast variables, phase, treatment and time (pre-exercise, 3 min and 6 min during exercise) were used to analyse data from the bicycle exercise tests, again using a repeated measures model. Statistical significance was inferred when $P < 0.05$.

Results

Six of the 12 patients improved by 1 NYHA class during the 8 week open phase on chronic flosequinan therapy: 4 to class I (patients 3, 5, 7 and 10); and 2 to class II (patients 6 and 12). The functional class of the remaining 6 patients was unaltered. One patient developed atrial fibrillation during the 8 week period (patient 1) but this did not affect his functional status. Haemodynamic data obtained at the 8 week assessment from this patient have been omitted. Cardiothoracic ratios were significantly decreased over the 8 week period: 0.55 ± 0.01 (mean $\pm$ s.e. mean) vs 0.58 ± 0.01 , $P < 0.01$. Treadmill exercise capacity appeared to improve following chronic flosequinan therapy (24 h after the last dose), 10.53 ± 0.85 min vs 8.96 ± 1.27 min, but did not reach statistical significance. The improvement in bicycle exercise time was significant overall ($P = 0.03$). The increase on week 1 (12.9 ± 0.8 min vs 11.2 ± 0.9 min, $P = 0.06$) failed to reach significance, and although the increase at week 8 appeared to be less than at week 1, it did reach statistical significance (12.6 ± 0.6 min vs 11.9 ± 0.8 min, $P = 0.03$). Flosequinan was well tolerated in all patients during the 8-week open phase of the study.

Recumbent haemodynamics

Haemodynamic responses following a single oral dose of flosequinan are illustrated in Figure 2. The pattern of haemodynamic responses was similar prior to and following chronic treatment. Significant reductions in right atrial pressure, pulmonary artery pressure and pulmonary wedge pressure were observed. The maximal reduction in right atrial, pulmonary artery and pulmonary wedge pressures following oral flosequinan was greater on week 1 than week 8. These pre-load responses appeared more marked on week 1, but using the phase of treatment (week 1 or week 8) as a contrast variable in the repeated measures procedure, there was no alteration of response for any of the measured parameters. Acute flosequinan also significantly decreased mean arterial pressure and systemic vascular resistance, and

Figure 2 Supine haemodynamics: Changes in supine resting haemodynamic parameters over 24 h following acute administration of flosequinan (125 mg orally) prior to (closed circles, week 1) and following (closed triangles, week 8) chronic therapy with flosequinan 125 mg daily. HR, heart rate; MAP, mean arterial pressure; CI, cardiac index; SV, stroke volume; MPAP, mean pulmonary artery pressure; MPWP, mean pulmonary wedge pressure; SVR, systemic vascular resistance; MRAP, mean right atrial pressure.
 ○ $P < 0.05$ compared with baseline * $P < 0.01$ compared with baseline.

increased heart rate and systemic vascular resistance (Figure 2). Unlike its pre-load effects, which were maximal at 2 h, these systemic effects were maximal at 4 h. Mean arterial pressure decreased from 96 ± 4 mm Hg to a nadir of 90 ± 4 mm Hg, and systemic vascular resistance decreased from 1461 ± 132 dyn s^{-5} to 1194 ± 110 dyn s^{-5} . Thus although flosequinan produced both venous and arteriolar dilatation, the former was greater and occurred significantly earlier than the latter.

There were no significant changes in baseline haemodynamics, measured 24 h post dose, between week 1 and week 8. There was a trend towards a lower pulmonary wedge pressure (19.33 ± 2.73 vs 14.86 ± 2.63 mm Hg, $P = 0.052$) and an increased cardiac index (2.95 ± 0.17 vs 2.62 ± 0.17 $l \cdot min^{-1}$, $P = 0.091$), but otherwise there was no evidence of any change in resting haemodynamics following 8 weeks of treatment.

Exercise haemodynamics

Changes in haemodynamics during bicycle exercise are illustrated in Figure 3. Exercise, as expected, significantly

reduced systemic and pulmonary vascular resistances and increased all other parameters at 3 and 6 min, $P < 0.001$ in each case. No significant differences were observed in exercise haemodynamics measured prior to acute flosequinan on week 1 and 24 h post-dose on week 8. Thus chronic treatment did not alter exercise haemodynamics. Acute flosequinan did however significantly decrease right atrial, pulmonary artery and pulmonary wedge pressures during exercise (Figure 3). The reduction in pulmonary wedge pressures at 6 min exercise was of the order of 20 to 30%; from 17.9 ± 2.7 mm Hg to 11.3 ± 2.5 mm Hg ($P = 0.03$) on week 1, and from 19.6 ± 3.6 mm Hg to 14.4 ± 2.7 mm Hg ($P = 0.02$) on week 8. There was a small reduction in mean systemic pressure throughout exercise. Flosequinan had no other effects on haemodynamics, despite significant effects at rest.

Haemodynamic effects of glyceryl trinitrate

As expected sublingual glyceryl trinitrate reduced right atrial and pulmonary wedge pressures significantly (Figure 4). The changes observed were similar in magnitude to those seen 2 h following flosequinan. The addition of glyceryl trinitrate to flosequinan resulted in a further reduction of pulmonary artery pressure of 3.7 mm Hg (95% confidence interval 5.86 to 1.58 mm Hg) on week 1 and 3.9 mm Hg (95% C.I. 7.39 to 0.43 mm Hg) on week 8. There was a small reduction in right atrial pressure on week 1 (mean 1.1 mm Hg, 95% C.I. 2.05 to 0.13 mm Hg). Glyceryl trinitrate differed from flosequinan in that it did not reduce systemic vascular resistance (Figure 4).

Erect haemodynamics

In the erect position, flosequinan reduced pulmonary wedge pressure ($P = 0.016$) and tended to reduce systemic vascular resistance ($P = 0.059$), without a change in mean systemic pressure (Figure 5). Glyceryl trinitrate decreased mean arterial pressure ($P = 0.008$) and tended to increase heart rate ($P = 0.052$) and reduce pulmonary wedge pressure ($P = 0.072$).

Discussion

The main findings of the present study are that flosequinan decreased left and right ventricular filling pressures due to its venodilating effect in patients with congestive cardiac failure, with the peak effect at 1 to 2 h following oral administration and significant effects lasting 4 to 8 h. Flosequinan also reduced systemic vascular resistance mean arterial pressure, and increased heart rate and cardiac index. These effects were maximal at 4 h following oral treatment and were less pronounced than the pre-load reducing effects. There was no significant haemodynamic effect 24 h after the last dose, following 8 weeks of treatment. The haemodynamic response to a 125 mg dose of flosequinan was unchanged after chronic therapy.

Flosequinan attenuated the rise in pulmonary and systemic pressures during exercise and these changes may account for the increase in exercise duration. The

Figure 3 Response to exercise: Changes in exercise duration, mean systemic pressure, pulmonary wedge pressure and right atrial pressure during exercise before and after acute flosequinan (125 mg orally) on week 1 (closed bar and stippled bar respectively) and week 8 (hatched bar and spotted bar respectively). Measurements obtained at baseline, 3 and 6 min exercise are illustrated. Exercise duration was increased following flosequinan ($P = 0.03$), there was an attenuation of the rise in mean systemic pressure ($P = 0.006$) and mean pulmonary artery pressure ($P = 0.02$) throughout the exercise period. Despite significant attenuation of the rise in pulmonary wedge pressure at 6 min of exercise, the overall effect failed to reach statistical significance ($P = 0.09$).

Figure 4 Response to glyceryl trinitrate: Systemic vascular resistance (SVR), pulmonary artery pressure, pulmonary wedge pressure and right atrial pressure on week 1 (closed bar) and week 8 (hatched bar) at baseline, 5 min following sublingual glyceryl trinitrate (GTN), 2 h following oral flosequinan (125 mg), and following combined flosequinan and GTN. There was no difference in the response during the two periods. Both glyceryl trinitrate and flosequinan reduced pulmonary artery (GTN $P = 0.003$, flosequinan $P = 0.003$), pulmonary wedge (GTN $P = 0.003$, flosequinan $P = 0.001$) and right atrial pressures (GTN $P = 0.001$, flosequinan $P = 0.02$). GTN following flosequinan caused a further decrease in pulmonary artery pressure ($P = 0.003$) and pulmonary wedge pressure ($P = 0.013$) with a small rise in heart rate ($P = 0.03$). Flosequinan significantly reduced SVR ($P = 0.016$), whereas there was no change following GTN.

Figure 5 Erect haemodynamics: Pulmonary wedge pressure, systemic vascular resistance, mean arterial pressure and heart rate at baseline (closed bar) and 2 h following flosequinan or 5 min after GTN (hatched bar) measured on week 1 or week 8. Flosequinan reduced pulmonary wedge pressure ($P = 0.016$) and tended to reduce systemic vascular resistance ($P = 0.059$), without any change in mean arterial pressure. Glyceryl trinitrate decreased mean arterial pressure ($P = 0.008$) and there was a trend towards an increased heart rate ($P = 0.052$) and a reduced pulmonary wedge pressure ($P = 0.072$).

smaller effect on systemic pressure may be explained by the timing of the exercise tests, which were carried out 2 h following acute treatment when the maximal effects of flosequinan on pre-load were present, but earlier than its maximal effects on after load.

The pre-load reducing effect of flosequinan was similar to that following sublingual glyceryl trinitrate and only a small additive effect was observed when the agents were combined. Glyceryl trinitrate lacks the arteriolar dilating properties of flosequinan.

Flosequinan produces a more favourable haemodynamic response in the erect posture, reducing both preload and afterload, without a deleterious effect on mean systemic pressure. This would contribute to an improvement in functional class in the ambulant patient. Glyceryl trinitrate, on the other hand, tended to reduce the pulmonary wedge pressure at the expense of systemic hypotension and reflex tachycardia.

The acute haemodynamic effects of flosequinan observed in this study are broadly similar to previous reports [14, 15], in which combined venous and arteriolar vasodilation have been observed. In contrast to previous reports we found a significant difference in the timing of the peak effects on ventricular filling pressures and systemic vascular resistance, with the latter occurring later. Thus the nadir value for pulmonary wedge pressure occurred at 2.3 ± 0.7 h post-dosing compared with 7.6 ± 2.8 h for systemic vascular resistance on week 1, $P < 0.01$. This differential response has not been noted previously even when responses were monitored over 24 h periods [14, 18]. The basis for this difference is not

clear but could reflect the appearance of an active metabolite of flosequinan [11]. In general the magnitude of the venous effects was greater than those on the arterioles in the present study. Some previous reports indicate more marked arteriolar effects than those reported here, while others have reported modest systemic effects [19]. This is likely to reflect lower baseline values in the present study since the response to flosequinan appears to be directly related to baseline levels of systemic vascular resistance [14].

Repeat challenge with flosequinan following eight weeks chronic treatment produced a similar pattern of haemodynamic effects. Baseline measurements on week 8 were obtained 24 h following the last dose of flosequinan. The presence of some residual drug or active metabolite could have contributed to the reduced maximal venodilator response to acute flosequinan on week 8. This seems unlikely, however, since despite similar baseline values on week 1 and week 8, the nadir values were lower on week 1 (Figure 2). In addition to the pre-load and after-load reducing effects of flosequinan, some previous reports have observed a positive inotropic action *in vivo* [20] and *in vitro* [21] including patients with cardiac failure [22], while others have failed to detect such an effect [23].

Bicycle exercise produced the expected decrease in systemic vascular resistance and increased ventricular filling pressures. Exercise haemodynamics measured 24 h following the last dose of flosequinan were not altered by chronic treatment. Acute flosequinan did however reduce ventricular filling pressures and limited the rise

in systemic pressure. Thus acute but not chronic treatment improved exercise haemodynamics and this was reflected in treadmill exercise tolerance which showed little change in response to chronic treatment (24 h after previous dose), whereas bicycle exercise tolerance did improve following acute treatment in line with acute haemodynamic effects of flosequinan. There are no previous reports of the effects of flosequinan on exercise haemodynamics. Two previous studies have demonstrated improved exercise tolerance in response to flosequinan following 7 days treatment [19] and following 8 weeks chronic treatment [17] although in the latter study the timing in relation to previous dosing is unclear.

The lack of a placebo group in this study is a potential limitation particularly for the assessment of exercise tolerance. To avoid possible distortion of the effects of treatment on resting and exercise haemodynamics, measurements were obtained at predetermined levels of exercise, prior to and following acute treatment.

Sublingual glyceryl trinitrate and oral flosequinan had

similar effects on ventricular filling pressure. When given together only a small additive effect was observed however. Glyceryl trinitrate did not alter systemic vascular resistance unlike flosequinan.

In conclusion, acute treatment with flosequinan has venous and arteriolar dilating effects. In the present study the former were more pronounced and occurred earlier in patients with mild to moderate heart failure. The beneficial effects of acute flosequinan on resting and exercise haemodynamics were maintained following chronic treatment. There was no evidence of tolerance in the overall haemodynamic response to flosequinan, although there was a small reduction in the maximal venodilator effect achieved after 8 weeks of treatment. Flosequinan and glyceryl trinitrate have similar effects on ventricular filling pressures, but only a small additive effect when combined. Flosequinan has the added benefit of arteriolar vasodilation and has a more favourable haemodynamic profile in the ambulant patient.

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