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Acute effects of flosequinan (BTS 49465) in untreated moderate to severe hypertension

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Summary:

Flosequinan (BTS 49465, 7-fluoro-1-methyl-3-methylsulphonyl-4-quinolone), a recently developed direct-acting vasodilator that should cause relatively less reflex tachycardia, was given in a single oral dose of 200 mg to 10 untreated patients with moderate to severe hypertension. Flosequinan caused a fall in blood pressure (BP) from $181/116 \pm 7/4$ to $161/102 \pm 5/4$ mm Hg ($P < 0.05$). The proportional decrease of mean arterial pressure (MAP) was 14.6% ($P < 0.01$). Together with the decrease of BP an increase of heart rate from 79 ± 5 to 96 ± 5 beats/min occurred ($31 \pm 4\%$, $P < 0.01$). Forearm blood flow increased insignificantly (NS) from 3.7 ± 0.6 to 5.5 ± 1.5 ml/100 ml/min together with a small decrease in forearm vascular resistance from 47 ± 7 to 39 ± 7 arbitrary units (NS). Forearm venous distensibility remained stable around 0.03% mm Hg (NS). Neuro-

hormonal parameters showed the consequences of systemic vasodilation: noradrenaline rose from 1.25 ± 0.10 to 2.88 ± 0.34 nmol/l ($P < 0.01$), adrenaline from 0.16 ± 0.03 to 0.35 ± 0.10 nmol/l (NS), plasma renin activity from 2.33 ± 0.46 to 3.27 ± 0.73 ng/ml/h ($P < 0.05$) and aldosterone from 14.31 ± 2.47 to 26.3 ± 8.02 ng/ml ($P < 0.05$). The serum concentrations of flosequinan and its major metabolite were within the therapeutic limits. Nine patients experienced minor side-effects such as headache, nausea and palpitations.

We conclude that flosequinan has hypotensive efficacy with signs of systemic counter-regulatory mechanisms but without a clear forearm vasodilation. Particularly the venous dilation, claimed in normotensives, could not be established in hypertensives.

Keywords: flosequinan (BTS 49465); vasodilation; hypertension

Introduction

In most patients with hypertension there is an increased total peripheral vascular resistance. A logical approach in the treatment of hypertension, therefore, is the reduction of the elevated resistance by means of vasodilating agents.¹ The so called direct-acting vasodilators such as hydralazine, cause a relaxation of the vascular smooth muscles, especially in the pre-capillary resistance vessels and they have minimal effect on veins.² The direct vasodilation stimulates counter-regulatory mechanisms such as activation of the sympathetic system (reflex tachycardia), activation of the renin-angiotensin-aldosterone system and sodium retention by the kidney.

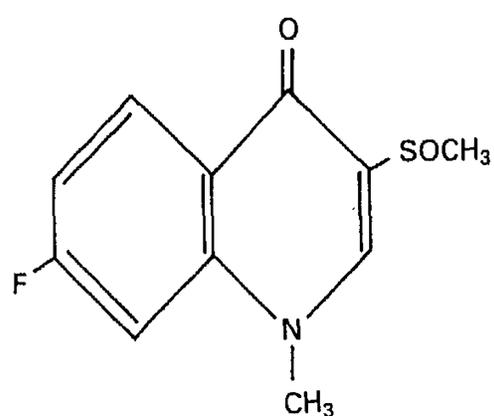
Flosequinan (BTS 49465, 7-fluoro-1-methyl-3-methylsulphonyl-4-quinolone) is a newly developed direct-acting vasodilator. Its hypotensive effect has been demonstrated in a number of animal models.³

Figure 1 gives the chemical structure. After oral intake flosequinan is rapidly absorbed reaching peak plasma concentrations after 0.5–1.5 h. It is eliminated by oxidation in the liver with a half-life of 1.6 h. In contrast, the major and active sulphon metabolite, BTS 53554, reaches peak plasma concentrations after 6 h with a slow clearance (half-life of 37.6 h). This suggests the advantage that the drug may be effective when administered once daily.⁴

A previous study suggests that this drug should cause less reflex tachycardia compared with for example hydralazine.⁵ This was thought to result from a tendency to a simultaneous dilating activity on the venous system, decreasing the venous return which offsets the compensatory rise in cardiac output, potentially leading to complaints from the patients. Previously these venous effects were studied *in vitro* with human tissue⁶ or *in vivo* with normotensive volunteers⁵ and appeared to be marginal in these subjects. Therefore, the present study was undertaken to determine the acute haemodynamic and humoral effects of ingestion of 200 mg flosequinan in 10 patients with moderate to severe hypertension who were withdrawn from previous treatment at least 1 week before the start of the study.

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Received 27 September 1994; revised 9 January 1994; accepted 12 January 1994



BTS 49465 structure

Figure 1 Chemical structure of flosequinan (BTS 49465, 7-fluoro-1-methyl-3-methylsulphonyl-4-quinolone)

Patients and methods

Ten patients with a mean DBP of > 105 mm Hg during at least three control visits at the outpatient department were selected. They gave their written informed consent for participation in this study. The study was approved by the local ethics committee. Table 1 lists some of the clinical characteristics of the patients. Six patients had electrocardiographic and/or echocardiographic evidence of left ventricular hypertrophy. Grade 1 to 2 hypertensive retinopathy was found at fundoscopy in all patients except three. No patient had significant macroalbuminuria. Seven patients had been treated with various anti-hypertensive agents until 1 week before the study. Subsequently two patients (nos 6 and 9) were found to have a renal artery stenosis. The dietary sodium was not restricted.

All patients were studied in the same quiet room after an overnight fast. BP was continuously recorded non-invasively by means of an Arteriosonde 1225 blood pressure device (Roche Medical Electronics Division, Hoffmann-La Roche Oranjeburg, NY) and heart rate was calculated from an electrocardiographic registration. After 30 min rest, supine BP and heart rate were measured every 5 min before and every 10 min until 6 h after the oral ingestion of 200 mg flosequinan. Because we did not know the precise effect of the drug the first patient (no 1) received only 100 mg. Two hours

after ingestion of the drug all patients were allowed to eat a small breakfast in semi-sitting position.

Mean arterial pressure (MAP) was calculated according to the formula: $MAP = \text{diastolic BP} + 1/3$ of the pulse pressure. Forearm blood flow (FBF) was measured (mean of at least three FBF readings at every time point) before and every 30 min after ingestion of flosequinan until 2 h, thereafter every hour, by using venous occlusion plethysmography with mercury in rubber strain gauges. Forearm vascular resistance (FVR) was calculated from the formula: $FVR = MAP/FBF$ and expressed in arbitrary units (AU). Using the same plethysmographic method venous distensibility was measured⁷ according to a similar time schedule. Briefly: venous congestion at three different inflation pressure values of the upper arm BP cuff (usually about 20, 30 and 40 mm Hg) yielded corresponding forearm volume changes; the percentage of volume change was plotted against cuff pressure. Linear relation was assumed and venous distensibility expressed as $\% \text{ mm Hg}^{-1}$. Before and after ingestion of flosequinan at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h venous blood was drawn from an indwelling cannula, inserted at the start of the study, for determination of noradrenaline (NA), adrenaline, plasma renin activity (PRA), aldosterone and flosequinan and its metabolite BTS 53554. Methods used for the determination of catecholamines by radio-enzymatic assay and PRA and aldosterone by radioimmuno assay have all been published previously.⁸⁻¹⁰ Levels of flosequinan and its metabolite were measured by HPLC with UV detection, at the laboratories of the Boots Company, Nottingham (UK). Before and some days after the test, blood was drawn for determination of haemoglobin, leucocytes, thrombocytes, prothrombin time, activated partial thromboplastin time, and biochemistry including electrolytes, urea, creatinine, total protein, albumin, alkaline phosphatase, transaminases and gamma glutamyl transferase.

Statistical analysis

The Student *t*-test for paired observations was used. Differences were considered to be significant at *P*

Table 1 Clinical characteristics of the patients

Patient no.	Sex	Age (years)	QI (kg/m ²)	BP at entry (mm Hg)	Serum creatinine (mmol/l)	Type of hypertension
1	F	44	33.2	159/109	77	Essential
2	F	35	23.4	153/108	62	Essential
3	M	58	29.8	190/130	96	Essential
4	M	43	32.8	145/97	83	Essential
5	M	51	24.9	163/120	97	Essential
6	F	45	38.8	204/100	75	URAS
7	F	48	35.0	204/134	71	Essential
8	F	49	39.1	199/124	74	Essential
9	F	30	21.3	189/137	58	URAS
10	F	52	27.9	183/106	70	Essential
Mean		46	30.7	195/119	76	
Range		30-58	21.3-39.1	174-220 109-130	58-79	

QI: Quetelet index; URAS: unilateral renal artery stenosis

values of ≤ 0.05 . Two-sided results are presented as mean \pm s.e. unless indicated otherwise.

Results

Table 1 summarises some patient characteristics and the automatically measured baseline BPs. As known, the arteriosonde BPs are nearly always 6–8 mmHg lower than the sphygmomanometer readings and indeed two patients (nos 4 and 6) appeared to have DBP of < 105 mmHg despite outpatient DBP of > 105 mmHg. Besides by the method, the difference can also partly be ascribed to the level of the arm above the heart and to the quiet room with constant temperature.

Although the 100 mg dose of flosequinan in patient no 1 resulted in a smaller decrease of MAP (9 mmHg) compared with the mean effect of the 200 mg dose in the other nine patients ($23 \text{ mmHg} \pm 4 \text{ mmHg}$), the results of all 10 patients are presented together.

Figure 2 shows the course of the BP, MAP and heart rate throughout the test period. After ingestion of flosequinan, BP gradually decreased from an average of $181 \pm 7/116 \pm 4$ to $161 \pm 5/102 \pm 4$ mmHg after 2 h ($P < 0.025$ except at 30 min) and remained approximately constant thereafter. MAP fell from 137 ± 5 to 117 ± 2 mmHg ($P < 0.01$ at all times except at 360 min, $P < 0.05$) with a percentage fall of 14.6. In individual patients the maximal MAP reduction ranged from 3.5 to 27.1%, mean $15.8 \pm 2.8\%$. The two patients with renal artery stenosis showed a maximal MAP response of 20.8 ± 1.9 mmHg compared with 14.6 ± 2.9 mmHg in the remaining eight patients. Together with BP reduction heart rate rose from 79 ± 5 to 96 ± 5 beats/min ($31 \pm 4\%$, $P < 0.01$ at all times except at 30 min, $P < 0.05$) and started to return to baseline at 5 h.

The FBF increased insignificantly (NS) and only transiently from 3.7 ± 0.6 to 5.5 ± 1.5 ml/100 ml/

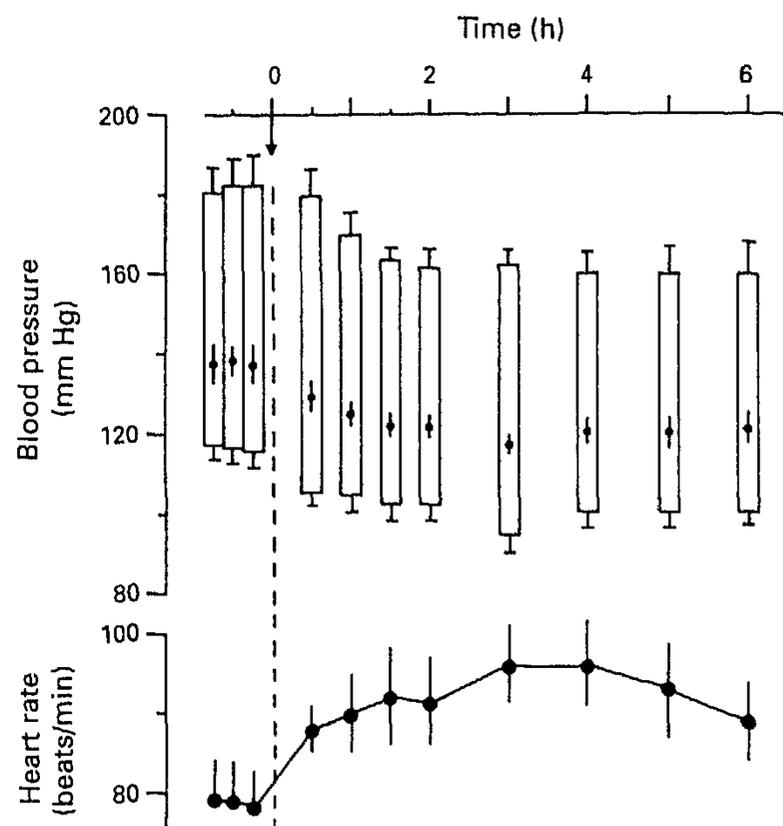


Figure 2 Course of BP and heart rate before and after ingestion of flosequinan in the 10 hypertensive patients. Systolic, diastolic and mean arterial blood pressure (black dots in the columns) are given as mean \pm s.e. BP significantly lower ($P < 0.025$) than baseline at all times except at 30 min. Heart rate changes are significant ($P < 0.01$) at all times except at 30 min ($P < 0.05$)

min during the first hour, together with a small decrease in FVR from 47 ± 7 to 39 ± 7 AU (NS). No change, especially no increase of the venous distensibility could be detected: it remained stable around $0.03\% \text{ mmHg}^{-1}$ (NS) (Figure 3).

Figure 4 shows the humoral compensatory reactions to the systemic hypotensive effect of the vasodilator. Plasma NA level rose from 1.25 ± 0.10 to a maximum of 2.88 ± 0.34 nmol/l ($P < 0.01$), adrenaline rose gradually from 0.16 ± 0.03 to 0.35 ± 0.10 nmol/l (NS), PRA rose from 2.33 ± 0.46 to 3.27 ± 0.73 ng/ml/h ($P < 0.05$). Aldosterone rose from 14.31 ± 2.47 to 26.30 ± 8.02 ng/100 ml ($P < 0.05$).

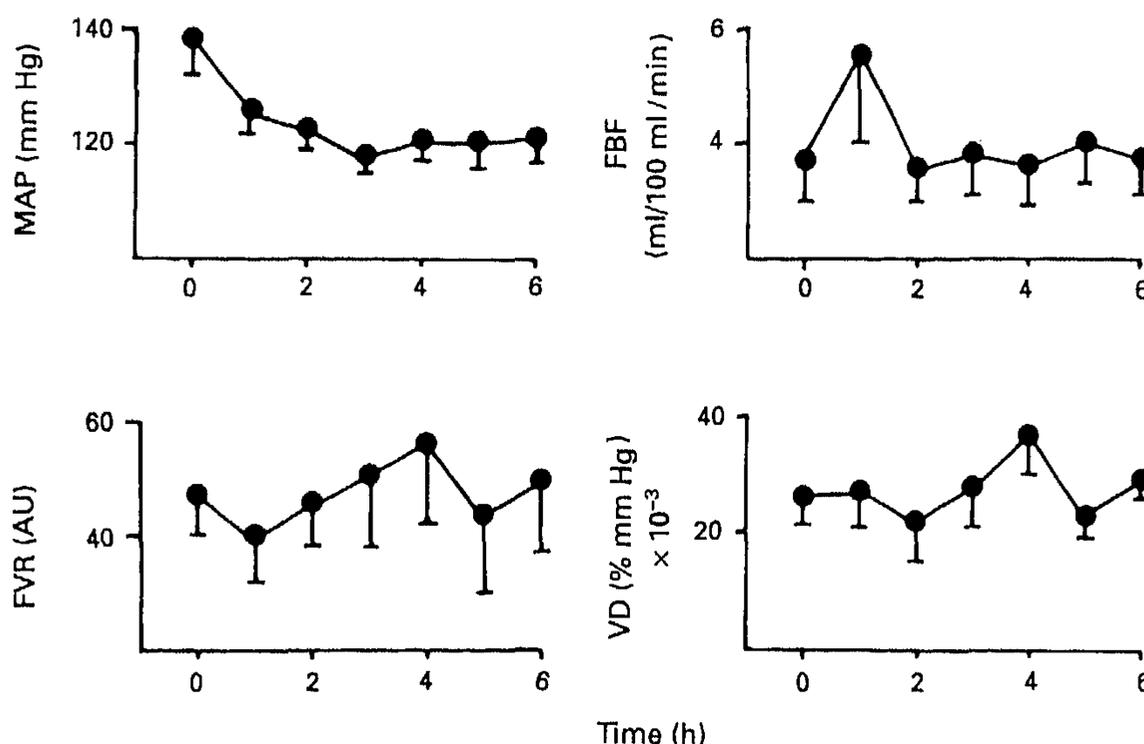


Figure 3 Course of mean arterial pressure (MAP), forearm blood flow (FBF), forearm vascular resistance (FVR) and venous distensibility (VD) after ingestion of flosequinan in the 10 patients with moderate to severe hypertension. Mean \pm s.e. are presented. MAP: $P < 0.01$ at all times except at 360 min ($P < 0.05$); FBF, FVR, VD: NS. Note: the x axis does not start at 0

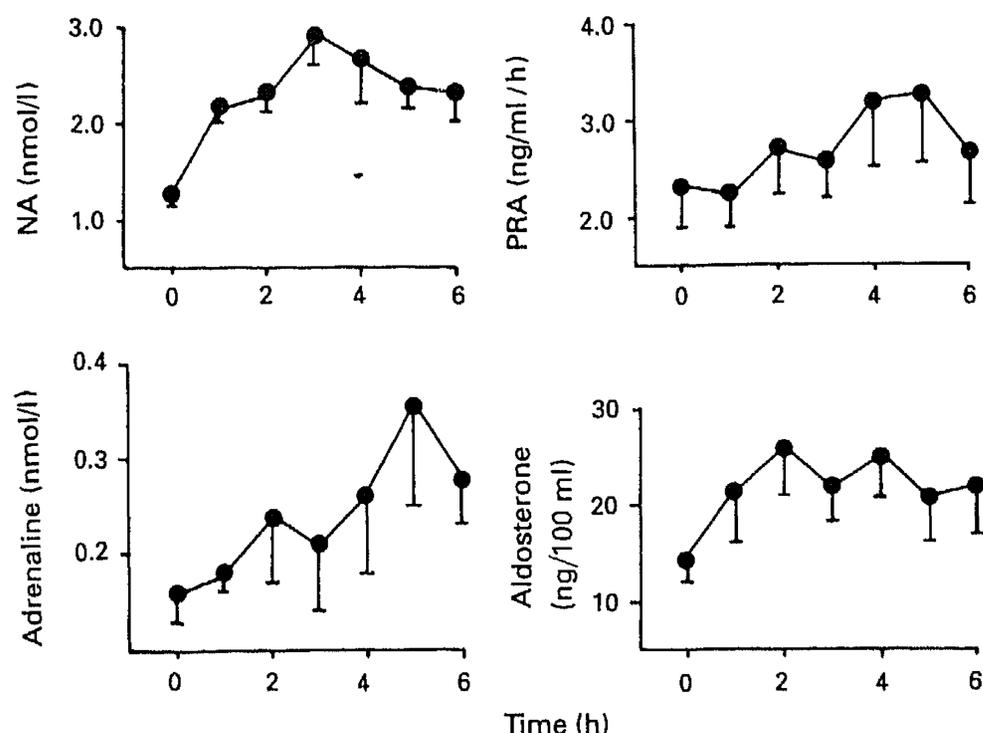


Figure 4 Effects of flosequinan on noradrenaline (NA), adrenaline, plasma renin activity (PRA) and aldosterone in the 10 patients. Mean \pm s.e. are presented. NA: $P < 0.01$; adrenaline: NS; PRA: $P < 0.02$; aldosterone: $P < 0.05$. Note: the x axis does not start at 0

Figure 5 shows the serum levels of flosequinan (BTS 49465) and its major metabolite (BTS 53554) at different time points. Flosequinan reached its peak plasma concentration in 1 h after oral intake; the metabolite levels gradually increased and seemed to reach a maximum at 6 h. The concentration of flosequinan and its metabolite together reached a peak at 3 h and then started to fall slowly.

Adverse events like headache, palpitations, nausea, vomiting and eructation were mentioned (Table 2). One patient experienced a vagal reaction: he became pale and complained of nausea and

giddiness. BP (lowest value 121/80 mm Hg) and heart rate (from 93 to 63 beats/min) decreased. Head down tilting and voluntary leg exercise for a few minutes induced a complete recovery.

No haematological or biochemical derangements were noted.

Discussion

The present study demonstrates that flosequinan given as an oral dose of 200 mg to patients with moderate to severe hypertension effectively lowers BP with signs of systemic counter-regulatory mechanisms, but without a clear forearm vasodilation. Particularly, the claimed trend towards venous dilation found in normotensives⁵ could not be established in our hypertensive patients.

It has been proven in other studies that flosequinan is a vasodilator, acting directly on vascular smooth muscle, probably by modifying the availability of intracellular free ionised calcium.^{11,12} The systemic vasodilatory capacity is supported by the occurrence of increases in heart rate, found in this study and in other reports,^{4,13,14} and by the changes in the respective neurohormonal parameters.

In contrast to the study of Cowley *et al*,⁵ we were not able to demonstrate a clear and consistent arteriolar and venous dilation in the forearm. This discrepancy can be explained by a number of differences between the two studies. Firstly, we studied moderate to severe hypertensives with more advanced atherosclerosis whereas Cowley *et al* studied six normotensives. It might be possible that the blunted vasodilatory response in terms of FBF and venous distensibility in hypertensive patients is due to reduced baroreflex sensitivity. Other possible differences between the two studies may be the mean age, mean body mass index and mean dose (400 vs. 200 mg).

Some authors claim that because of the effect on both arteries and veins flosequinan has the advantage of a relatively small rise in heart rate.^{5,15} In our

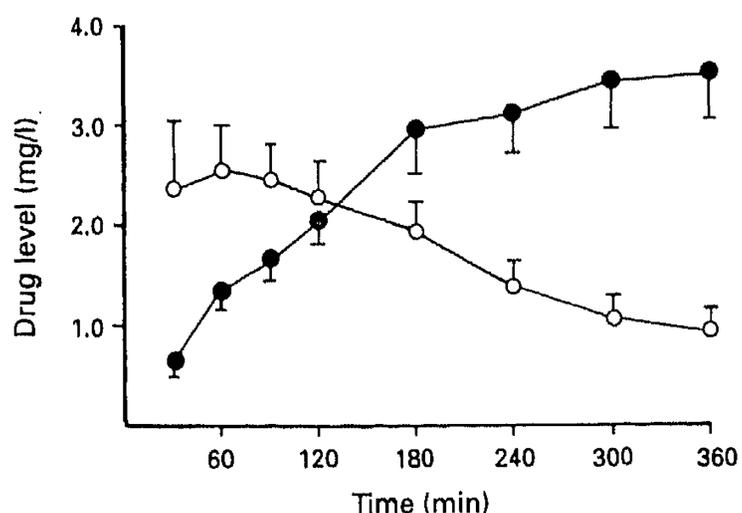


Figure 5 Serum levels of flosequinan (○) and its major metabolite (BTS 53554; ●) at 30, 60, 90, 120, 180, 240, 300 and 360 min after oral ingestion of 200 mg flosequinan in the 10 patients. Mean \pm s.e. are presented

Table 2 Spontaneously reported side-effects

Side-effects	No. of patients
Compensatory reactions	
Headache	7
Palpitations	2
Abdominal discomfort	
Nausea	5
Vomiting	2
Eructation	1
Vagal reaction	1

study at the time point of the maximal hypotensive effect (MAP - 14.6%), the heart rate increased by 31.4%. This is similar or even more pronounced than the results of some previous workers^{13,14} and represents a normal physiological response to systemic vasodilation which partly attenuates the reduction in BP by the drug. In comparison with our own previous studies, flosequinan results in a similar increase in heart rate when compared with monotherapy with nifedipine,¹⁶ endralazine,¹⁷ diazoxide¹⁸ and pinacidil.¹⁹ On the other hand, when flosequinan, like other vasodilators, is administered in a chronic regimen together with beta-adrenoceptor blocking agents and diuretics, there is hardly any change in heart rate.^{4,14} Furthermore, the hypotensive activity of flosequinan at the time point of the maximal heart rate increase was not stronger than the effects of other vasodilators, previously studied by us in similar protocols in other patients.

In contrast to previous clinical trials in which flosequinan reduced BP in hypertensive patients without changing renal blood flow, glomerular filtration rate or PRA, aldosterone and NA,^{15,20,21} we detected significant increases. It has to be emphasised that Dupont *et al* performed a chronic study with a dose of 100 mg and that Cowley *et al* used flosequinan as a third agent next to a diuretic and a beta-blocker.

Our observation was too short to measure sodium retention, another important effect of vasodilators, possibly leading to subjective side-effects.¹

Serum levels of flosequinan and its metabolite were measured to see if they were comparable with the levels obtained in other studies. The values in the present study were within the expected limits.⁴

With this single dose of 200 mg, nine of 10 patients experienced side-effects: compensatory reactions such as headache and palpitations, and abdominal discomfort such as nausea and vomiting. Another study reported also that the frequency of reported adverse events is statistically larger than with placebo.¹²

Our study has some weaknesses. Firstly it was uncontrolled, although most parameters were measured objectively. The FBF and venous distensibility values were calculated from the curves by a blinded observer. Secondly, the results of a single dose study can not be extrapolated to the chronic use of the drug. Once steady-state levels of the drug have been reached results may be different and counter-regulatory reactions may be less prominent. Thirdly our study includes only a small number of patients.

In recent studies flosequinan is used effectively in patients with severe heart failure.²²⁻²⁸ Despite encouraging symptomatic improvement the company withdrew the drug from the market because preliminary results showed that in patients with heart failure the use of 100 mg caused an increased mortality, 75 mg caused an increase in hospital admissions and that the efficacy of 50 mg had not been proven.²⁹ The consequences from these findings in heart failure to hypertension are limited because of differences in pathophysiology, comorbidity and comedication. However, the effect of compounds similar to flosequinan that may be

developed in the future should be studied both in hypertension as well as in heart failure.

Conclusions

We conclude that flosequinan after oral ingestion of 200 mg has a hypotensive effect via systemic vasodilation although we could not demonstrate this vasodilation in the forearm of hypertensive patients, either on the arterial, or on the venous side. Up to now flosequinan, as hypotensive drug, has no major advantages compared with other well-known direct-acting vasodilators. The drug exhibits the expected side-effects when given as monotherapy in a single dose of 200 mg.

Acknowledgement

We thank the Boots Company for determining the plasma levels of the drug and its metabolite.

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