

Cardiovascular effects of the novel arteriovenous dilator agent, flosequinan in conscious dogs and cats

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1 Flosequinan (BTS 49 465, 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone) a novel arteriovenous dilator agent was orally effective in conscious renal hypertensive dogs and normotensive cats. The hypotensive potency of flosequinan was approximately ten times less than that of hydralazine in renal hypertensive dogs, 10 mg kg⁻¹ and 20 mg kg⁻¹ flosequinan causing similar falls in mean blood pressure to 1 mg kg⁻¹ and 3 mg kg⁻¹ hydralazine respectively. In normotensive cats, 5 mg kg⁻¹ flosequinan caused similar falls to 0.5 and 1.0 mg kg⁻¹ hydralazine. The onset of hypotensive effect after flosequinan appeared to be slightly slower than after hydralazine in the dog and slightly faster than hydralazine in the cat.

2 The degree of tachycardia and increase in plasma renin activity (PRA) for equivalent falls in mean blood pressure in both species was significantly less for flosequinan than for hydralazine ($P < 0.05$).

3 In normotensive dogs, flosequinan, 10 and 20 mg kg⁻¹ orally, caused a small but non-significant increase in sodium and chloride excretion and had little effect on urine volume whereas hydralazine, 1 and 3 mg kg⁻¹ orally, caused a marked retention of sodium and chloride ions and a reduction in urine volume ($P < 0.01$).

4 Neither flosequinan, 10 mg kg⁻¹ orally, nor hydralazine 1 mg kg⁻¹ orally, affected either glomerular filtration rate measured as creatinine clearance or effective renal plasma flow measured as *p*-aminohippuric acid clearance in normotensive dogs.

5 The lesser degree of tachycardia and increase in plasma renin activity together with a lack of sodium retaining activity associated with flosequinan suggest that this agent may have potential advantages over existing therapy as an antihypertensive in man.

Introduction

Mild to moderate essential hypertension is associated with increased total peripheral resistance (TPR) (Frohlich *et al.*, 1970). The logical therapeutic approach to this is the use of arterial dilator agents such as hydralazine or minoxidil but the administration of this type of agent results in reflex tachycardia and sodium retention, often necessitating the concomitant use of β -adrenoceptor blockers and diuretics (Gottlieb *et al.*, 1972; Zacest *et al.*, 1972).

Sodium nitroprusside, an arteriovenous dilator agent, causes less tachycardia than hydralazine in renal hypertensive dogs (Yates, 1982a) and patients with essential hypertension (Shepherd & Irvine, 1986). However, sodium nitroprusside has a very short half-life and must be administered by intravenous infusion as it is not orally absorbed. Preliminary

observations suggest that flosequinan (BTS 49 465, 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone, Figure 1), a novel quinolone hypotensive compound (Davies *et al.*, 1983), is an orally effective hypotensive agent with mixed arteriovenous dilator properties and a prolonged duration of action in man (Cowley *et al.*, 1984). This paper describes some effects of flosequinan in conscious dogs and cats.

Methods

Studies in the dog

Blood pressure, heart rate and plasma renin activity (PRA) studies in conscious renal hypertensive dogs Adult male beagles weighing 12.75 to 16 kg were previously made hypertensive by renal encapsu-

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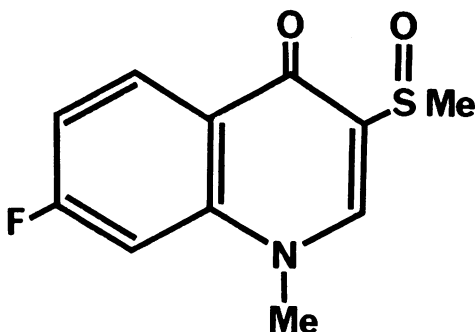


Figure 1 The chemical structure of flosequinan (BTS 49 465, 7-fluoro-1-methyl-3-methylsulphonyl-4-quinolone).

lation by latex capsule, using a technique similar to that described for the rat (Abrams & Sobin, 1947). The experiments in this study were carried out 9 to 17 months after renal encapsulation. The dogs were deprived of food but allowed free access to water overnight. On the day of the test, each dog stood in a sling supported by a frame. Blood pressure was measured by direct puncture of a carotid artery previously made accessible in the form of a carotid loop (Parkinson, 1978). A teflon catheter was inserted into the artery by use of the Seldinger technique (Seldinger, 1953). A continuous infusion of 0.1 ml min^{-1} of sterile 0.9% w/v sodium chloride solution containing heparin 10 units ml^{-1} was maintained during the period of measurement. The arterial catheter was connected to a Bell and Howell pressure transducer and mean blood pressure, derived electronically by use of a long time constant, was displayed on a Lectromed twin channel recorder. Heart rate was counted from the recorder trace. Measurement of mean blood pressure and heart rate were made before and at 30 min intervals after dosing, in each case the measurement being the mean of three readings made at 5 min intervals centred at the time stated.

Arterial blood samples were taken from the carotid artery before dosing and at 45, 105 and 300 min after dosing for PRA determination, using the RIANEN Angiotensin I ^{125}I Radioimmunoassay Kit.

The experiment followed an 8×8 cross-over design. Each dog received each treatment and placebo control in rotation at weekly intervals. At the completion of the experiment, each treatment had been tested in all eight dogs. Since it was possible to measure only four dogs at a time, the test was carried out on two days each week and the same four dogs were measured together on each occasion. Two placebo treatments were used, allocated so that each day's test had a placebo control present. Flose-

quinan and hydralazine were given orally in hard gelatine capsules; empty gelatin capsules were given as placebo.

Renal studies in normotensive dogs

Effects on urine volume and electrolyte excretion in conscious normotensive dogs A technique similar to that described for diuretic studies in the dog was used (Cooling & Sim, 1981). Normotensive beagle bitches, weighing 10 to 15.5 kg, were fasted as above, placed in slings supported by frames and their bladders catheterised. The contents of the bladder were drained and the bladder washed out with 20 ml sterile distilled water. A fluid load of 10 ml kg^{-1} of a 150 mM sodium chloride solution was administered via stomach tube and urine collected hourly for 4 h. In drug-treated animals the appropriate dose of either flosequinan or hydralazine was contained in the fluid load. The hourly urine volume was measured and urine samples taken for determination of electrolyte content. The experiment was designed as an 8×8 cross-over, each dog received each drug treatment and two control treatments and there was an interval of one week between each treatment.

Urine electrolyte concentrations were determined with an autoanalyser, sodium and potassium by flame photometry (Technicon method SE-007 FH4) and chloride colorimetrically (Technicon method N-56).

Renal clearance studies in conscious normotensive dogs Normotensive beagle bitches weighing 11 to 16 kg were fasted and their bladders catheterised as above. Both cephalic veins were also catheterised to allow administration of marker substances and withdrawal of blood. The dogs were loaded intravenously with 50 mg kg^{-1} creatinine and 5 mg kg^{-1} *p*-aminohippuric acid (PAH), each contained in 1 ml kg^{-1} of a 100 mM sodium chloride solution. The loading dose was followed with an infusion of 100 mM sodium chloride solution containing creatinine 1 mg ml^{-1} and PAH 0.3 mg ml^{-1} and given at approximately 5 ml min^{-1} to maintain blood concentrations. An equilibration period of 80 min was allowed and, when urine output was constant, clearance studies were started. Urine was collected for periods of 20 min and blood samples taken at about the midpoint of each period. After three control periods either flosequinan, 10 mg kg^{-1} or hydralazine 1 mg kg^{-1} in 1 ml kg^{-1} of a 100 mM sodium chloride solution or the same volume of vehicle was administered to each dog by stomach tube. Clearance measurements were continued for 120 min.

Creatinine was determined by the method of Raabo & Walloe-Hanson (1972) and PAH by that of Brun (1951). Urine volume was measured and

urinary electrolytes determined for each sample using the method described above. A 3×4 crossover design was used, each dog receiving each treatment with at least 1 week between treatments. Clearances were calculated by use of the formula: $C = UV/P$ where C = clearance ml min^{-1} , V = urine volume ml min^{-1} , U = urine concentration mg ml^{-1} and P = plasma concentration mg ml^{-1} .

Studies in the cat

Blood pressure, heart rate and PRA in conscious normotensive cats The method of pressure recording used in normotensive conscious cats (Yates, 1982b) was essentially the same as that described above for dogs. Castrated male cats weighing 5.5 to 6.5 kg were used. The cats were deprived of food but allowed free access to water overnight before each test. Blood pressure was displayed on a Lectromed 4-channel recorder and recorded on a Racal 7-channel tape recorder for subsequent computer evaluation of mean blood pressure and heart rate using the Cambridge Electronic Design SLAM system. After 45 min control reading the cats were dosed orally with hard gelatine capsules containing flosequinan or hydralazine or with empty hard gelatine capsules as placebo. Blood pressure was measured for a further 270 min.

Arterial blood samples were taken from the carotid loop before dosing and at 60, 150 and 240 min after dosing for radioimmunoassay of PRA using the RIANEN Angiotensin I ^{125}I Radioimmunoassay kit.

The experiment followed a 6×6 crossover design involving three doses of flosequinan, two doses of hydralazine and one placebo dose. Each cat received each treatment or placebo control at weekly intervals.

Statistical evaluation

Repeat measures analysis of covariance were carried out in which overall treatment means were compared using a variance ratio test (F test) (Winer, 1971). Pre-dose baseline values where available (i.e. cardiovascular studies in the renal hypertensive dog and normotensive cat; renal clearance studies in the normotensive dog) were used as covariates. The use of overall treatment means provides a sensitive method for comparing data from several treatments, each involving multiple time point measurements. The data were analysed using the GLIM (Generalised Linear Interactive Modelling) Statistical Computing Package with a development described by Channon (1981a, b). Comparison of treated and control groups were made by Williams' or Dunnett's test and between treatment groups by Newman-Keuls test (Dunnett & Goldsmith, 1981).

Drugs

The following drugs were used: flosequinan (Boots – batch TL7); hydralazine (Ciba-Geigy – batch 13806).

Results

Effects in conscious renal hypertensive dogs

Both flosequinan (Figure 2) and hydralazine (Figure 3) caused dose-related falls in mean blood pressure and increases in heart rate. A small but significant reduction in pressure associated with a small significant tachycardia occurred after 5.0 mg kg^{-1} flosequinan, the lowest dose used. However, the lowest dose of hydralazine, 0.3 mg kg^{-1} , caused a significant tachycardia but had no significant effect on mean blood pressure.

Flosequinan 10 mg kg^{-1} and hydralazine 1 mg kg^{-1} had very similar hypotensive effects but the tachycardia after hydralazine was significantly greater than that after flosequinan, the overall difference between the two treatments being $28 \text{ beats min}^{-1}$ ($P < 0.05$ Newman-Keuls test). The onset of hypotension after flosequinan appeared to be slightly slower than that of hydralazine. The hypotensive effects of 20 mg kg^{-1} flosequinan and 3 mg kg^{-1} hydralazine were similar but again hydralazine caused a significantly greater tachycardia (overall difference $29 \text{ beats min}^{-1}$, $P < 0.05$ Newman-Keuls test).

The effects of flosequinan and hydralazine on PRA in this experiment are shown in Table 1. Flosequinan had no effect on PRA at 5 mg kg^{-1} and the small increases in PRA after flosequinan, 10 or 20 mg kg^{-1} , were not significantly different from controls. All doses of hydralazine caused significant increases in PRA. Hydralazine caused significantly greater increases in PRA than equihypotensive doses of flosequinan as can be seen by comparing effects of hydralazine at 1 mg kg^{-1} and flosequinan at 10 mg kg^{-1} or hydralazine at 3 mg kg^{-1} and flosequinan at 20 mg kg^{-1} ($P < 0.05$ Newman-Keuls test).

Effects in conscious normotensive dogs

Hydralazine at 1 or 3 mg kg^{-1} caused a marked and significant reduction of sodium and chloride excretion and urine volume in conscious normotensive dogs (Table 2). The antidiuretic effects of hydralazine were apparent at 120 min after dosing and persisted for the remainder of the experiment. Flosequinan had no effect on sodium and chloride excretion at 5 mg kg^{-1} but caused small though insignificant increases at 10 and 20 mg kg^{-1} . Urine volume was

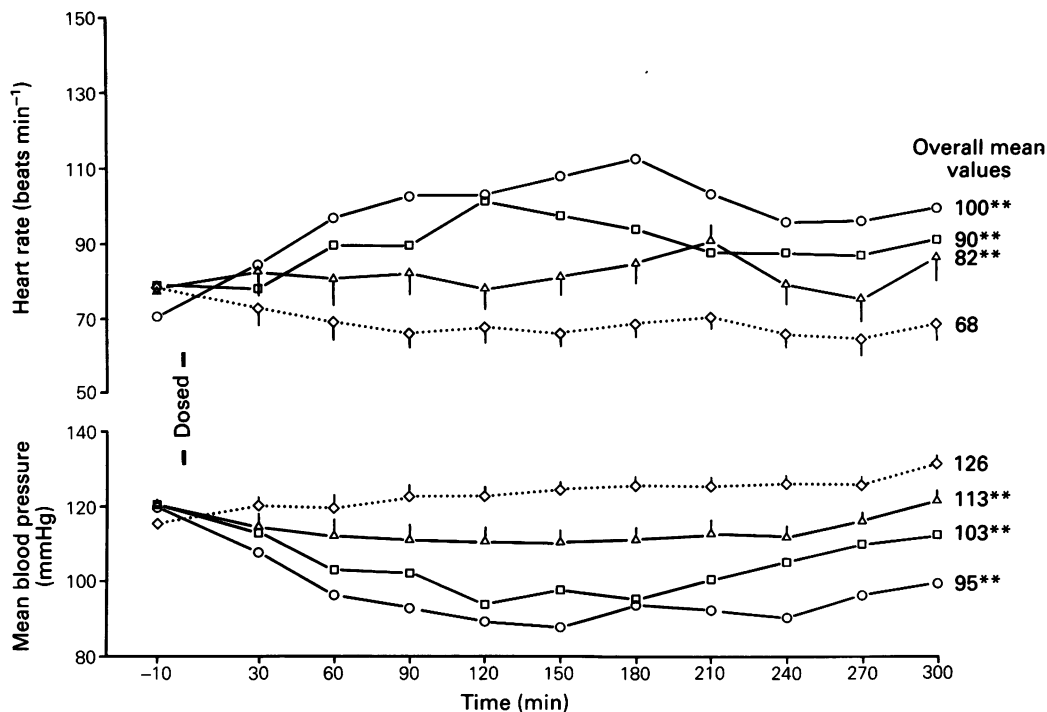


Figure 2 Effects of flosequinan on the blood pressure and heart rate of conscious renal hypertensive dogs ($n = 8$). Each dog received placebo treatment twice ($n = 16$). The results in this figure are part of an 8×8 crossover experiment making a comparison with hydralazine (see Figure 3 for the hydralazine results). Placebo (\diamond); flosequinan: 5 mg kg^{-1} orally (Δ); 10 mg kg^{-1} orally (\square); 20 mg kg^{-1} orally (\circ). Vertical lines indicate s.e. mean for within animal variation. $n = 16$ for placebo group; $n = 8$ for treatment group and error bars, identical for the three treatment groups, are shown for low dose only. Overall mean values for each treatment averaged over the 300 min following dosing are also shown.

** $P < 0.01$ for multiple comparisons against placebo (Williams' test).

Table 1 Effects of flosequinan and hydralazine on the plasma renin activity of arterial blood collected from conscious renal hypertensive dogs

	n	Predose†	Plasma renin activity ($\text{ng ml}^{-1} \text{ h}^{-1}$)			Overall mean value
			Time after dosing (min)	45†	105†	
Placebo	16	0.9 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	0.8 ± 0.1	0.9
Flosequinan (mg kg^{-1} orally)						
5.0	8	0.8 ± 0.2	0.8 ± 0.1	0.9 ± 0.2	0.8 ± 0.2	0.7
10.0	8	0.7 ± 0.1	0.9 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.1
20.0	8	0.7 ± 0.1	0.9 ± 0.2	1.3 ± 0.2	1.5 ± 0.3	1.1
Hydralazine (mg kg^{-1} orally)						
0.3	8	0.8 ± 0.2	1.9 ± 0.4	2.3 ± 0.5	1.6 ± 0.3	1.9**
1.0	8	0.7 ± 0.2	2.5 ± 0.7	2.6 ± 0.8	1.8 ± 0.4	2.0**
3.0	8	0.9 ± 0.2	3.1 ± 0.7	4.5 ± 1.1	4.1 ± 1.2	3.3**

† Each value is the mean \pm s.e. mean of n dogs in an 8×8 crossover experiment. Each dog received the placebo treatment twice. Each overall mean value is for n dogs averaged over the 300 min following dosing. Statistical evaluation was carried out after square root transformation due to the skewed distribution of the original data.

** $P < 0.01$ for multiple comparisons against control (Williams' test).

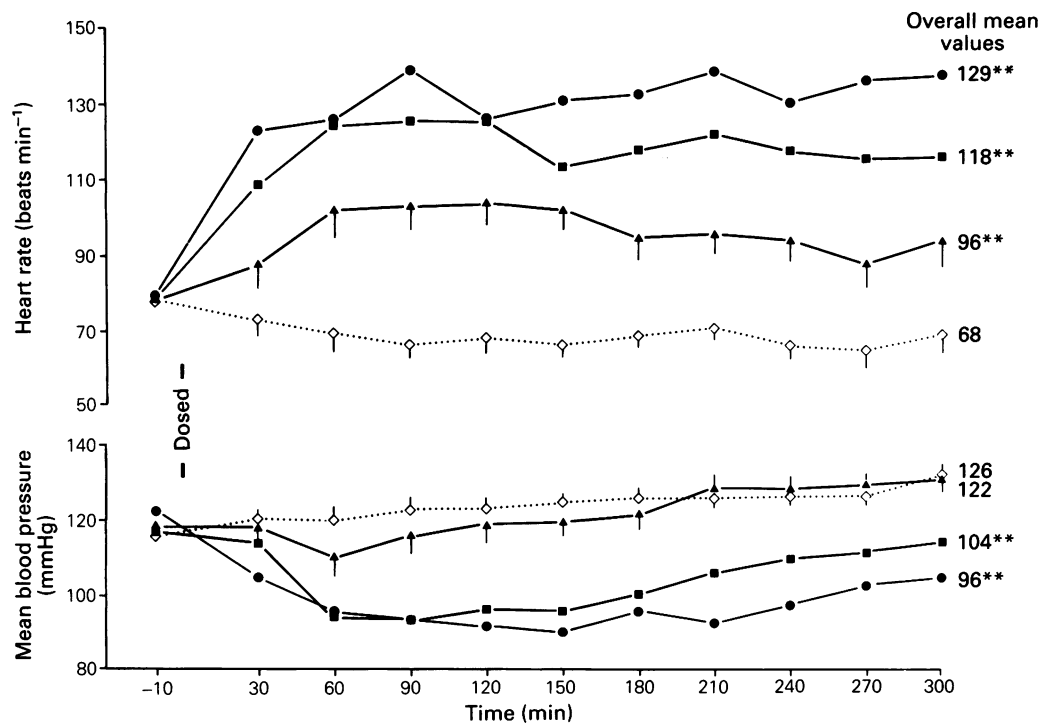


Figure 3 Effects of hydralazine on the blood pressure and heart rate of conscious renal hypertensive dogs ($n = 8$). Each dog received placebo treatment twice ($n = 16$). The results in this figure are part of an 8×8 crossover experiment making a comparison with flosequinan (see Figure 2 for the flosequinan results). Placebo (\diamond); hydralazine: 0.3 mg kg^{-1} oraly (\triangle); 1 mg kg^{-1} oraly (\blacksquare); 3 mg kg^{-1} oraly (\bullet). Vertical lines indicate s.e. mean for within animal variation. $n = 16$ for placebo group; $n = 8$ for treatment group and error bars, identical for the three treatment groups, are shown for the low dose only. Overall mean values for each treatment averaged over the 300 min following dosing are also shown.

** $P < 0.01$ for multiple comparisons against placebo (Williams' test).

Table 2 Overall mean values for sodium excretion, potassium excretion, chloride excretion and urine volume after flosequinan or hydralazine in conscious normotensive dogs loaded orally with sodium chloride solution

	n	Na^+ excretion (mmol kg^{-1})	Overall mean values		
			K^+ excretion (mmol kg^{-1})	Cl^- excretion (mmol kg^{-1})	Urine volume (ml kg^{-1})
Placebo	16	0.31	0.069	0.34	3.05
Flosequinan (mg kg^{-1} oraly)					
5.0	8	0.28	0.086	0.33	2.58
10.0	8	0.36	0.089	0.39	2.74
20.0	8	0.39	0.117**	0.41	2.89
Hydralazine (mg kg^{-1} oraly)					
0.3	8	0.25	0.067	0.26	2.71
1.0	8	0.10**	0.059	0.12**	1.54**
3.0	8	0.11**	0.110*	0.12**	1.46**

The dogs were loaded orally with 10 ml kg^{-1} 150 mm sodium chloride solution. Urine was collected hourly for the 4 h following treatment. Each value is the overall mean of the 4 hourly collection for n dogs. Each of the 8 dogs received the placebo treatment twice (8×8 crossover experiment).

** $P < 0.01$, * $P < 0.05$ for multiple comparison against placebo (Williams' test).

Table 3 Overall mean values for *p*-aminohippurate (PAH) and creatinine clearances, electrolyte excretion and urine volume after flosequinan or hydralazine in conscious normotensive dogs

	PAH clearance (ml min ⁻¹)	Creatinine clearance (ml min ⁻¹)	Overall mean values		Cl ⁻ excretion (mmol kg ⁻¹ min ⁻¹)	Urine volume (ml kg ⁻¹ min ⁻¹)
			Na ⁺ excretion (mmol kg ⁻¹ min ⁻¹)	K ⁺ excretion (mmol kg ⁻¹ min ⁻¹)		
Placebo	125.1	54.6	0.025	0.002	0.027	0.31
Flosequinan (10.0 mg kg ⁻¹ orally)	135.6	53.8	0.024	0.001	0.025	0.24
Hydralazine (1.0 mg kg ⁻¹ orally)	124.0	48.9	0.007*	0.002	0.008*	0.15*

Each value is the overall mean of 4 dogs calculated from six 20 min clearance periods following dosing (3 × 4 crossover experiment).

**P* < 0.05 for multiple comparisons against placebo (Dunnett's test was used as there were only three groups).

not affected by the higher doses of flosequinan. The highest doses of both agents caused significant increases in potassium excretion.

Neither flosequinan nor hydralazine modify effective renal plasma flow (ERPF) measured by PAH clearance, or glomerular filtration rate (GFR) measured by creatinine clearance (Table 3). Flosequinan 10 mg kg⁻¹ did not affect electrolyte excretion or urine volume whereas 1 mg kg⁻¹ hydralazine produced the expected retention of sodium and chloride ions and reduction in urine volume.

Effects in conscious normotensive cats

Flosequinan caused dose-related falls in mean blood pressure which were significant at all doses (Figure 4), but the hypotensive responses to hydralazine were significant and similar for both 0.5 and 1.0 mg kg⁻¹ (Figure 5). Only the lowest dose of flosequinan caused a significant tachycardia, the responses to 5.0 and 10.0 mg kg⁻¹ being greater than placebo, but not significantly so (Figure 4). Each dose of hydralazine produced a significant tachycardia but, like flosequinan, the low dose caused a greater tachycardia than the higher dose. The tachycardia at equihypotensive doses (flosequinan 5 mg kg⁻¹, hydralazine 0.5 mg kg⁻¹) was significantly less for flosequinan than for hydralazine (a difference in overall mean values of 17 beats min⁻¹, *P* < 0.01 Newman-Keuls test.) The highest dose of flosequinan, 10 mg kg⁻¹, had a greater hypotensive effect and caused less tachycardia than 1 mg kg⁻¹ hydralazine though the differences were not significant.

The onset of hypotensive activity after flosequinan occurred between 15 and 45 min and was almost maximal at 45 min. There was some recovery towards normal from about 180 min after flosequinan

an 10 mg kg⁻¹ and between 90 and 120 min after 2.5 and 5 mg kg⁻¹. The blood pressure responses to hydralazine reached a maximum at about 60 min and then gradually returned to pre-treatment values.

Both flosequinan and hydralazine caused increases in PRA (Table 4). The marked increase in PRA 60 min after hydralazine was followed by declining activity at 150 and 240 min but the moderate increases after flosequinan were similar at each time interval. The increases after the three doses of flosequinan and the two doses of hydralazine were significantly different from controls. The increases in PRA after all doses of flosequinan were significantly less than those after hydralazine (flosequinan 10.0 mg kg⁻¹ vs hydralazine 0.5 mg kg⁻¹ or 1.0 mg kg⁻¹ *P* < 0.05, all other comparisons *P* < 0.01, Newman-Keuls test).

Discussion

Flosequinan, an orally effective hypotensive agent in the conscious renal hypertensive dog, was approximately ten times less potent than hydralazine and the rate of onset of hypotensive effect was slightly slower after flosequinan. Hypotensive potency comparison in the cat is not possible since the two doses of hydralazine caused similar falls in mean pressure suggesting that the maximal hypotensive dose of hydralazine is 0.5 mg kg⁻¹ or less. The rate of onset of hypotensive activity in the cat was possibly slightly faster with flosequinan than with hydralazine. Taylor *et al.* (1981) using a different blood pressure recording technique (indwelling aortic cannulae) reported 5–10 mmHg lower pre-dose mean blood pressures in their conscious normotensive cats (sex not stated) and found that high oral doses of

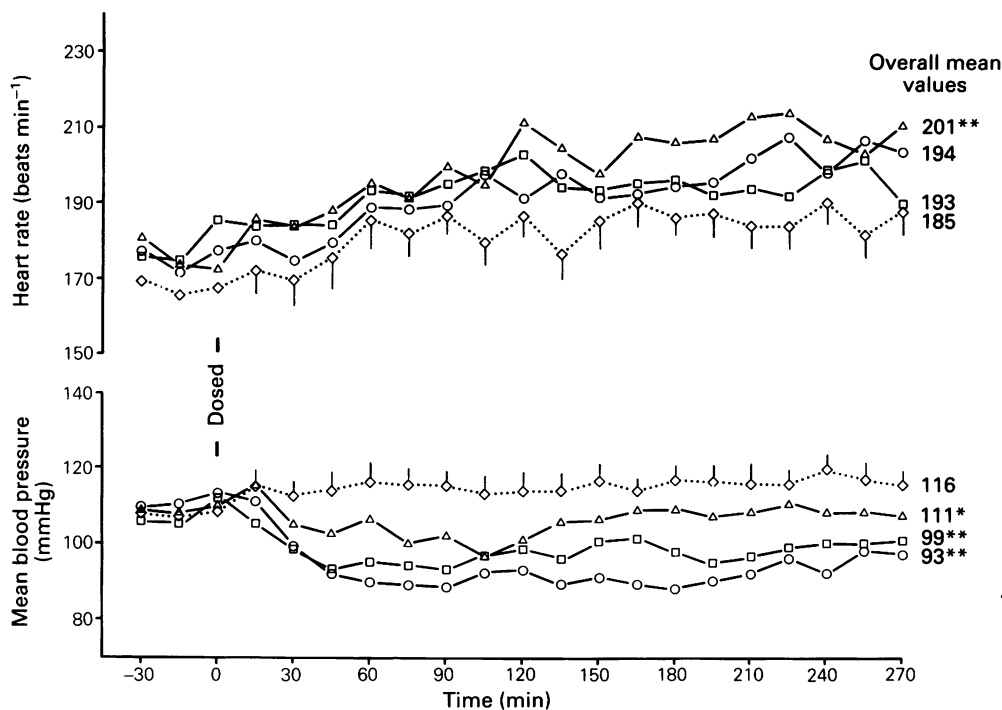


Figure 4 Effects of flosequinan on the blood pressure and heart rate of conscious normotensive cats ($n = 6$). The results in this figure are part of a 6×6 crossover experiment making a comparison with hydralazine (see Figure 5 for the hydralazine results). Placebo (\diamond); flosequinan: 2.5 mg kg^{-1} orally (Δ); 5 mg kg^{-1} orally (\square); 10 mg kg^{-1} orally (\circ). Vertical lines indicate s.e. mean for within animal variation; error bars, identical for all groups, are shown for controls only. Overall mean values for each treatment averaged over the 270 min following dosing are also shown.

** $P < 0.01$, * $P < 0.05$ for multiple comparisons of mean blood pressure against control (Williams' test) and for multiple comparisons of heart rate against control (Dunnett's test used since the heart rate dose-response relationship showed a negative correlation).

Table 4 Effects of flosequinan and hydralazine on plasma renin activity in conscious normotensive cats

	Plasma renin activity ($\text{ng ml}^{-1} \text{ h}^{-1}$)				Overall mean value
	Predose†	60†	150†	240†	
Placebo	1.0 ± 0.2	1.7 ± 0.4	1.8 ± 0.5	1.8 ± 0.3	1.5
Flosequinan (mg kg^{-1} orally)					
2.5	1.5 ± 0.4	2.7 ± 0.5	2.7 ± 0.4	2.7 ± 0.6	2.7*
5.0	1.5 ± 0.3	3.1 ± 0.7	3.4 ± 0.5	2.9 ± 0.6	3.1**
10.0	1.7 ± 0.4	4.3 ± 1.1	4.8 ± 1.3	3.7 ± 0.8	4.2**
Hydralazine (mg kg^{-1} orally)					
0.5	1.4 ± 0.3	9.9 ± 1.9	6.8 ± 1.3	4.5 ± 0.9	6.6**
1.0	1.0 ± 0.2	11.1 ± 2.3	7.8 ± 1.5	4.4 ± 1.1	6.6**

† Each value is the mean \pm s.e. mean for 6 cats in a 6×6 crossover experiment. Each overall mean value is for the 6 cats averaged over the 270 min following dosing. Statistical evaluation was carried out after square root transformation due to the skewed distribution of the original data.

** $P < 0.01$, * $P < 0.05$ for multiple comparisons against control (Williams' test).

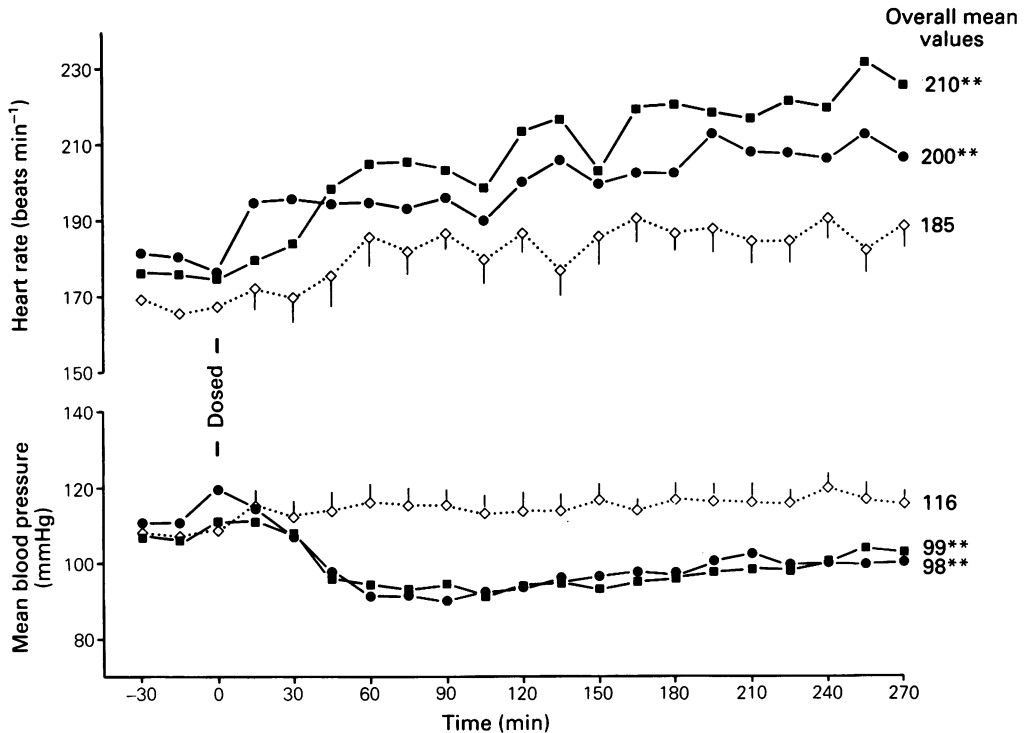


Figure 5 Effects of hydralazine on the blood pressure and heart rate of conscious normotensive cats ($n = 6$). The results in this figure are part of a 6×6 crossover experiment making a comparison with flosequinan (see Figure 4 for the flosequinan results). Placebo (\diamond); hydralazine: 0.5 mg kg^{-1} orally (\blacksquare); 1 mg kg^{-1} orally (\bullet). Vertical lines indicate s.e. mean for within animal variation; error bars, identical for all groups, are shown for controls only. Overall mean values for each treatment averaged over the 270 min following dosing are also shown.

** $P < 0.01$ for multiple comparisons of mean blood pressure against control (Williams' test) and for comparison of heart rate against control (Dunnett's test used since heart rate dose-response relationships showed a negative correlation).

hydralazine (5 and 10 mg kg^{-1}) had no hypotensive activity.

The hypotensive effects of flosequinan and hydralazine were associated with tachycardia in both species but the tachycardia for equivalent blood pressure falls was less with flosequinan. The lowest dose of hydralazine in dogs caused a significant tachycardia in the absence of hypotensive activity. This dose was associated with tachycardia and increases in PRA, factors possibly counterbalancing the vasodilator activity of low but not higher doses of hydralazine. Both compounds caused less tachycardia as the dose was increased in cats, a phenomenon for which there appears to be no obvious explanation. These results suggest possible differences from those of Taylor *et al.* (1981) who reported that higher oral doses of hydralazine (5 and 10 mg kg^{-1}) caused a similar increase in heart rate to the low dose in our study. Their experimental tech-

nique differed and the pre-dose heart rates of their conscious normotensive cats were greater (approximately $20 \text{ beats min}^{-1}$) than those in our study. Further dose-response studies are required to elucidate this difference.

Hydralazine-induced tachycardia has long been considered to be due to reflexes triggered by hypotension but the Bainbridge reflex may be partially involved since hydralazine increases venous return and hence may trigger this reflex via the right atrial stretch receptors (Spokas & Wang, 1980). Flosequinan appears to be an arteriovenous dilator agent (Cowley *et al.*, 1984) and may thus be expected to cause a smaller increase in venous return than the pure arterial dilator, hydralazine. Furthermore, sodium nitroprusside, another arteriovenous dilator agent, causes less tachycardia than hydralazine at doses causing similar falls in blood pressure in conscious renal hypertensive dogs (Yates, 1982a). We

have observed that other arterial dilator agents such as minoxidil, nifedipine and budralazine cause greater tachycardia than flosequinan in conscious renal hypertensive dogs and conscious normotensive cats (Yates & Parkinson, unpublished).

A striking difference was observed between flosequinan and hydralazine in respect of the renal response observed in normotensive dogs. Hydralazine had a marked antidiuretic effect whereas flosequinan did not significantly modify urine output or sodium and chloride ion excretion. Neither compound affected ERPF or GFR. In another study on renal hypertensive dogs, flosequinan, 10 mg kg^{-1} orally, again had no antidiuretic activity (Parkinson, unpublished). Our observations with hydralazine are in agreement with studies reported by Zins (1974) who found that other arterial dilators, minoxidil, diazoxide and guanicydine, which cause sodium retention, also had little effect on ERPF or GFR in dogs. This author considered that the antidiuretic action of these compounds was associated with enhanced sodium reabsorption at the level of the proximal tubule. The antidiuretic activity of vasodilator agents may result from reflex stimulation of the sympathetic nervous system (Brouhard *et al.*, 1981). Further work is required to elucidate the difference in renal response of the dog to flosequinan and arterial dilators such as minoxidil or hydralazine.

Our study relates PRA changes to mean blood pressure since change in mean renal perfusion pressure rather than in pulse pressure, appears to be the primary pressure factor governing renal renin release (Skinner *et al.*, 1963; Davis & Freeman, 1976). The increase in PRA due to hydralazine was expected and is well documented in man (Gottlieb *et al.*, 1972) and the dog (Massingham & Hayden, 1975). A study in 20 hypertensive patients revealed that the elevation of PRA after hydralazine was not correlated with changes in mean arterial pressure, renal blood flow or glomerular filtration rate but there was a strong correlation with heart rate (Ueda *et al.*, 1970). Our results in renal hypertensive dogs support this observation since the low dose of hydralazine had no effect on mean blood pressure but caused a significant increase in heart rate and PRA and higher doses caused a dose-related increase in heart rate and PRA. These findings would appear to support the concept that the increase in PRA after hydralazine may be elicited by reflex sympathetic discharge to the juxtaglomerular cells of the kidney (Pettinger *et al.*, 1973). Alternatively, increased PRA after hydralazine might result from its antidiuretic effect since this would reduce the sodium load reaching the macula densa segment of the distal tubule and thereby stimulate renin release according to Vander's hypothesis (Vander, 1967).

Flosequinan caused smaller increases in PRA than

hydralazine for equivalent blood pressure falls in renal hypertensive dogs. There appeared to be no correlation between PRA and heart rate or mean blood pressure after flosequinan in dogs since PRA was unaffected despite dose-related falls in mean blood pressure and increase in heart rate. Moreover flosequinan was not antidiuretic in the dog, suggesting that it would be unlikely that the sodium load at the macula densa was affected, thus providing at least a partial explanation for the lack of effect on PRA.

Similarly in cats, flosequinan caused smaller increases in PRA than hydralazine for equivalent mean blood pressure falls. In contrast to the dog, however, the effects of flosequinan on PRA may be correlated with changes in blood pressure since this agent caused a dose-related fall in pressure and increase in PRA. There was no correlation between heart rate and PRA after flosequinan in this species. The hydralazine-induced increase in PRA in the cat also appeared to correlate with falls in mean blood pressure since the two doses caused similar falls in mean blood pressure and similar increases in PRA.

The use of peripherally-acting arterial dilator agents would appear to be the most appropriate form of antihypertensive therapy since the major haemodynamic disturbance observed in most hypertensive patients is increased peripheral resistance. However, in the clinic, arterial dilators such as hydralazine or minoxidil suffer from the disadvantage of inducing tachycardia and sodium retention provoked by the haemodynamic effects of these compounds. Consequently concurrent diuretic and β -blocking therapy is usually required. Moreover both compounds cause marked increases in PRA, a further disadvantage, since the resultant increase of angiotensin II will oppose and blunt the vasodilator effects. Flosequinan is a novel arteriovenous dilator agent which causes less tachycardia and a smaller increase in PRA than hydralazine in dogs and cats. Unlike hydralazine, flosequinan is not antidiuretic in the dog. In normal human volunteers flosequinan caused only small increases in PRA, had no effect on urine volume, and was well tolerated in terms of haematological and biochemical parameters as well as subjective side effects (Wynne *et al.*, 1985). Flosequinan should have clinical potential as an antihypertensive agent with advantages over existing therapy if it proves to possess these properties in hypertensive patients. Clinical studies are in progress.

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