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Pharmacological studies with SK&F 94120, a novel positive inotropic agent with vasodilator activity

R. W. GRISTWOOD, R. J. EDEN, D. A. A. OWEN* AND E. M. TAYLOR

Department of Pharmacology, Smith Kline & French Research Limited, The Frythe, Welwyn, Hertfordshire, UK

The pharmacological properties of SK&F 94120 on the cardiovascular system have been studied in laboratory animal species. The compound was shown to have positive inotropic activity on hearts from guinea-pig, cat, dog and marmoset in-vitro and in cat and dog in-vivo. These responses in-vivo occurred in association with minimal changes in heart rate. Positive inotropic activity was not caused by SK&F 94120 in rat or hamster hearts in-vitro, thereby indicating a species dependence in myocardial response. SK&F 94120 was shown to have vasodilator activity in cats in-vivo. Detailed studies carried out on anaesthetized cats indicated that the compound caused a balanced dilatation of both resistance and capacitance blood vessels. Haemodynamic studies in anaesthetized cats indicated that, as a consequence of the positive inotropic and vasodilator actions, SK&F 94120 causes significant increases in cardiac output and stroke volume. Studies in conscious dogs showed the compound to be active as a positive inotrope after oral administration. The above properties suggest that this compound possesses useful haemodynamic properties for the treatment of congestive heart failure.

Treatment of cardiac failure is based on the use of diuretics, positive inotropic agents and vasodilators, used either separately or in combination. Whilst a variety of diuretic agents and vasodilator drugs are available, cardiac glycosides are the only positive inotropic agents used for the long-term treatment of congestive heart failure. The need for new, orally active positive inotropic agents with improved therapeutic ratios has been long recognized.

SK&F 94120, 5-(4-acetamidophenyl)pyrazin-2[1*H*]-one, is an orally active, positive inotropic agent which additionally causes vasodilatation. The present paper describes its pharmacological properties.

MATERIALS

In-vitro studies

Ventricular preparations

Ventricular preparations were set up from hearts of guinea-pigs (Dunkin Hartley strain, 400–750 g), golden hamsters (108–119 g), cats (after anaesthesia with sodium pentobarbitone 60 mg kg^{-1} i.p., 1·0–2·5 kg), dogs (after anaesthesia with sodium pentobarbitone, 30 mg kg^{-1} i.v., 8·5–13·5 kg), and marmosets (anaesthetized with nitrous oxide, 200–300 g).

For all species, preparations (dimensions ca 1·0 cm × 0·1–0·2 cm) were cut, mounted vertically in 50 ml organ baths containing Krebs solution at 37 °C and bubbled with 95% O_2, 5% CO_2. The base of the preparation was positioned between two point electrodes and the top attached by a short length of cotton to an isometric force transducer (Harvard Model 363). Preparations were placed under, and maintained at, 1 g resting tension and electrically stimulated to contract (1 Hz, 2 × threshold voltage, 5 ms pulse width: Palmer stimulator) whilst isometric tension was recorded on a Grass (Model 79D) 4 channel recorder.

Preparations were allowed to stabilize for 1 h; the perfusion medium was changed at regular intervals (ca 20 min). The responsiveness of tissues to drugs was assessed by the administration of isoprenaline to the bath. If responsive, tissues were washed and allowed 1 h (washed at 20 min intervals) to restabilize. SK&F 94120 and other drugs were added to the bath cumulatively (allowing responses to stabilize before increasing the bath concentration) to provide concentration-response curves.

Drug effects were assessed as the percentage increase in force of contraction over pre-drug control values. From these data, the concentration of drug causing a 50% mean increase (CI50% value) in force of contraction was obtained by interpolation of data.

Isolated working heart preparations

Guinea-pigs. Male, Dunkin Hartley guinea-pigs, 450–600 g, were killed 20 min after heparin administration (2000 u i.p.). The heart (with lungs attached) was quickly excised and placed in a beaker containing ice cold Krebs solution, where the lungs and any

* Correspondence.

remaining pericardial tissue were removed. The heart was then mounted on the working heart apparatus as described by Flynn et al (1978). When working, Krebs solution (equilibrated with 5% CO_2 in O_2 at 37·5 °C) entered the left atrium at a fixed filling pressure of 10 cm H_2O and cardiac output was ejected by the left ventricle against a fluid column of height 70 cm. The perfusion system was closed circuit so that under normal conditions both coronary flow and aortic flow were recirculated.

Cats. Kittens, 0·85–1·0 kg, were anaesthetized with sodium pentobarbitone (60 mg kg^{-1} i.p.), administered heparin 2000 u i.p., the chest opened and the heart removed and preparations established as described for guinea-pigs. For these preparations, aortic and atrial cannulae had internal diameters of 0·4 cm.

Rats. Male Wistar rats, 315–330 g, were administered heparin 2000 u i.p., killed by cranial impact, hearts removed and preparations established as described above. For these preparations, normal ($2·55 \times 10^{-3}$ M) or half ($1·275 \times 10^{-3}$ M) calcium concentration Krebs solution was used, as indicated. Once set up, preparations were left to stabilize for 15–20 min and experiments were routinely completed within a further 60 min. SK&F 94120 was added to the perfusion system at known concentrations, and cumulative concentration-response curves constructed. Responses were measured as absolute changes from pre-drug values. In rat hearts, following exposure to the highest concentration of SK&F 94120, preparations were given isoprenaline, 5×10^{-9} M, to test for responsiveness.

In-vivo studies

Studies in anaesthetized cats

Effect on intestinal resistance and capacitance blood vessels. Cats of either sex (1·7 to 4·3 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. Intravenous injections were given through a cannula in the right superficial cephalic vein. Relative vasodilator activity 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).

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.

Positive inotropic activity in anaesthetized cats. Animals were anaesthetized with sodium pentobarbitone, 60 mg kg^{-1}. The trachea was cannulated. Mean blood pressure was calculated by adding 1/3 of the pulse pressure to the diastolic pressure. Blood pressure pulsations were used to trigger a heart rate recorder. A long polyethylene cannula (Portex, internal diameter 1·0 mm) was passed down the right carotid cartery and manipulated through the semilunar valves into the left ventricle. The record of left ventricular pressure was electronically differentiated to give a continuous linear record of left ventricular dp/dt max, taken as a measure of left ventricular contractility. Atropine (1 mg kg^{-1} i.v.) and mecamylamine (5 mg kg^{-1} i.v.) were given to inhibit the functioning of the autonomic nervous system, including reflex activity (pharmacological denervation), and so produce a stable preparation with low heart rate and 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.). Only those preparations responding with an increase in left ventricular contractility of at least 100% were used in these experiments. Once the sensitivity of the preparation had been checked, propranolol (1 mg kg^{-1} i.v. plus 3 to 4 mg kg^{-1} s.c.) was given, and produced an immediate and prolonged β-adrenoceptor blockade. When the preparation was stable SK&F 94120 was given by bolus intravenous injection. In most experiments only one dose of compound was given and the time course of the response followed for 1 h, or until the response had recovered to control values. In a further 4 cats, SK&F 94120 was infused intravenously (0·1 mg kg^{-1} min^{-1}) to determine if the increase in left ventricular contractility was well maintained for the duration of the infusion period (20 min).

Haemodynamic studies

Electromagnetic flow probes. Fourteen cats were anaesthetized with 90 mg kg^{-1} chloralose i.v. after induction with halothane in oxygen. The trachea was cannulated. Drugs were administered via a catheter in the brachial vein. Systemic blood pressure was recorded by inserting a cannula into an appropriate superficial artery. Cardiac output, and hindquarters (HQ), renal and mesenteric blood flow were measured using electromagnetic flow-meters (Biotronex Ltd), by placing flow-probes around the ascending aorta, abdominal aorta, left renal artery and superior mesenteric artery, respectively.

Radio-labelled microspheres. Sixteen cats were anaesthetized with sodium pentobarbitone, 60 mg kg^{-1}. The trachea was cannulated. Blood pressure was measured from the right brachial artery. The right brachial vein was cannulated for drug infusion. A long polyethylene cannula was passed down the right cartoid artery and manipulated through the semilunar valves into the left ventricle of the heart to record ventricular pressure and to permit injection of radio-labelled 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 20% v/v polyethylene glycol 400 in saline (drug vehicle) at 0·55 ml min^{-1}. A second group of cats received SK&F 94120, 0·1 mg kg^{-1} min^{-1}, at the same rate. After 20 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. In four cats, the proportion of microspheres in the lungs in the control measurement exceeded 10%. Data from these animals have been excluded from analysis.

Conscious, instrumented dogs. Eleven beagle dogs (3 female and 8 male, 12 to 20 kg), selected for their quiet temperament were used. Pamergan 0·5 ml and chlorpromazine 0·5 mg kg^{-1} i.m. were administered 2 h before surgery (Pamergan, M&B = 0·06% atropine, 10% pethidine and 2·5% promethazine). Anaesthesia was induced with sodium thiopentone intravenously and maintained with halothane in 50% nitrous oxide in oxygen, using a closed circuit system.

A left thoracotomy was made in the fifth intercostal space. A vinyl blood pressure cannula was introduced into the thoracic aorta via the first intercostal artery, to which it had been led, through the dorsal musculature, from a teflon ball valve which protruded through the skin at the back of the neck. A Konigsberg P-22 solid state pressure transducer was inserted into the left ventricle through a stab wound in the apex of the heart and secured by a previously placed purse string ligature. The transducer cable entered the thorax through a stab wound in the sixth intercostal space. The cable terminated in an exteriorizing connecting plug protruding through the skin between the scapulae. Both catheter and cable were sprayed with Polybactrin antibiotic powder (Wellcome) before implantation. The thorax was closed during the application of positive end expiratory pressure to exclude air in order to avoid a pneumothorax. Pethidine (50 mg) was given if and when considered necessary. Ampicillin (Penbritin) treatment (100 mg per dog i.m.) was initiated on the day of surgery and continued for five days. All the dogs were freely mobile on the morning following the operation. The animals were allowed a minimum of one week to recover from the surgery before the first experiment was performed during which time they became accustomed to the experimental environment.

During experiments, aortic blood pressure was measured by connecting the implanted cannula valve with a fluid filled tube to a Bell & Howell 0–75 cm Hg physiological pressure transducer mounted on a stand at heart level beside the dog which was lightly restrained in a Pavlov sling. The left ventricular pressure signal was electronically differentiated to give dp/dt max. Signals were recorded on a Lectromed M19 polygraph.

Mean blood pressure was calculated as diastolic pressure plus one third pulse pressure. Heart rate was determined by periodically running the recorder chart at a speed of 150 mm min^{-1} and counting individual heart beats over a 10 s period.

Before each experiment the animals were allowed food and some exercise. They were then brought to the laboratory, placed in the Pavlov sling. After base line values had been established the dog's cardiovascular reactivity was determined by intravenous bolus injections of isoprenaline. The doses used were 0·5, 1·0 and 2·0 μg per dog.

SK&F 94120 was then administered, either as a bolus intravenous injection dissolved in 2 ml 25% polyethylene glycol/saline or 2 ml NaOH/saline at pH 9·5, or as an intravenous infusion in NaOH/saline (pH 9·5) for 30 min at a rate of 0·6 ml min^{-1}. Dogs were given a single dose of drug or vehicle on any one day and the interval between experiments was a minimum of 24 h.

Drugs used

For all in-vitro studies drugs were dissolved in perfusion medium. For administration in-vivo, SK&F 94120 was prepared in solution in 25% polyethylene glycol 400 in saline, or by dissolving the compound in NaOH/saline at pH 9·5. Isoprenaline sulphate (Sigma Chemical Company) was dissolved in saline. Papaverine base (BDH) was dissolved in the minimum quantity of 1 M acetic acid and diluted

in saline. Amrinone (a gift from Sterling Winthrop) was dissolved in saline. Milrinone (synthesized in these laboratories) was dissolved in 25% polyethylene glycol 400 in saline.

Statistical analysis

Results are given as mean ± s.e.m. Two way analysis of variance and Student's *t*-test for paired observations were used for statistical evaluation. *P* values less than 0·05 were regarded as significant.

RESULTS

In-vitro studies

Ventricular preparations

SK&F 94120 increased the force of contraction of ventricular muscle preparations from guinea-pigs, cats, marmosets and dogs, but was inactive at concentrations up to 1×10^{-4} M in hamster ventricle preparations.

The threshold concentration of SK&F 94120 and the subsequent concentration-response curve varied from species to species with marmoset hearts being the most responsive. The relative activities of SK&F 94120 across species, with isoprenaline data for comparison are shown in Table 1. For comparison, data obtained with amrinone (guinea-pig and cat) and milrinone (guinea-pig) are included in Table 1. Milrinone and SK&F 94120 have similar potency on guinea-pig preparations; amrinone is less potent than SK&F 94120 on guinea-pig and cat preparations.

Isolated working heart preparation

SK&F 94120, with a threshold concentration of $3·16 \times 10^{-7}$ M, caused concentration-dependent increases in sinus rate, dp/dt max, coronary flow, aortic flow and cardiac output in guinea-pig isolated working heart preparations (Fig. 1). Reponses of coronary flow, aortic flow and cardiac output appeared maximal at 1×10^{-5} M. However, maximal responses to sinus rate and dp/dt max were not observed (SK&F 94120 has limited aqueous solubility). Stroke volume was minimally altered by SK&F 94120, except at high concentrations when it tended to decrease.

In the kitten isolated working heart, SK&F 94120 consistently caused concentration-dependent responses, over the range $3·16 \times 10^{-7}$ to 1×10^{-4} M, similar to those observed in the guinea-pig preparation (Fig. 1).

In the rat heart (using $1·275 \times 10^{-3}$ M calcium concentration Krebs solution), SK&F 94120 caused concentration-related increases in sinus rate and coronary flow, but caused concentration-related decreases in dp/dt max and stroke volume (Fig. 1). Over the concentration range studied, aortic flow tended to decrease although changes in total cardiac output were small. The ability of the rat heart to respond, was tested by exposing hearts to isoprenaline, 5×10^{-9} M, which produced very large increases in both dp/dt max, 4046 ± 498 mmHg s^{-1}, and sinus rate, 83 ± 14 beats min^{-1}. In a single rat heart perfused with Krebs containing calcium, $2·55 \times 10^{-3}$ M, SK&F 94120 increased sinus rate but, as with half calcium concentration Krebs solution, produced decreases in dp/dt max over the concentration range studied ($3·16 \times 10^{-7}$ to $3·16 \times 10^{-5}$ M).

The actions of SK&F 94120 were compared with those of amrinone and milrinone in the guinea-pig

Table 1. CI50% concentrations (= concentration causing a mean 50% increase in force of contraction) for isoprenaline and SK&F 94120 on isolated ventricular preparations from various species.

Species	Preparation	CI50% concentrations M (95% confidence limits, n) Isoprenaline	SK&F 94120	Amrinone	Milrinone
Guinea-pig	Right ventricular strip	$2·3 \times 10^{-9}$ ($1·8$–$4·0 \times 10^{-9}$, n = 7)	$3·0 \times 10^{-6}$ ($1·4$–$6·4 \times 10^{-6}$, n = 6)	$1·7 \times 10^{-5}$ ($3·9 \times 10^{-6}$–$7·8 \times 10^{-5}$, n = 4)	$4·0 \times 10^{-6}$ ($1·3 \times 10^{-6}$–$1·2 \times 10^{-5}$, n = 8)
Cat	Right ventricular papillary muscle	$6·3 \times 10^{-9}$ ($1·3 \times 10^{-9}$–$3·0 \times 10^{-8}$, n = 10)	$6·6 \times 10^{-6}$ ($3·2 \times 10^{-6}$–$1·3 \times 10^{-5}$, n = 11)	$3·0 \times 10^{-5}$ (n = 2)	—
Marmoset	Right ventricular strip	$3·0 \times 10^{-9}$ ($1·3$–$6·9 \times 10^{-5}$, n = 4)	$5·0 \times 10^{-7}$ ($1·8 \times 10^{-7}$–$1·4 \times 10^{-6}$, n = 4)	—	—
Hamster	Right ventricular strip	$4·0 \times 10^{-7}$ ($1·2 \times 10^{-7}$–$1·3 \times 10^{-6}$, n = 3)	Inactive up to 1×10^{-4}	—	—
Dog	Left ventricular papillary muscle	$4·2 \times 10^{-9}$ (n = 2)	$4·6 \times 10^{-5}$ ($9·3 \times 10^{-6}$–$2·2 \times 10^{-4}$, n = 4)	—	—

— Not measured.

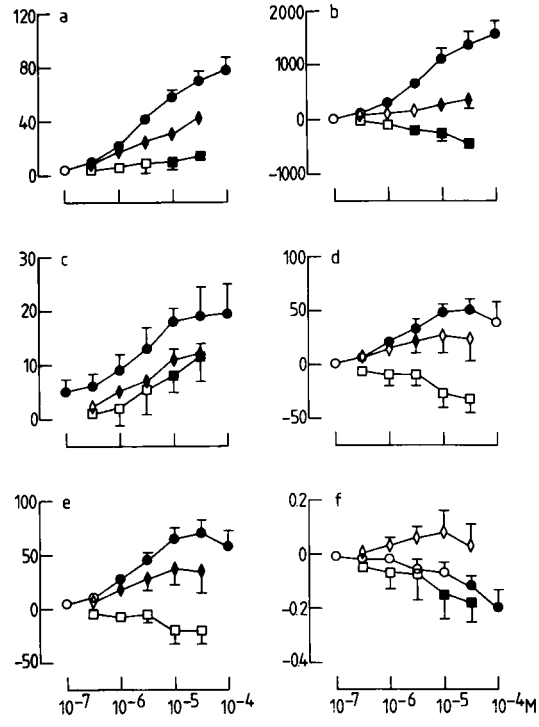

FIG. 1. Responses to SK&F 94120 in isolated, working hearts from guinea-pigs (●, n = 5), cats (◆, n = 3) and rats (■, n = 3). Cumulative concentration response curves are shown for (a) increases in heart rate (beats min^{-1}), (b) change in dp/dt max (mmHg s^{-1}), (c) increase in coronary flow (ml min^{-1} g^{-1} dry weight), (d) change in aortic flow (ml min^{-1} g^{-1} dry weight), (e) change in cardiac output (ml min^{-1} g^{-1} dry weight) and (f) change in stroke volume (ml g^{-1} dry weight). Values are mean ± s.e.m. Filled symbols indicate statistically significant changes from paired pretreatment values.

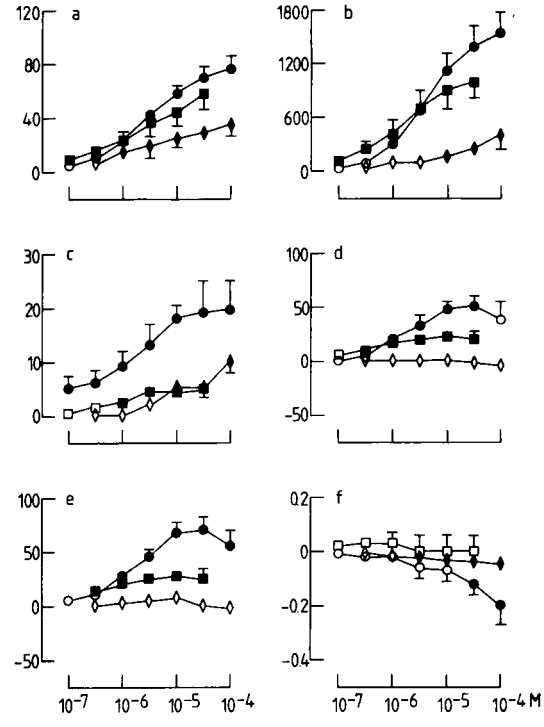

FIG. 2. Responses to SK&F 94120 (●, n = 5), milrinone (■, n = 3) and amrinone (◆, n = 3) in isolated, working hearts from guinea-pigs. Cumulative concentration response curves are shown for (a) increase in heart rate (beats min^{-1}), (b) change in dp/dt max (mmHg s^{-1}), (c) increase in coronary flow (ml min^{-1} g^{-1} dry weight), (d) change in aortic flow (ml min^{-1} g^{-1} dry weight), (e) change in cardiac output (ml min^{-1} g^{-1} dry weight) and (f) change in stroke volume (ml g^{-1} dry weight). Values are mean ± s.e.m. Filled symbols indicate statistically significant changes from paired pretreatment values.

working heart preparation (Fig. 2). Milrinone and SK&F 94120 show similar potency on heart rate and dp/dt max and were both more potent than amrinone. SK&F 94120 had a greater effect than either of the other compounds on coronary flow, aortic flow and cardiac output. Changes in stroke volume only occurred at the higher concentrations for amrinone and SK&F 94120; milrinone caused no change in this variable.

In-vivo studies

Intestinal resistance and capacitance blood vessels in anaesthetized cats

Both SK&F 94120 and papaverine (used as a standard control vasodilator) caused dose-dependent decreases in Pa and Pv indicating non-selective dilatation of both resistance and capacitance blood vessels. The effects of papaverine were transient, lasting less than 5 min, whereas the SK&F 94120-induced vasodilatation lasted up to 20 min. SK&F 94120 was slightly more effective on capacitance vessels than resistance vessels relative to papaverine (Fig. 3), although the differences were not significantly different.

Positive inotropic activity in anaesthetized cats

SK&F 94120, 31·6, 100 and 316 μg kg^{-1} i.v., caused significant increases in left ventricular dp/dt max ranging from 27 to 78·4% of control values. These effects were maximal about 2 min after dosing and subsequently declined to approach control values by about 30 min. SK&F 94120 caused very small (less than 10 beats min^{-1} peak response at the highest dose), dose-dependent increases in heart rate; the

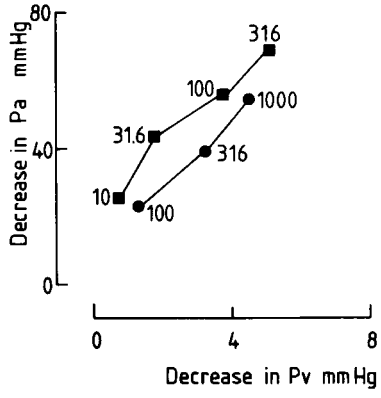

FIG. 3. Relative effects of SK&F 94120 (●) and papaverine (■) on pre-capillary (Pa) and post-capillary (Pv) vessels in cat mesenteric vasculature. The values shown against each point are the doses, in μg, administered intra-arterially.

peak increases occurred 5 to 10 min after dosing. The two higher doses of SK&F 94120 caused very transient hypotension.

Amrinone caused similar increases in dp/dt max but over the higher dose range, 1–3·16 mg kg^{-1}. Milrinone, like SK&F 94120 increased dp/dt max at 31·6 and 100 μg kg^{-1}.

SK&F 94120, infused at 0·1 mg kg^{-1} min^{-1} i.v. for 20 min, caused a large increase in dp/dt max, a small increase in heart rate, but no change in blood pressure. These responses were well sustained throughout the infusion.

Haemodynamic studies

Electromagnetic flow probes

Infusion of SK&F 94120, 0·1 mg kg^{-1} min^{-1}, increased cardiac output ($P < 0·01$), stroke volume ($P < 0·05$), heart rate ($P < 0·02$) and dp/dt max ($P < 0·01$), and decreased total peripheral vascular resistance ($P < 0·02$) and systemic blood pressure ($P < 0·05$). These changes are shown in Fig. 4. SK&F 94120 did not significantly change blood flow to the kidneys, hindquarters or mesentery, although a small significant reduction in renal resistance occurred from 5·39 ± 1·44 to 3·86 ± 0·43 mmHg ml^{-1} min^{-1} ($P < 0·05$).

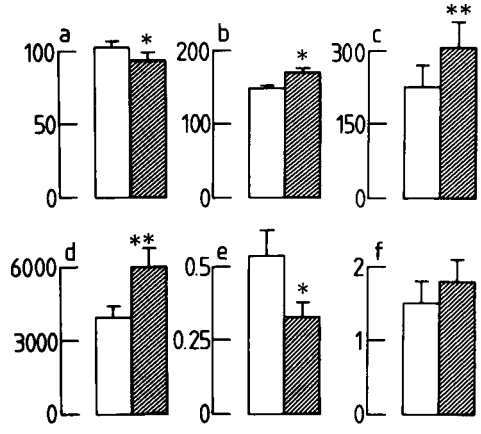

FIG. 4. Haemodynamic changes during infusion of SK&F 94120, 0·1 mg kg^{-1} min^{-1}, for 20 min in anaesthetized cats. Parameters measured were (a) blood pressure (mmHg), (b) heart rate (beats min^{-1}), (c) aortic blood flow (ml min^{-1}), (d) left ventricular dp/dt max (mmHg s^{-1}), (e) peripheral vascular resistance (mmHg ml^{-1} min^{-1}), and (f) stroke volume (ml). Values before the infusion are shown by the open columns, values measured 20 min into the infusion are shown by the hatched columns. Values are mean ± s.e.m., n = 6. Differences from pre-infusion values are indicated $*P < 0·05$, $**P < 0·01$.

Table 2. Regional blood flow and vascular resistance in anaesthetized cats before and during infusion of SK&F 94120, 0·1 mg kg^{-1} min^{-1}. Values are mean ± s.e.m., n = 4.

	Blood flow ml min^{-1}/100 g		Resistance mmHg ml^{-1} min^{-1}/100 g	
Tissue	Pre	During	Pre	During
Skin	4·40 ± 0·87	4·60 ± 1·01	23·10 ± 6·6	17·90 ± 3·74
Heart	120·30 ± 8·28	168·60 ± 13·5*	0·66 ± 0·06	0·41 ± 0·03***
Liver	80·10 ± 16·95	69·00 ± 10·4	1·14 ± 0·18	1·08 ± 0·13
Kidneys	265·30 ± 12·0	287·10 ± 23·2	0·29 ± 0·01	0·25 ± 0·01***
Stomach	23·60 ± 3·41	34·60 ± 4·9*	3·95 ± 0·97	2·38 ± 0·61*
Duodenum	60·30 ± 5·45	74·60 ± 6·3*	1·37 ± 0·21	0·96 ± 0·13***
Small intestine	49·40 ± 8·5	56·40 ± 11·0	1·87 ± 0·38	1·45 ± 0·26
Voluntary muscle	4·12 ± 0·86	3·82 ± 0·36	24·50 ± 2·54	21·10 ± 2·68
Brain	41·80 ± 4·3	37·90 ± 3·6	2·06 ± 0·41	1·91 ± 0·25

Difference from pre-infusion value significant (paired *t*-test): $*P < 0·05$; $***P < 0·01$.

Radioactive microspheres

The infusion of 0·1 mg kg^{-1} min^{-1} SK&F 94120 caused a significant increase in cardiac output ($P < 0·01$), stroke volume ($P < 0·01$) and heart rate ($P < 0·02$) with a decrease in total peripheral vascular resistance ($P < 0·01$) similar to those measured using electromagnetic flow probes. Blood flow to the heart, stomach and duodenum increased significantly ($P < 0·05$) and vascular resistance decreased significantly in the heart, kidneys, duodenum ($P < 0·01$) and stomach ($P < 0·05$). These regional changes are shown in Table 2. The changes in coronary blood flow occurred throughout the right and left atria, right and left ventricles and the septum.

Studies in conscious, instrumented dogs

SK&F 94120, 0·125, 0·25 and 0·5 mg kg^{-1} i.v., caused immediate increases in dp/dt max. At the higher doses, the large increases in dp/dt max were accompanied by small increases in heart rate and small decreases in mean blood pressure.

Intravenous infusion of SK&F 94120, 0·0125 and 0·05 mg kg^{-1} min^{-1}, caused significant, dose-dependent increases in left ventricular dp/dt max which were well sustained throughout each infusion but which recovered over 30–60 min after cessation of the infusion. SK&F 94120 also caused a significant increase in heart rate towards the end of the higher infusion but had no significant effect on mean blood pressure (Fig. 5).

Oral administration of SK&F 94120, 5 mg kg^{-1} in alkaline solution or in a tragacanth suspension, caused large, significant increases in dp/dt max without significant change in either heart rate or blood pressure (Fig. 6).

In similar studies, amrinone increased dp/dt max over the dose-range 1–3·16 mg kg^{-1} when administered by intravenous injection.

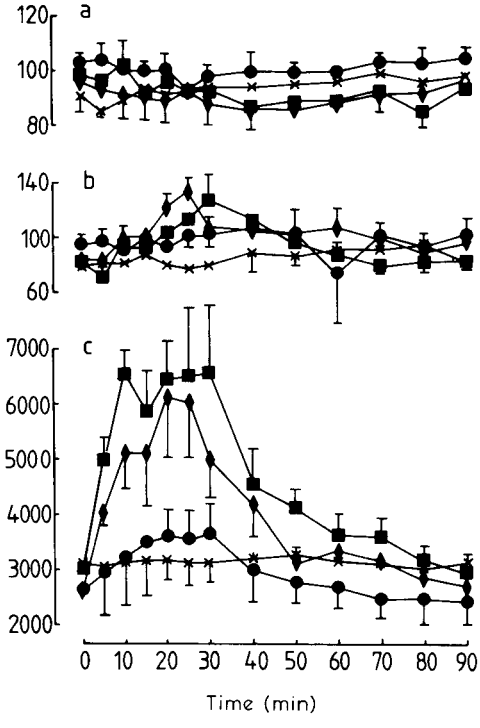

FIG. 5. Haemodynamic responses to SK&F 94120 in conscious dogs. SK&F 94120 was administered by intravenous infusion from time 0 to 30 min, at 12·5 μg kg^{-1} min^{-1} (●, n = 3), 25 μg kg^{-1} min^{-1} (◆, n = 4) and 50 μg kg^{-1} min^{-1} (■, n = 3). Vehicle control study (×, n = 3). The parameters 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 ± s.e.m.

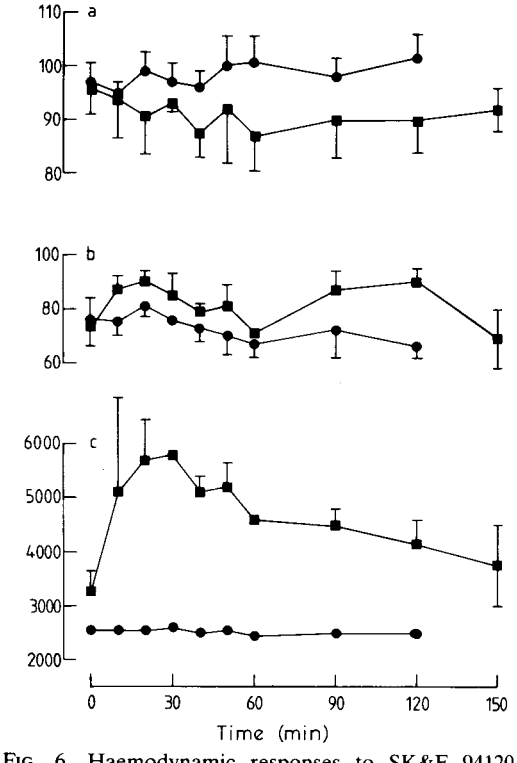

FIG. 6. Haemodynamic responses to SK&F 94120 in conscious dogs. SK&F 94120 5 mg kg^{-1} in alkaline saline, was administered orally at time 0 min (■, n = 3). Vehicle control study (●, n = 5). The parameters measured were (a) mean blood pressure (mmHg), (b) heart rate (beats min^{-1}) and (c) left ventricular dp/dt max (mmHg s^{-1}). Points are means ± s.e.m.

DISCUSSION

The present paper describes some pharmacological properties of SK&F 94120, a novel agent with both positive inotropic and vasodilator activities.

The compound elicits a direct action on the heart as demonstrated in isolated cardiac preparations. In the isolated working heart preparation, SK&F 94120 causes increases in both the rate and force of contraction whereas in-vivo in cats and dogs, its positive inotropic activity occurs with minimal increases in heart rate.

The compound's inotropic activity was demonstrated in several species of laboratory animals but did not occur in myocardial preparations from rats. The reason for the lack of activity in rat myocardium is not known although it is not unusual for positive inotropic agents to be inactive on the rat myocardium (see e.g. Flynn et al 1978).

In addition to positive inotropic activity, SK&F 94120 possesses vasodilator activity. This property appears to be present in all species tested including the rat, which shows coronary vasodilator activity independent of positive inotropic activity. The vasodilator activity of SK&F 94120 leads to changes in the vascular loading of the heart. Studies on pre- and post-capillary resistance vessels in cat mesenteric vasculature show that SK&F 94120 is both an arterial and venous dilator which should, if representative of effects on other vascular areas, cause a reduction in both pre- and post-cardiac loading.

The positive inotropic and vasodilator activity of SK&F 94120 leads to a change in haemodynamic function with an increase in cardiac output. This increase probably arises from both the positive inotropic activity of SK&F 94120 and the reduction in cardiac afterload due to the vasodilator activity of SK&F 94120 which allows more complete emptying of the left ventricle. The relative contribution of these two properties to the total haemodynamic responses to SK&F 94120 cannot be established from the present studies.

Experiments in conscious dogs show that SK&F 94120 causes relatively selective inotropic actions and that a positive chronotropic response occurs only at high doses which cause very large, almost maximal inotropic responses. SK&F 94120 is also active after oral administration in conscious dogs.

The detailed mechanism of action of SK&F 94120 is currently under investigation. The compound has been shown to be a specific inhibitor of the phosphodiesterase isozyme, PDE III (Gristwood et al 1985), and the rank order of potency of milrinone, SK&F 94120 and amrinone, as both PDE III inhibitors and positive inotropic agents, is similar (England et al 1985) suggesting the importance of this mechanism of inotropic activity.

Although the positive inotropic activity of SK&F 94120 described in these studies has been assessed on healthy hearts, we are accumulating data which demonstrate that SK&F 94120 elicits a positive inotropic response in ventricular preparations obtained from human subjects with severe (New York Heart Assn Class III or IV patients) heart failure requiring either mitral valve replacement or cardiac transplant (Cameron et al 1985).

The positive inotropic and vasodilator activities of SK&F 94120 constitute complementary properties, thought likely to be useful for the treatment of congestive heart failure.

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