Br. J. Pharmacol. (1988), **93**, 893–901

In vivo pharmacological studies with SK&F 94836, a potent inotrope/vasodilator with a sustained duration of action

[1]R.W. Gristwood, M.B. Comer, R.J. Eden, E.M. Taylor, J.A. Turner, M. Wallduck & D.A.A. Owen

Department of Pharmacology, Smith Kline & French Research Limited, The Frythe, Welwyn, Hertfordshire AL6 9AR

1 SK&F 94836 (racemate) was studied *in vivo* for its cardiovascular properties in cats and dogs.

2 In anaesthetized cats and dogs SK&F 94836 administered intravenously caused increases in left ventricular contractility and decreases in peripheral vascular resistance at similar doses, thus demonstrating the compound to be a mixed acting positive inotropic/vasodilator agent.

3 In conscious instrumented dogs SK&F 94836 was active via the oral as well as intravenous route.

4 The inodilator activity of SK&F 94836 in conscious and anaesthetized animals occurred in association with minimal changes in either blood pressure or heart rate.

5 Detailed studies carried out on anaesthetized cats indicated that SK&F 94836 caused a balanced dilatation of both resistance and capacitance blood vessels.

6 Haemodynamic studies in anaesthetized cats indicated that as a consequence of the inotropic/vasodilator actions, SK&F 94836 caused significant increases in cardiac output and stroke volume.

7 Detailed studies in anaesthetized dogs indicated that significant inodilator activity occurred in the absence of an increase in myocardial oxygen consumption.

8 The duration of action of SK&F 94836 was sustained following both i.v. and oral administration.

9 We conclude that SK&F 94836, as an orally active inotropic/vasodilator agent with a sustained duration *in vivo*, has potential utility in the treatment of congestive heart failure.

Introduction

Current therapeutic procedures for the treatment of congestive heart failure (CHF) include the use of diuretics, vasodilators and positive inotropic agents alone or in combination. Whilst orally active diuretics and vasodilators are commercially available, cardiac glycosides remain the only commercially available, orally active positive inotropic agents, and for the long term treatment of CHF, the need for new, orally active positive inotropic agents with improved therapeutic ratios has long been recognized. A number of orally active agents possessing combined positive inotropic and vasodilator activity are currently under development. These agents include the cyclic nucleotide phosphodiesterase inhibitors, milrinone (Alousi *et al.*, 1983), piroximone (Dage *et al.*, 1984), imazodan (CI 914) and CI 930 (Bristol *et al.*, 1984).

The potential role for the long-term use of phosphodiesterase inhibitors in the therapy of congestive heart failure is still under intense clinical evaluation. However, there is evidence that these agents may, have a future major role in CHF treatment (e.g. Jafri *et al.*, 1986; Arbogast *et al.*, 1986).

As part of our strategy at SK&F for the identification of new agents for the treatment of CHF, we synthesized and tested novel compounds for combined positive inotropic/vasodilator activity, and in particular sought compounds which exhibited a sustained duration of action *in vivo*. We now describe the *in vivo* pharmacology of one such agent, SK&F 94836

[1] Author for correspondence at present address: Laboratorios Almirall, S.A. Cardoner, 68–74, 08024 Barcelona, Spain.

(R,S-2-cyano-1-methyl-3-[4-(-methyl-6-oxo-1,4,5,6-tetrahydropyridazine-3-yl)phenyl]-guanidine, molecular weight 284), a potent selective inhibitor of cyclic nucleotide phosphodiesterase type III (Reeves *et al.*, 1987).

Methods

Anaesthetized cats

Animals of either sex (1.7–4.6 kg) were anaesthetized with sodium pentobarbitone (Sagatal), 60 mg kg^{-1}, i.p. The trachea was cannulated and blood pressure recorded from the left femoral artery. Mean blood pressure was calculated by adding 1/3 of the pulse pressure to the diastolic pressure. Blood pressure pulses were used to trigger a heart rate meter (instantaneous, SK&F electrical workshop).

Inodilator activity A polythene cannula (Portex, internal diameter 1.0 mm) connected to a pressure transducer was passed down the right carotid artery and manipulated through the semi-lunar valves into the left ventricle. The frequency response of this system was measured according to the method of Fry (1960), and was flat (±0.5%) up to 47 Hz. The record of left ventricular pressure was electronically differentiated to give a continuous linear record of left ventricular (LV) *dp/dt max*, taken as a measure of left ventricular contractility (e.g. Gleason & Braunwald 1962). Pempidine (5 mg kg^{-1}, i.v.) was given to inhibit reflex activity and produce a stable preparation with a low heart rate and left ventricular contractility, which was very responsive to positive inotropic compounds, such as isoprenaline. The sensitivity of each preparation was tested with isoprenaline given in a range of doses (0.01 to 0.1 μg kg^{-1}, i.v.). Once the sensitivity of the preparation had been checked, propranolol (1 mg kg^{-1}, i.v. plus 3–4 mg kg^{-1}, s.c.) was given, which produced an immediate and prolonged β-adrenoceptor blockade.

In order to evaluate the vasodilator activity of drugs, the abdominal aorta, caudal to the renal arteries was subjected to a double cannulation. The animals were treated with 500 units kg^{-1} i.v. heparin to prevent coagulation of the blood in the extracorporeal circuit. Blood was withdrawn from the cannulated proximal aorta and pumped distally to the hindquarters at constant flow, using a peristaltic roller pump (Watson Marlow) and hindquarters vascular resistance calculated. The caudal mesenteric artery was ligated in order to exclude the influence of drug-induced changes in mesenteric blood flow.

Effect on intestinal resistance and capacitance blood vessels Relative vasodilator activity of drugs was assessed on the acutely denervated superior mesenteric vasculature according to the method of Taylor (1973), and validated in studies by Fielden *et al.* (1974) and Taylor *et al.* (1981). In brief, two pulsatile pumps, both operating at constant flow, were used to control total blood flow in and out of the intestinal vasculature. Blood to prime the 'arterial' roller pump was taken from the left carotid artery and was pumped into the cannulated anterior mesenteric artery. Venous blood draining from the intestines was pumped (by the 'venous' roller pump) from the mesenteric vein and returned to the cat through a cannula in the left femoral vein. Transducers in the extracorporeal circuit recorded arterial perfusion pressure (P_a) and venous outflow pressure (P_v).

The flow rates of the 'arterial' and 'venous' roller pumps were carefully balanced so that the vascular bed remained isovolaemic and the pressure, P_v stable at about 10 mmHg. Pressure P_a was usually in the range 100 to 150 mmHg. Decreases in P_a and P_v indicate vasodilatation in arterial and venous blood vessels, respectively, while conversely, increases in P_a and P_v follow vasoconstriction. It has been shown that changes in P_a and P_v represent independent measures of arterial and venous tone.

The vascular reactivity of each preparation was tested with the standard vasodilator, papaverine hydrochloride, injected intra-arterially (i.a.) at doses of 10, 31.6, 100 and 316 μg. The volume of injection did not exceed 0.2 ml.

Detailed haemodynamic studies A polythene cannula was passed down the right carotid artery and manipulated through the semilunar valves into the left ventricle of the heart to record ventricular pressure and to permit injection of radiolabelled microspheres. In all experiments, control values for regional blood flows and cardiac output were obtained from the distribution of approximately one million ^{46}Sc-labelled microspheres (15 μm in diameter) injected into the left ventricle, as described by Johnston (1975) and Johnston & Owen (1977). Animals of one group were infused intravenously with 10% v/v polyethylene glycol 400 in saline (drug vehicle) at 0.55 ml min^{-1} for 15 min. A second group of cats received SK&F 94836, 100 μg kg^{-1} total dose, at the same rate. After 15 min, when the effects of the drug on ventricular pressure and blood pressure had achieved a steady state, an injection of approximately one million ^{103}Ru-labelled microspheres (15 μm in diameter) was given.

Positive inotropic activity in conscious instrumented dogs

Beagle dogs in the weight range 10.8 to 15.6 kg, were used for this study.

Surgical preparation of animals was carried out under general anaesthesia induced with intravenous sodium thiopentone and maintained at surgical level with halothane in 50% nitrous oxide in oxygen.

Following preparation of the skin, two parallel incisions were made in the neck, 4 cm apart, starting at the level of the manubrium and running cranially for approximately 10 cm, one on the mid-line the other distal to the right jugular vein. The skin between the two incisions was carefully dissected from the underlying tissues and wrapped in saline dampened swabs. The right common carotid artery, from its emergence from the thorax to the bifurcation at the carotid sinus, was exposed and freed through the sternocephalic and sternothyroid muscle. The thyroid artery was tied and cut.

The carotid artery was enclosed in the previously separated skin strip by taking the edge from the midline incision underneath the vessel and suturing it to the side edge using plain gut intradermal and ethilon monofilament interrupted sutures (Ethicon Ltd.). The suture line faced the right side. The divided muscles were reapproximated and the wound closed. By this method a carotid loop approximately 7 cm long was produced and could be used 6 weeks after surgery. No dressings were used unless the animal scratched the wounds and then a loose fitting plaster of Paris collar was applied for protection.

When the carotid loops were healed a second surgical procedure was performed to implant a Konigsberg P-22 solid state pressure transducer into the left ventricle using the methods previously described (Gristwood *et al.*, 1986). The animals were allowed a minimum of six weeks to recover from the surgery before the first experiment was performed, during this time they became accustomed to the experimental environment.

Carotid blood pressure was measured by introducing a teflon cannula (Surflo or Angiocath 20 gauge 2 inch) into the looped carotid artery and connecting it via a three-way tap to a Micron miniature pressure transducer, Model MP 15D (Micron Instruments Inc). Blood pressure, left ventricular pressure and lead II ECG signals were recorded on a Lectromed recorder and fed to a micro vax computer with which blood pressure, heart rate and LVP *dp/dt max* were computed using software written by Dr Simon Marlow, Dept. of CS&S, SK&F Research Ltd.

Effects on myocardial oxygen consumption and haemodynamics in anaesthetized dogs

Six beagle dogs of either sex weighing between 8.9 and 18.6 kg were anaesthetized with sodium pentobarbitone, 30 mg kg^{-1}, administered via a catheter in a cephalic vein. The trachea was intubated in preparation for mechanical ventilation during open-chest surgery. The left femoral artery was cannulated for measurement of blood pressure and the left femoral vein cannulated for drug administration. The animal was laid on its left side and a right thoracotomy performed in the 5th intercostal space. The ascending aorta was cleared of surrounding tissue and an electromagnetic flow probe (Gould-Statham 12–16 mm) placed around it for measurement of aortic flow. A fluid filled polythene cannula connected to a pressure transducer was inserted into the left ventricular lumen via the left ventricular apex and the pressure and *dp/dt max* recorded.

The coronary sinus was cannulated using a Portex coronary perfusion cannula (4.0 or 5.0 mm) inserted through the right atrial appendage. The right jugular vein was also cannulated and when the circuit was completed, blood flowed from the coronary sinus into the jugular vein via an extra-corporeal circuit. A cannulating type electromagnetic flow probe (Gould-Statham 4.0 mm) was included in the circuit for measurement of coronary sinus flow. A sample of the coronary sinus outflow was continuously pumped into the venous channel of an arterio-venous oxygen difference analyser (A-VOX; A-VOX Systems) and was returned to the animal via the coronary sinus-jugular vein circuit. Arterial blood was withdrawn from a cannula inserted into the right brachial artery and was pumped through the arterial channel of the A-VOX meter and returned to the jugular vein. Blood was pumped through both arterial and venous channels at exactly the same rate (3–5 ml min^{-1}) by means of a peristaltic pump (Gilson minipulse). Before the completion of the extracorporeal circuit through the A-VOX meter, heparin 500 units kg^{-1} was administered.

Following surgery animals were allowed to stabilize before administration of the drug.

In all anaesthetized animal preparations fluid and acid-base balance were maintained within normal values.

Drugs

For i.v. studies SK&F 94836 (racemate) was dissolved in solution in 25% polyethylene glycol 400 in saline (unless stated otherwise).

Papaverine base (BDH) was dissolved in the minimum quantity of 1 M hydrochloric acid and diluted in saline. For oral studies SK&F 94836 was either dissolved in distilled water and given by a gavage in a constant volume of 100 ml or administered in a 2% soya lecithin in soya bean oil fat mix suspension contained in a soft gelatin capsule as indicated. (±)-Isoprenaline sulphate (Sigma Chemical Company) was dissolved in saline. (±)-

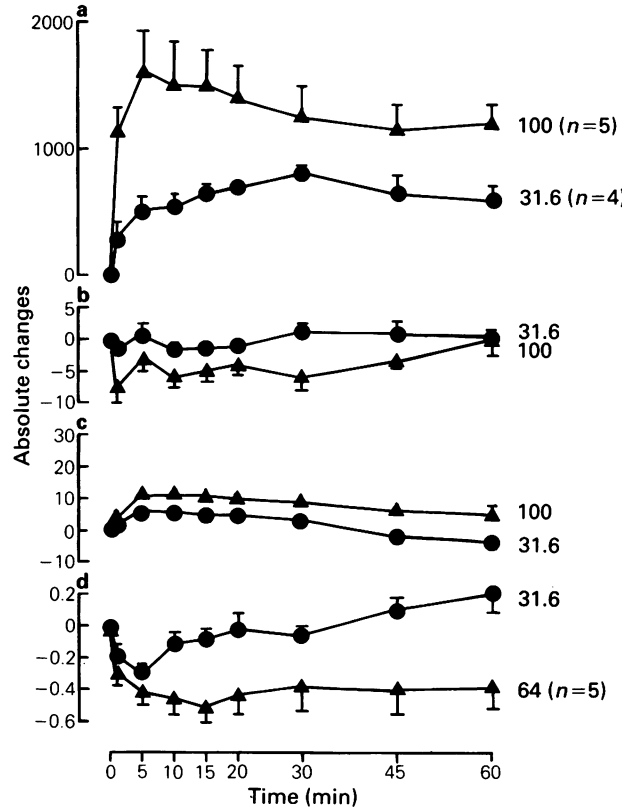

Figure 1 Potency and duration of the haemodynamic effects of SK&F 94836 in anaesthetized cats. SK&F 94836 was administered by intravenous bolus injection at time 0 at doses indicated ($\mu g\,kg^{-1}$). The parameters shown are: (a) left ventricular *dp/dt max* ($mmHg\,s^{-1}$), (b) mean systemic blood pressure (mmHg), (c) heart rate ($beats\,min^{-1}$) and (d) hindquarters vascular resistance ($mmHg\,ml^{-1}\,min^{-1}$). Pooled mean pre-drug values for parameters were as follows ($n = 9$): *dp/dt max* $2685 \pm 189\,mmHg\,s^{-1}$, heart rate $138 \pm 9\,beats\,min^{-1}$, mean blood pressure $67.6 \pm 3.6\,mmHg$ and hindquarters vascular resistance $2.53 \pm 0.1\,mmHg\,ml^{-1}\,min^{-1}$.

Propranolol (Sigma Chemical Company) was dissolved in distilled water.

Statistical analysis

The results are expressed as means ± s.e. mean. Two way analysis of variance or Student's *t* test for paired observations was used for statistical evaluation. *P* values less than 0.05 were taken as significant.

Results

Positive inotropic and vasodilator activity in anaesthetized cats

SK&F 94836 administered intravenously caused significant dose-related increases in left ventricular *dp/dt max* with minimal effects on mean blood pressure or heart rate (Figure 1). The mean peak increases in *dp/dt max* at 31.6 and $100\,\mu g\,kg^{-1}$ represented increases of 30 ± 4% ($n = 4$) and 63 ± 12% ($n = 5$) respectively. These positive inotropic responses were rapid in onset and were well maintained over the one hour recording period. Statistically significant changes in heart rate at $31.6\,\mu g\,kg^{-1}$ ($4\,beats\,min^{-1}$ increase) and in both blood pressure and heart rate occurred at the highest dose of SK&F 94836, $100\,\mu g\,kg^{-1}$ (heart rate $9\,beats\,min^{-1}$ increase, blood pressure 9 mmHg decrease), although these changes in comparison to the large contractility effects are considered to be biologically trivial.

SK&F 94836 also caused significant dose-related decreases in hindquarters vascular resistance (Figure 1). Like the positive inotropic actions of the compound this vasodilator action was rapid in onset and at $64\,\mu g\,kg^{-1}$ was maintained over the 1 hour

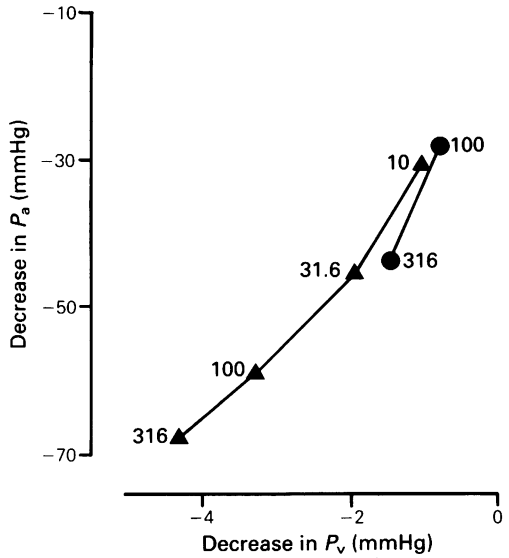

Figure 2 Relative effects of SK&F 94836 (●) and papaverine (▲) on pre-capillary (P_a) and post-capillary (P_v) vessels in cat mesenteric vasculature. The values shown at each point are the doses, in μg, administered intra-arterially. Mean resting values of P_a and P_v were 132.4 ± 3.7 and 14.7 ± 0.50 mmHg, respectively.

recording period. The mean peak decreases in hindquarters vascular resistance at 31.6 and 64 $\mu g\,kg^{-1}$ represented decreases of 13 ± 0.3% ($n = 4$) and 25 ± 3% ($n = 5$) respectively.

Relative effects on resistance and capacitance blood vessels in anaesthetized cats

Both SK&F 94836 (100 μg and 316 μg i.a.) and papaverine (10, 32, 100, 316 μg i.a.), caused dose-dependent decreases in P_a and P_v indicating a non-selective dilatation of both resistance and capacitance blood vessels (Figure 2). The limited solubility of SK&F 94836 precluded the study of larger doses in these experiments. Compared with papaverine the duration of the SK&F 94836 vasodilatation was prolonged. The total duration of effects of SK&F 94836 on P_a and P_v was not ascertained. Injection of SK&F 94836 vehicle alone caused only very transient changes in any of the measured variables.

Haemodynamic studies in anaesthetized cats

The infusion of SK&F 94836 vehicle alone (10% polyethylene glycol 400 in saline) caused some changes in haemodynamic variables, of which the following only were significant, an increase in mean blood pressure (74.2 ± 3.2 to 85.0 ± 3.6 mmHg), and a decrease in heart rate (184 ± 6.0 to 168 ± 8.0 beats min^{-1}), changes in blood flow to skin (2.75 ± 0.79 to 4.52 ± 1.0 ml min^{-1} 100 g^{-1}), kidneys (217.9 ± 12.7 to 193.6 ± 8.9 ml min^{-1} 100 g^{-1}), stomach (17.2 ± 4.3 to 28.3 ± 6.0 ml min^{-1} 100 g^{-1}) and duodenum (56.8 ± 13 to 70.2 ± 14 ml min^{-1} 100 g^{-1}) and an increase in vascular resistance in the kidneys (0.348 ± 0.018 to 0.446 ± 0.020 mmHg ml min^{-1} 100 g^{-1}), for all values, $n = 5$.

Administration of SK&F 94836, 100 $\mu g\,kg^{-1}$ ($n = 6$), caused large increases in left ventricular *dp/dt max* (from 2744 ± 381 to 4094 ± 465 mmHg s^{-1}, $P < 0.001$), cardiac output (from 292 ± 28 to 343 ± 27 ml min^{-1}, $P < 0.001$), stroke volume (from 1.69 ± 0.17 to 1.98 ± 0.21 ml, $P < 0.01$) and decreases in total peripheral resistance (from 0.312 ± 0.03 to 0.237 ± 0.02 mmHg ml min^{-1}, $P < 0.05$), with minimal effects on blood pressure and heart rate.

Significant changes caused by SK&F 94836 on regional blood flows and vascular resistance are summarized in Table 1. In particular, myocardial blood flow was significantly increased, and vascular resistance significantly decreased in heart and kidney and vascular resistance increased in voluntary muscle. Other changes in blood flow and vascular resistance were minimal. Significant regional myocardial changes in blood flow and resistance are shown in Table 1. Flows to the left and right ventricles increased significantly and resistances in left and right ventricles and interventricular septum decreased significantly.

Conscious instrumented dogs

When administered by i.v. bolus, SK&F 94836, 25, 50 and 100 $\mu g\,kg^{-1}$, caused significant dose-related increases in LV *dp/dt max* with minimal changes in blood pressure or heart rate ($n = 3$) (Figure 3). The positive inotropic response was rapid in onset, the time to peak effect was about 10 min and the response was maintained for at least 4 h after dosing.

For comparison the relative inotropic and chronotropic actions of SK&F 94836 and isoprenaline, both following intravenous injection, are shown in Figure 4. The data clearly show that SK&F 94836 is contractility selective, compared with isoprenaline, which at doses causing similar inotropic responses to SK&F 94836 causes a pronounced tachycardia.

When administered orally in aqueous solution, SK&F 94836 10, 50 and 100 $\mu g\,kg^{-1}$ caused dose-dependent, significant increases in LV *dp/dt max*. There were no significant effects on blood pressure or heart rate, Figure 5. The positive inotropic responses were rapid in onset and were well maintained over the 4 h post-dose observation period at all 3 doses.

Table 1 Regional blood flow and vascular resistance in anaesthetised cats before and after administration of SK&F 94836 100 $\mu g\,kg^{-1}$

	Blood flow ($ml\,min^{-1}\,100\,g^{-1}$)		*Resistance* ($mmHg\,ml^{-1}\,min^{-1}\,100\,g^{-1}$)	
a *Tissue*	*Pre*	*Post*	*Pre*	*Post*
Heart	129.0 ± 13.0	161.0 ± 21.0*	0.728 ± 0.100	0.585 ± 0.081**
Kidneys	199.2 ± 15.2	214.7 ± 15.2	0.467 ± 0.042	0.428 ± 0.041*
Voluntary muscle	3.88 ± 0.50	3.36 ± 0.34	26.7 ± 2.4	29.7 ± 2.6*
b *Region*				
Left ventricle	141.5 ± 11.0	172.2 ± 19.0*	0.643 ± 0.070	0.533 ± 0.064**
Right ventricle	98.5 ± 12.0	145.4 ± 25.0*	0.980 ± 0.150	0.675 ± 0.100**
Interventricular septum	154.0 ± 18.0	186.6 ± 29.0	0.637 ± 0.110	0.526 ± 0.087*

Values are means ± s.e. mean, $n = 6$. Difference from pre-infusion value significant (paired t test) * $P < 0.05$, ** $P < 0.01$.

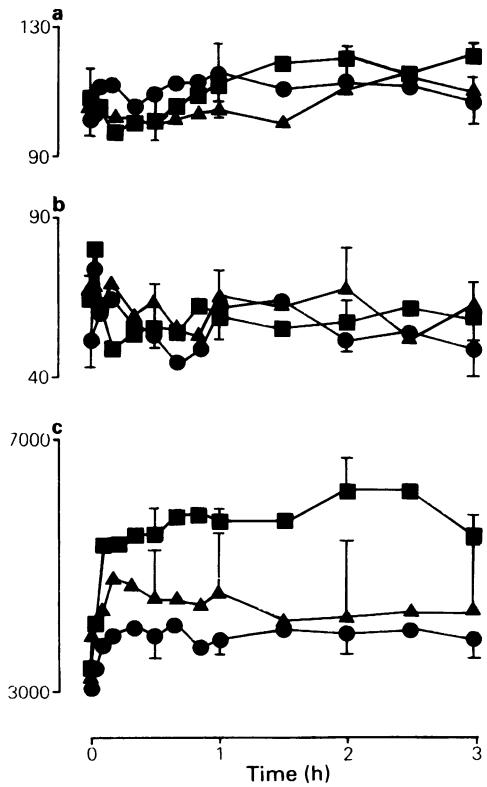

Figure 3 Haemodynamic changes following three doses of SK&F 94836, administered as bolus intravenous injections in conscious instrumented dogs. Doses used were: (●) 25 $\mu g\,kg^{-1}$, (▲) 50 $\mu g\,kg^{-1}$ and (■) 100 $\mu g\,kg^{-1}$. The parameters measured were (a) mean blood pressure (mmHg), (b) heart rate ($beats\,min^{-1}$) and (c) left ventricular *dp/dt max* ($mmHg\,s^{-1}$). Points are means, with vertical lines indicating representative s.e. mean ($n = 3$). Significant increases in *dp/dt max* occurred at all dose levels.

In 2 dogs, left ventricular contractility measurements were taken for 24 h after oral administration of SK&F 94836, 250 $\mu g\,kg^{-1}$ in fat oil suspension. Inotropic responses were maximal after approximately 2 h and contractility did not return to pre-drug values until 12 h after drug administration. Over this time period changes in heart rate were minimal.

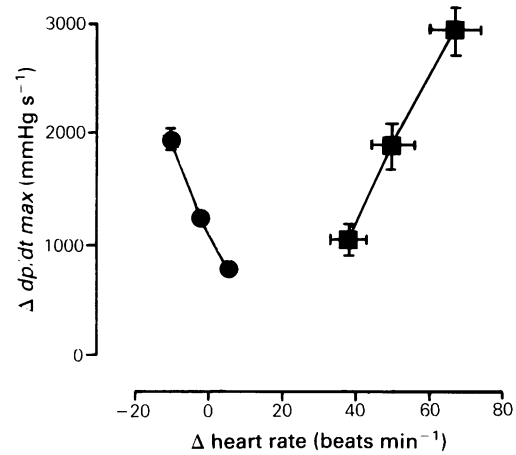

Figure 4 A comparison of the contractility/rate response relationship between SK&F 94836 (●) and isoprenaline (■) administered by bolus intravenous injections, to conscious instrumented dogs. SK&F 94836 values represent the mean ± s.e. mean of isochronous measurements taken at 5 min intervals during the hour following a single bolus injection. Doses of SK&F 94836 used were 25 ($n = 3$), 50 ($n = 3$) and 100 ($n = 4$) $\mu g\,kg^{-1}$. The values for isoprenaline represent the mean ± s.e. mean of isochronous measurements taken at the peak inotropic response to a single bolus injection of 0.5 ($n = 16$), 1.0 ($n = 17$) or 2.0 ($n = 15$) μg. Both drugs caused a dose-related increase in left ventricular *dp/dt max*.

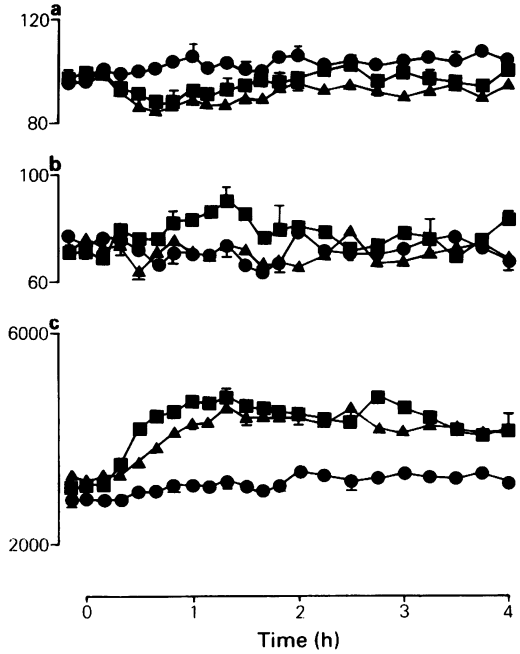

Figure 5 Haemodynamic changes following three doses of SK&F 94836 administered orally (in distilled water) to conscious instrumented dogs. Doses used were: (●) $10\,\mu g\,kg^{-1}$, (▲) $50\,\mu g\,kg^{-1}$ and (■) $100\,\mu g\,kg^{-1}$. The parameters measured were (a) mean blood pressure (mmHg), (b) heart rate (beats min^{-1}) and (c) left ventricular *dp/dt max* ($mmHg\,s^{-1}$). Points are means, with vertical lines indicating representative s.e. mean ($n = 4$). Significant increases in *dp/dt max* occurred at all dose levels.

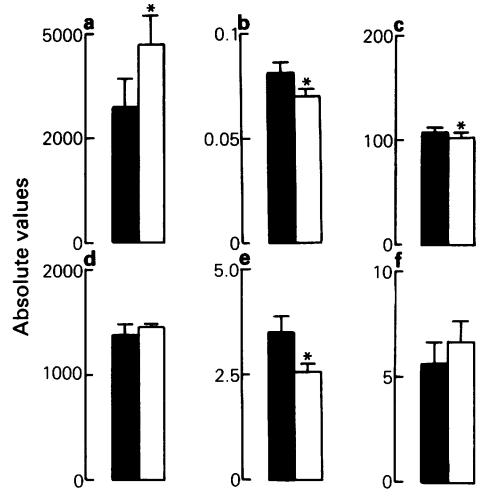

Figure 6 The effects of SK&F 94836, $50\,\mu g\,kg^{-1}$ i.v. on haemodynamics and myocardial oxygen consumption in anaesthetized dogs. Parameters shown are (a) left ventricular *dp/dt max* ($mmHg\,s^{-1}$), (b) peripheral vascular resistance ($mmHg\,ml^{-1}\,min^{-1}$), (c) mean systemic blood pressure (mmHg), (d) cardiac output ($ml\,min^{-1}$), (e) coronary vascular resistance ($mmHg\,ml^{-1}\,min^{-1}$), (f) myocardial oxygen consumption ($ml\,O_2\,min^{-1}\,100\,g^{-1}$). Control values are shown by the solid columns and mean values at 10 min post dosing are shown by the open columns. Points are means ($n = 4$) and vertical lines indicate s.e. mean; * $P < 0.05$. Coronary blood flow was calculated as: (coronary sinus outflow × 100)/(heart weight × 0.7) (see Ono *et al.*, 1982).

Effects on myocardial oxygen consumption and haemodynamics in anaesthetized dogs

Injection of SK&F 94836 vehicle alone (20% polyethylene glycol 400 in saline) caused no significant changes in any of the parameters measured.

SK&F 94836, $50\,\mu g\,kg^{-1}$ i.v. caused a significant peak increase in left ventricular *dp/dt max* of $54 \pm 6\%$ ($n = 4$), and a significant decrease in total peripheral resistance of $20 \pm 3\%$, thereby demonstrating inotropic/vasodilator activity in the dog (Figure 6). Cardiac output tended to increase although this was not statistically significant. At the same time there were small effects on both heart rate (not significant) and blood pressure (significant). There was a significant increase in coronary blood flow ($33 \pm 9\%$), and decreases in coronary vascular resistance ($27 \pm 4\%$) and A–VO_2 difference ($8.9 \pm 1.6\%$) whilst there were no significant changes in myocardial oxygen consumption, as shown in Figure 6.

Discussion

This paper describes some *in vivo* pharmacological properties of SK&F 94836, a compound which has been administered to man and is currently under development at SK&F for the treatment of congestive heart failure.

SK&F 94836 has been found to possess properties likely to be beneficial in CHF patients, namely positive inotropic activity associated with vasodilator activity. Both actions occurred over similar dose ranges in anaesthetized cats. Whilst vasodilator activity has not been assessed in conscious dogs, this activity was observed to occur in parallel with positive inotropic activity in anaesthetized dogs. Thus, the demonstration of inotropic activity following oral administration in conscious dogs in the present study strongly suggests that the compound acts as an inodilator following oral administration.

The vasodilator activity of SK&F 94836 causes changes in the loading conditions of the heart. A drug-induced decrease in afterload (total peripheral

resistance) was demonstrated in anaesthetized cats using radiolabelled microspheres, and in anaesthetised dogs using flow probes. The study on pre- and post-capillary resistance vessels in cat mesenteric vasculature demonstrated that SK&F 94836 is both an arterial and venous dilator which indicates that the drug should, if these data are representative of effects on other vascular areas, cause balanced reductions in cardiac after-load and pre-load. Reductions in pre- and after-load are considered to be twin objectives in CHF therapy (e.g. Cohn *et al.*, 1986).

The inotropic/vasodilator activity of SK&F 94836 in anaesthetized cats leads to changes in haemodynamics with increases in cardiac output and stroke volume. The increases in cardiac output which occurred in the absence of increases in heart rate were probably due to both the positive inotropic and vasodilator activity of SK&F 94836, although the relative contribution of these properties was not established.

The detailed haemodynamics study in anaesthetized cats indicated that the reduction in total peripheral resistance caused by SK&F 94836 was due to widespread vasodilatation. Thus, apart from a large significant increase in myocardial blood flow, changes in flow to other areas were small and no one tissue received disproportionate amounts of the increased cardiac output.

In anaesthetised dogs SK&F 94836 tended to increase cardiac output, although this effect was not significant. The lack of significance may have been due to the high resting ventricular ejection fraction in the animals which would make it difficult to increase stroke volume. Studies in anaesthetized dogs with anaesthetic-induced myocardial depression have confirmed that SK&F 94836 can increase cardiac output where ejection fraction is compromised.

In anaesthetized dogs, coronary blood flow was increased significantly by SK&F 94836 and, since at the same time coronary venous oxygen content significantly increased, these data are consistent with SK&F 94836 having direct coronary artery dilator properties.

The experiments in conscious dogs showed that SK&F 94836, following both intravenous and oral administration, causes positive inotropic responses with no positive chronotropic responses at the doses studied. Such a profile would be useful in man, since the induction of tachycardia in CHF patients is undesirable due to the increase in myocardial oxygen demand.

In fact, SK&F 94836 at a dose causing significant inodilator activity in anaesthetized dogs was found to have no significant effect on myocardial oxygen consumption. The main determinants of myocardial oxygen consumption are cardiac contractility, heart rate and ventricular wall tension (Mason *et al.*, 1976). In the present study SK&F 94836 caused a significant increase in cardiac contractility without significantly increasing myocardial oxygen consumption. The vasodilator effect of SK&F 94836 would have reduced ventricular wall tension. Therefore, it is likely that the lack of effect of SK&F 94836 on myocardial oxygen consumption in these experiments resulted from a balance of a decrease in ventricular wall tension decreasing oxygen demand, versus an increase in oxygen demand due to the positive inotropic effect.

SK&F 94836 demonstrated a sustained duration of action following intravenous administration to cats and dogs and following oral administration to conscious dogs. This evidence of a sustained duration suggests that single daily dose regimes could be possible with this agent in man. This could be considered a virtue in the long-term treatment of CHF. Consistent with the sustained duration of action of SK&F 94836, there is evidence that the compound is not metabolized in the dog *in vivo* (Ross *et al.*, 1987).

In conclusion, the data presented in this paper show SK&F 94836 to be a potent orally active inotropic/vasodilator agent having a sustained duration *in vivo*. We consider that the compound has potential utility in the treatment of CHF.

References

ALOUSI, A.A., CANTER, J.M., MONTERANO, M.J., FORT, D.J. & FERRARI, R.A. (1983). Cardiotonic activity of milrinone, a new potent cardiac bypyridine, on the normal and failing heart of experimental animals. *J. Cardiovasc. Pharmacol.*, **5**, 792–803.

ARBOGAST, R.A., BRANDT, C.M., FINCKER, J.L. & SCHECUTER, P.J. (1986). Acute haemodynamic effects of Piroximone (MDL 19,205) in patients with moderate congestive heart failure: comparison with sodium nitroprusside. *J. Cardiovasc. Pharmacol.*, **8**, 82–89.

BRISTOL, J.A., SIRCAR, I., MOOS, W.H., EVANS, D.B. & WEISHAAR, R.E. (1984). Cardiotonic agents. 1. 4,5,Dihydro-6-[4-(1H-imidazol-l-yl) phenyl]-3(2H)-pyridazinones: novel positive inotropic agents for the treatment of congestive heart failure. *J. Med. Chem.*, **27**, 1099–1101.

COHN, J.N., ARCHIBALD, D.G., ZIESCHE, R.N., FRANCIOSA, J.A., HARSTEN, W.E., TRISTANI, F.E., DUNKMAN, W.B., JACOBS, W., FRANCIS, G.S., FLOHR, K.H., GOLDMAN, S., COBB, F.R., SHAH, P.M., SAUNDERS, R., FLETCHER, R.D., LOEB, H.S., HUGHES, V.C. & BAKER, B. (1986). Effects of vasodilator therapy on mortality in chronic congestive heart failure. *New Engl. J. Med.*, **314**, 1547–1552.

DAGE, R.C., ROEBEL, L.E., HSIEH, C.P. & WOODWARD, J.K.

(1984). Cardiovascular properties of a new cardiotonic agent MDL 19,205. *J. Cardiovasc. Pharmacol.*, **6**, 35–42.

FIELDEN, R., OWEN, D.A.A. & TAYLOR, E.M. (1974). Hypotensive and vasodilator actions of SK&F 24260, a new dihydropyridine derivative. *Br. J. Pharmacol.*, **52**, 323–332.

FRY, D.L. (1960). Physiological recording by modern instruments with particular reference to pressure recording. *Physiol. Rev.*, **40**, 753–788.

GLEASON, W.L. & BRAUNWALD, E. (1962). Studies on the first derivative of the ventricular pulse in man. *J. Clin. Invest.*, **41**, 80–91.

GRISTWOOD, R.W., EDEN, R.J., OWEN, D.A.A. & TAYLOR, E.M. (1986). Pharmacological studies with SK&F 94120 a novel positive inotropic agent with vasodilator activity. *J. Pharm. Pharmacol.*, **38**, 452–459.

JAFRI, S.M., BURLEN, B.S., GOLDBERG, A.D., ROGERS, A. & GOLDSTEIN, S. (1986). Haemodynamic effects of a new Type III phosphodiesterase inhibitor (CI-914) for congestive heart failure. *Am. J. Cardiol.*, **57**, 254–259.

JOHNSTON, B.M. (1975). The use of radio-labelled microspheres to compare the effects of hydralazine, guanethidine and SK&F 24260 on the re-distribution of cardiac output in anaesthetised rabbits. *Br. J. Pharmacol.*, **55**, 392–402.

JOHNSTON, B.M. & OWEN, D.A.A. (1977). Tissue blood flow and distribution of cardiac output in cats. Changes caused by intravenous infusions of histamine and histamine receptor agonists. *Br. J. Pharmacol.*, **60**, 173–180.

MASON, D.T., MILLAR, R.R., WILLIAMS, D.O., DeMARIA, A.N., SEGAL, L.D. & AMSTERDAM, E.A. (1976). In *Congestive Heart Failure*. ed. Mason, D.T. pp. 293–311. New York: Yorke Medical Books.

ONO, H., OHARA, N. & HASHIMOTO, K. (1982). Effect of an antianginal drug, perhexiline, on myocardial oxygen consumption in anesthetised open-chest dogs compared with verapamil and glycerol trinitrate. *Jap. Circ. J.*, **46**, 559–567.

REEVES, M.L., GRISTWOOD, R.W., LEIGH, B.K. & ENGLAND, P.J. (1987). SK&F 94836 a potent inotropic agent is a selective inhibitor of type III phosphodiesterase activity from several tissues. *Br. J. Pharmacol. Proc. Suppl.*, **92**, 773 P.

ROSS, D.A., SHEPARD, T.A., WALER, D., PUE, M.A., FRANKLIN, E.R., OSBORNE, P.M., ALLENBY, S.H. & VINEY, N.J. (1987). Disposition and metabolism of SK&F 94836 in rat and dog. Evidence of stereo selectivity. Abstracts *ISSX 2nd European Meeting on Foreign Compound Metabolism – Frankfurt* (in press).

TAYLOR, E.M. (1983). *The Effects of Drugs on Intestinal Resistance and Capacitance Blood Vessels of The Cat.* PhD Thesis: University of London.

TAYLOR, E.M., CAMERON, D., EDEN, R., FIELDEN, R. & OWEN, D.A.A. (1981). Haemodynamic profile of a new antihypertensive agent D,L-3-[2-(3-t-butylamino-2-hydroxypropyl)phenyl]-6-hydrazino pyridine (SK&F 92657). *J. Cardiovasc. Pharmacol.*, **3**, 337–354.

(Received May 29, 1987
Revised November 16, 1987
Accepted November 24, 1987)