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CARDIOVASCULAR EFFECTS OF DIETHYLCARBAMAZINE CITRATE

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1 The cardiovascular effects of the anthelmintic drug diethylcarbamazine citrate (DECC) were examined in cats anaesthetized with pentobarbitone. There were two quite distinct haemodynamic responses, an initial transient hypotension (occurring within 10 s of an intravenous injection) and a pronounced secondary hypertension which reached a peak 30–60 s after the injection.

2 Within 10 s of an intravenous injection of DECC (2.5 to 10 mg/kg) there was hypotension, bradycardia and there were reductions in left ventricular and carotid artery dP/dt *max*. These effects were most pronounced following injections into the pulmonary artery; they were not observed after bilateral vagotomy or after injections into the lumen of the left ventricle. It is suggested that DECC, like nicotine, stimulates vagal receptors in the pulmonary vascular bed.

3 The secondary phase was characterized by marked systemic and pulmonary hypertension, by contractions of the nictitating membrane and by increases in left ventricular dP/dt (at fixed isovolumic pressures), in cardiac output and in myocardial blood flow. All these effects were prevented, or markedly reduced, following the administration of hexamethonium or bethanidine and the pressor response was prevented by phentolamine. It is concluded that, in doses similar to those used in therapeutics, DECC stimulates sympathetic ganglia and releases noradrenaline. The relevance of this finding to the reported side effects of the drug are discussed.

4 DECC (5 or 10 mg/kg) significantly inhibited prostaglandin $F_{2\alpha}$-induced increases in peak inspiratory intra-tracheal pressure without modifying its pulmonary hypertensive effect. The possible relevance of this finding to the use of DECC in asthma is discussed.

Introduction

The anthelmintic diethylcarbamazine citrate (DECC) is the drug of choice in the treatment of *Wuchereria bancrofti*, *Brugia malayi* and *Loa loa*. It has been administered to millions of people and is generally regarded as a safe drug at therapeutic levels. Most of the side effects associated with its use have been attributed to the release of foreign protein from dying microfilariae and adult worms (Goldsmith, 1972). More recently, DECC has been used, with varying results, in the treatment of bronchial asthma (Mallen, 1965; Srinivas & Antani, 1971; Koivikko, 1973; Sly & Matzen, 1974).

Although only a few adverse reactions (chiefly nausea, vomiting and headache) have been directly attributed to the drug, Oomen (1969) has reported, from one hospital in Ethiopia, coma and death in seven out of 56 severely debilitated patients being treated for onchocerciasis. This reaction was apparently not allergic in nature. More recently, Fuglsang & Anderson (1974) have also emphasized that great care be taken when the drug is used to treat patients heavily infected with *Onchocerca volvulus*. In their study, from Cameroun, the more serious adverse reactions included a weak pulse, respiratory distress and coma; these reactions were partly attributed to the presence of microfilariae in the circulation.

Apart from the initial study of Harned, Cunningham, Halliday, Vessey, Yuda, Clark & Subba Row (1948) and a brief report by Forbes (1972), there have been no studies of the effects of DECC on the circulation. There have been no published accounts of effects of the drug on cardiac contractility either *in vivo* or *in vitro*. However, it is of some interest in this connection that Harned *et al.* (1948) reported sinus arrest, tachycardia and premature ventricular contractions following intravenous administration of the drug into conscious dogs. In the present paper we describe in detail the effects of DECC on systemic and pulmonary pressures, on myocardial contractility and blood flow, and on the electrocardiogram of anaesthetized cats.

Methods

Anaesthetized cats

Twenty-one cats, weighing between 1.5 and 3.5 kg, were anaesthetized with sodium pentobarbitone

(30 mg/kg, i.p.) and respired with room air by means of a Palmer positive-pressure ventilation pump (rate 20/min; stroke volume 40–60 ml). The volume of the pump was adjusted to give an arterial P_{O_2} between 80 and 100 mmHg (measured with a calibrated Radiometer electrode, for details see Parratt, 1973). A certain degree of hyperventilation was necessary (arterial P_{CO_2} 26 ± 2 mmHg); in spontaneously breathing cats anaesthetized with pentobarbitone it is 33 ± 1 mmHg (Parratt, 1973). Changes in respiration were assessed in spontaneously breathing cats with a copper-constantan thermocouple (similar to that used to record intramyocardial temperature; see below) placed within the tracheal cannula. The rate and depth of respiration were assessed from the changes in the respired air temperature and were recorded on a Kipp 2 Zonen BD5 recorder (full scale 200 mm = 1 mV = 25°C).

Systemic arterial blood pressure was recorded with a capacitance transducer (Elema-Schönander EMT 35) from a catheter, inserted by way of the carotid or femoral artery, so that the tip lay in the descending aorta or aortic arch. Systolic ejection time was measured (using a paper speed of 250 mm/s) from the beginning of the upstroke of the central aortic pressure pulse to the trough of the incisural notch and carotid artery dP/dt was continuously determined with an Elema-Schönander differentiating circuit. Mean arterial pressure was obtained by electronic integration.

After catheterizing a femoral vein, heparin (200 units/kg) was administered intravenously and a left thoracotomy performed. A wide-bore steel needle was inserted into the lumen of the left ventricle by direct puncture of the wall and pressure recorded with a capacitance transducer (EMT 34) both at high gain (10 mmHg = 25 mm; 1 mmHg = 1.333 mbar) for the accurate assessment of left ventricular end-diastolic pressure (LVEDP) and, at a lower gain (100 mmHg = 25 mm) for recording the full left ventricular pressure pulse. As an index of myocardial contractility the rate of rise of left ventricular pressure with time (dP/dt) was determined with an Elema-Schönander differentiating circuit and, to correct for changes in afterload (Mason, 1969), plots of dP/dt at different isovolumic pressures were obtained using a paper speed of 1000 mm/second. Either right atrial pressure (using a third capacitance transducer (EMT 33) from a catheter inserted by way of the right external jugular vein) or pulmonary artery pressure (from an indwelling needle in the main pulmonary artery) was also recorded, together with the ECG (usually limb leads I or II) on an eight-channel ink-jet writing recorder (Elema-Schönander mingograph 81).

In some of the experiments intratracheal pressure was measured from a side arm of the tracheal cannula with a Statham P23D6 pressure transducer. Cardiac output was measured by thermal dilution with room temperature 0.9% w/v NaCl solution (saline) (for details see Parratt, 1973) and myocardial blood flow was assessed by means of heated thermocouples implanted in the wall of the left ventricle. Because of the transient nature of the responses a constant heating current (0.15 A^2) was used as described by Parratt & Wadsworth (1972).

In three experiments the contractions of the nictitating membrane in response to pre-ganglionic sympathetic nerve stimulation were recorded with a Grass (model FT03) strain-gauge and a George Washington pen recorder (400 MD/2). Trains of rectangular pulses (0.5 ms duration) were delivered from a Grass S88 stimulator (frequency 10 Hz for 10 s at 100 ms intervals).

Diethylcarbamazine citrate (DECC; from Dr. A.F. Green, The Wellcome Research Laboratories) was dissolved in saline and injected, in doses of 2.5 (9 injections), 5.0 (17 injections) and 10 (36 injections) mg/kg (as salt) either intravenously or directly into the pulmonary artery or left ventricle.

Isolated coronary artery strips

Coronary arteries (o.d. 1.5–3.0 mm) were removed from pig hearts and cut into spiral strips approximately 3 cm long. They were suspended in Krebs solution, gassed with carbogen, at 37°C; the resting tension was 1 gram. Contractions were induced with potassium chloride (10–20 mM) and recorded isometrically.

Results

Haemodynamic effects in anaesthetized cats

There were two quite distinct haemodynamic responses to the injection of DECC: an initial transient hypotension (occurring within 10 s of the injection) and a pronounced secondary hypertension reaching a peak 30–60 s after the injection. These two phases (which are illustrated in Figure 1) will be described separately.

Initial hypotensive effect of diethylcarbamazine citrate Within 4–5 s of a rapid intravenous injection of DECC (2.5–10.0 mg/kg) there was bradycardia and slight reductions in systemic and pulmonary arterial pressures and also in left ventricular and carotid artery dP/dt *max.*; there was usually no reduction in pulse pressure. This initial effect of DECC is illustrated in Figure 1 and the results of all the experiments are summarized in Table 1. This initial effect of DECC was transient (lasting 3–6 s) and was observed more frequently with the higher doses of DECC. For example, it occurred in only 2 out of 9 experiments with a dose of 2.5 mg/kg, in 6 out of 17 experiments with a dose of 5.0 mg/kg and in 23 out of 36 experiments with 10 mg/kg. In

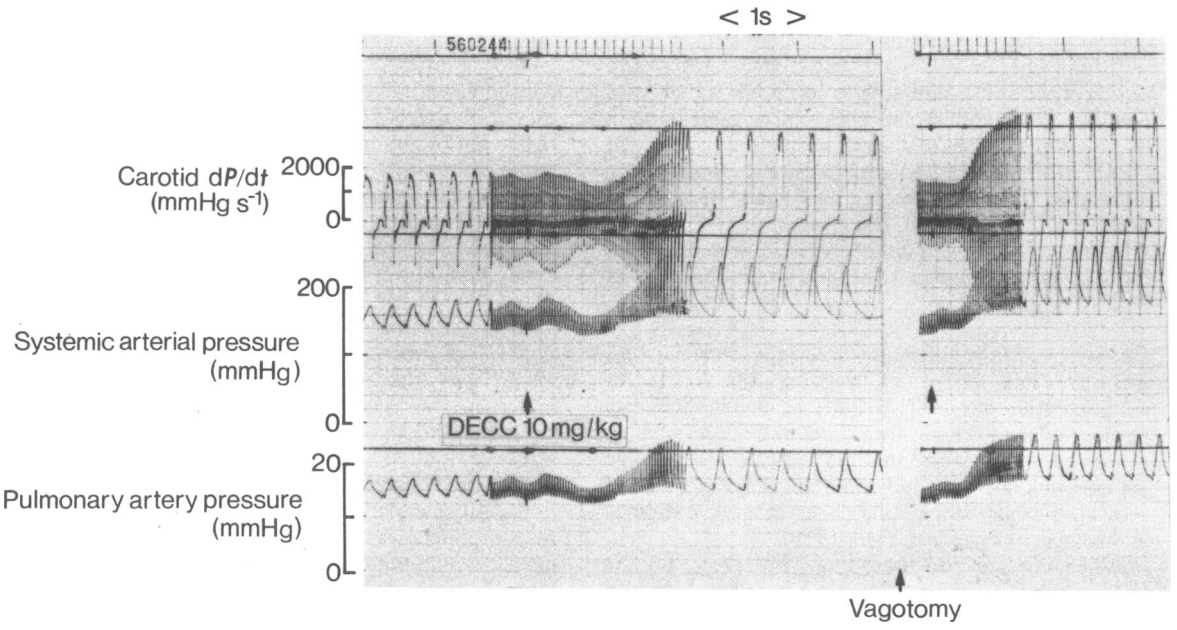

Figure 1 The effect, in an anaesthetized cat, of an intravenous injection of diethylcarbamazine citrate (DECC 10 mg/kg) on, from above, carotid artery d*P*/d*t* (mmHg s^{-1}) and on systemic and pulmonary artery pressures (mmHg). Within 10 s of the injection there was a transient hypotension and a reduction in d*P*/d*t max.*; this was followed by marked increases in pressure and d*P*/d*t max.* and by cardiac slowing. Both the initial hypotension and the secondary bradycardia were prevented by bilateral vagotomy (right hand panel).

spontaneously breathing cats this initial hypotension and bradycardia corresponded to a period of apnoea, lasting 7–10 seconds.

The effect of bilateral vagotomy Bilateral vagotomy itself had no significant haemodynamic effects in these pentobarbitone-anaesthetized cats (e.g. mean systemic blood pressure 96 ± 7 mmHg before and 91 ± 7 mmHg after vagotomy; heart rate 192 ± 7 beats/min before and 205 ± 10 beats/min after; carotid artery d*P*/d*t max.* 1690 ± 90 mmHg s^{-1} before and 1820 ± 110 mmHg s^{-1} after vagotomy; 10 experiments). In most of the experiments bilateral vagotomy greatly reduced the initial hypotensive effect of DECC (Figure 1). Thus in cats in which the effects of DECC (10 mg/kg) were examined both before and after vagotomy, the drug reduced mean blood pressure by 18 ± 4 mmHg (from 110 ± 12 mmHg) before vagotomy and by only 4–8 mmHg afterwards. Before vagotomy the heart rate change was -33 ± 12 beats/min (from a control of 196 ± 16 beats/min) but there was no reduction in heart rate following the administration of DECC in any experiment after vagotomy. The reduction in carotid artery d*P*/d*t max.*

Table 1 The initial (0–10 s) haemodynamic responses to the intravenous injection of diethylcarbamazine citrate (DECC, 2.5–10 mg/kg) in anaesthetized cats.

	Control	*Change from control induced by DECC*		
		2.5	*5.0*	*10.0 mg/kg*
Systolic blood pressure (mmHg)	124 ± 4	-7 (2)	-9 ± 1 (6)	-18 ± 2 (23)
Diastolic blood pressure (mmHg)	91 ± 4	-8 (2)	-9 ± 2 (7)	-19 ± 3 (23)
Carotid artery d*P*/d*t max.* (mmHg s^{-1})	2200 ± 120	0 (8)	-430 ± 75 (6)	-560 ± 80 (23)
Left ventricular d*P*/d*t max.* (mmHg s^{-1})	3880 ± 800	0 (1)	-420 (2)	-890 ± 190 (5)
Heart rate (beats/min)	203 ± 8	0 (9)	-13 ± 3 (7)	-28 ± 5 (24)

The values are the mean changes from control ± s.e. with the number of observations in parentheses.

was unchanged by vagotomy (− 450 ± 115 mmHg s^{-1} before and − 590 ± 120 mmHg s^{-1} afterwards).

In one cat, in which the initial hypotension and bradycardia were particularly pronounced, it was possible to determine the effect of hexamethonium (0.5 mg/kg, i.v.) on this initial response. In this cat, DECC (10 mg/kg) reduced diastolic pressure by 39 mmHg (from 85 mmHg) and heart rate by 90 beats/min (from 200 beats/minute). After hexamethonium there was no decrease in pressure when DECC was injected and the heart rate change was only 10 beats/minute.

The effect of intrapulmonary and interventricular injections The effect of varying the route of administration of DECC was determined in three cats because of the evidence from *in vitro* studies (Abaitey & Parratt, unpublished) that the drug has nicotine-like actions; nicotine often induces a fall in systemic blood pressure through stimulation of sensory nerve endings in the lungs (Armitage & Hall, 1969).

When injected into the pulmonary artery, DECC (10 mg/kg) caused a decrease in left ventricular pressure, in mean systemic arterial pressure (a reduction of 18 ± 8 mmHg from a pre-injection level of 71 ± 2 mmHg), in heart rate (− 28 ± 5 beats/min from 204 ± 10 beats/min) and in left ventricular d*P*/d*t max.* (− 1175 mmHg s^{-1} from a pre-injection level of 2230 ± 125 mmHg s^{-1}). These changes were similar to, but occurred 1–2 s sooner than, those observed in the same animals following the intravenous administration of DECC (10 mg/kg). When DECC was injected directly into the lumen of the left ventricle there was only a slight (< 10 mmHg) reduction in systemic pressure and the change in left ventricular d*P*/d*t max.* was much less marked (− 630 mmHg s^{-1}).

The secondary hypertensive effect of diethylcarbamazine citrate Within 10 s of the intravenous injection of DECC there were marked increases in systemic and pulmonary arterial pressures, in left ventricular d*P*/d*t max.* and, usually, also in carotid artery d*P*/d*t max.* These changes were dose related (Table 2) and the peak effect was reached in 30–60 seconds. At the height of the blood pressure response there was usually a pronounced bradycardia (Table 2 and Figure 1) and occasionally ventricular ectopic beats were present. The bradycardia was presumably reflex in origin (from stimulation of carotid and aortic baroceptors) since it was not

Table 2 Cardiovascular effects of intravenous diethylcarbamazine citrate (DECC, 2.5–10.0 mg/kg) in anaesthetized cats (after the initial 0–10 seconds)

	Control	*Maximum change from control induced by DECC*		
		2.5	5.0	10.0 mg/kg
Systolic blood pressure (mmHg)	124 ± 4	+ 19 ± 6 (9)	+ 40 ± 6 (17)	+ 82 ± 6 (36)
Diastolic blood pressure (mmHg)	91 ± 4	+ 14 ± 3 (9)	+ 31 ± 4 (17)	+ 52 ± 4 (36)
Mean blood pressure (mmHg)	102 ± 4	+ 16 ± 4 (9)	+ 34 ± 5 (17)	+ 62 ± 5 (36)
Heart rate (beats/min)*	203 ± 8	+ 6 ± 2 (6) − 4 ± 1 (3)	− 18 ± 3 (8) + 7 ± 1 (5)	− 25 ± 5 (24) + 20 ± 5 (7)
Systolic ejection time (ms)	116 ± 8	− 2(1)	− 4(1)	+ 12 ± 2 (9)
Left ventricular d*P*/d*t max.* (mmHg s^{-1})	3870 ± 800	+ 70(1)	+ 640 ± 210 (3)	+ 2100 ± 140 (6)
LVEDP (mmHg)	3.4 ± 0.4	0(1)	+ 0.5(2)	+ 0.7 ± 0.3 (5)
Carotid artery d*P*/d*t max** (mmHg s^{-1})	2200 ± 120	− 180 ± 40 (7) + 261 (1)	− 430 ± 120 (8) + 410 ± 60 (5)	− 250 ± 140 (3) + 980 ± 120 (25)
Pulmonary artery pressure (systolic, mmHg)	19 ± 1	+ 2.0 ± 0.5 (8)	+ 5 ± 1.0 (8)	+ 17 ± 3 (9)
Pulmonary artery pressure (diastolic, mmHg)	11 ± 0.5	1.0 ± 0.2 (8)	+ 2 ± 0.5	+ 7.5 ± 2.0 (9)

The values are the mean changes from control (± s.e.); number of observations in parentheses.
* The heart rate and carotid artery d*P*/d*t max.* responses to DECC varied; in some increases occurred, in others there were decreases. These have been separated in the Table. The changes induced by DECC were significantly different ($P < 0.001$) from those induced by an equivalent volume of saline.

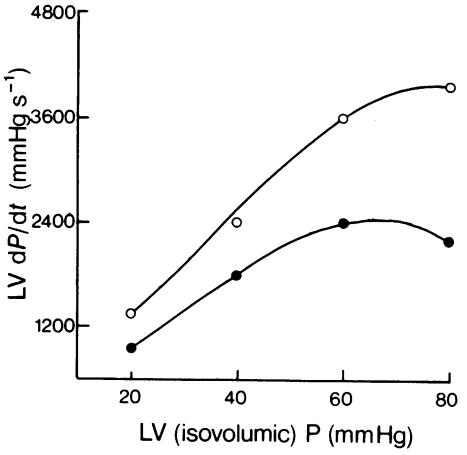

Figure 2 The effect of diethylcarbamazine citrate (DECC, 10 mg/kg i.v.) on the relationship between left ventricular d*P*/d*t* and left ventricular pressure during the period before the opening of the aortic valves (66 mmHg in the control situation). The higher ratio of d*P*/d*t* to peak common developed isovolumic pressure (CPIP, at 60 mmHg) after the administration of DECC indicates an increase in the contractile state of the ventricle. Control (●); DECC (○).

observed in cats subjected to bilateral vagotomy (Figure 1); under these conditions DECC increased heart rate. No ventricular arrhythmias were observed after vagotomy. There were indications that DECC increased myocardial contractility. Increases occurred in cardiac output (measured at the height of the pressure reponse) of 29 ml kg^{-1} min^{-1} (with a dose of 5 mg/kg DECC; single estimation) and of 73 ± 21 ml kg^{-1} min^{-1} with a dose of 10 mg/kg (3 estimations); the control cardiac output was 171 ± 6 ml kg^{-1} min^{-1}. Stroke volume was also increased (from 0.8 ± 0.04 ml/beat to 1.15 ± 0.15 ml/beat with a dose of 10 mg/kg). There was also substantial increases in pulse pressure, in carotid d*P*/d*t* *max.* and in left ventricular d*P*/d*t* *max.* (Table 2). Since there were also slight increases in LVEDP (Table 2) it is not possible to deduce with certainty from these results alone that a true increase in contractility had occurred. However it is doubtful whether an increase in LV d*P*/d*t* *max.* of 2100 ± 130 mmHg s^{-1} (from a pre-DECC level of 3870 ± 800 mmHg s^{-1} i.e. 55%) can be explained on the basis of the Frank-Starling mechanism alone, by an increase in ventricular filling pressure of only 0.7 mmHg (from 3.4 mmHg). Because of the marked changes in afterload, measurements were also made of d*P*/d*t* at fixed isovolumic left ventricular pressures before, and after, DECC. The results of one such experiment are illustrated in Figure 2. It is clear that the increases that occurred in d*P*/d*t* cannot be explained solely on the basis of changes in afterload.

Effects of diethycarbamazine citrate on myocardial blood flow The effect of DECC on myocardial temperature (measured with implanted heated thermocouples) was determined in four cats. The myocardial temperature was a mean of 0.2°C higher than that of the aortic blood and a constant heating current of 0.15 A^2 raised myocardial temperature by a further 0.90°C. Intravenous injections of DECC 5 mg/kg (3 injections) and 10 mg/kg (10 injections) decreased intramyocardial temperature by 0.075 ± 0.03°C and by 0.24 ± 0.03°C respectively; the peak change occurred 1–2 min after the injection and corresponded to the peak pressure response. The effect lasted for between 4 and 5 minutes.

Modification of the haemodynamic effects of diethylcarbamazine citrate by hexamethonium, phentolamine and bethanidine The secondary, hypertensive, effect of DECC was markedly reduced by the prior administration of hexamethonium (0.5 mg/kg intravenously; Figure 3). Thus in four control experiments DECC (10 mg/kg) increased systolic blood pressure by 97 ± 23 mmHg (from 109 ± 28 mmHg; mean ± s.e.), diastolic blood pressure by 62 ± 21 mmHg (from 78 ± 27 mmHg), heart rate by 17 ± 15 beats/min (from 178 ± 19 beats/min) and carotid d*P*/d*t* *max.* by 1440 ± 520 mmHg s^{-1} (from 1690 ± 140 mmHg s^{-1}). After the intravenous administration of hexamethonium the increases in pressure were only 15 ± 2 mmHg (from 77 ± 21 mmHg, systolic, and 13 ± 2 mmHg (from 51 ± 21 mmHg, diastolic); there was no change in heart rate and carotid d*P*/d*t* *max.* was actually reduced by a mean of 240 mmHg s^{-1} (from 1590 mmHg s^{-1}). Hexamethonium also prevented the DECC-induced changes in myocardial blood flow. Similar reductions in the secondary haemodynamic effects of DECC were also observed after the prior administration of bethanidine (3 mg/kg; 5 experiments, Table 3) and of phentolamine (0.5 mg/kg; 2 experiments). For example, in these 2 experiments, DECC raised systemic blood pressure by a mean of 65 mmHg (systolic) and by 53 mmHg (diastolic) and increased LV d*P*/d*t* *max.* by 1540 mmHg s^{-1} (77%) and heart rate by 9 beats/minute. The corresponding changes after phentolamine were 16 and 9 mmHg and + 60%; there was a decrease in heart rate of 30 beats/minute.

Effects of diethylcarbamazine citrate on intratracheal pressure; modification of response to prostaglandin $F_{2\alpha}$

DECC usually slightly increased intratracheal pressure at constant inflation volumes (i.e. it decreased pulmonary compliance); this effect was dose-related. From the pre-injection peak inspiratory pressure of 6.0 ± 0.4 mmHg the changes, following the administration of DECC (2.5, 5 and 10 mg/kg), were

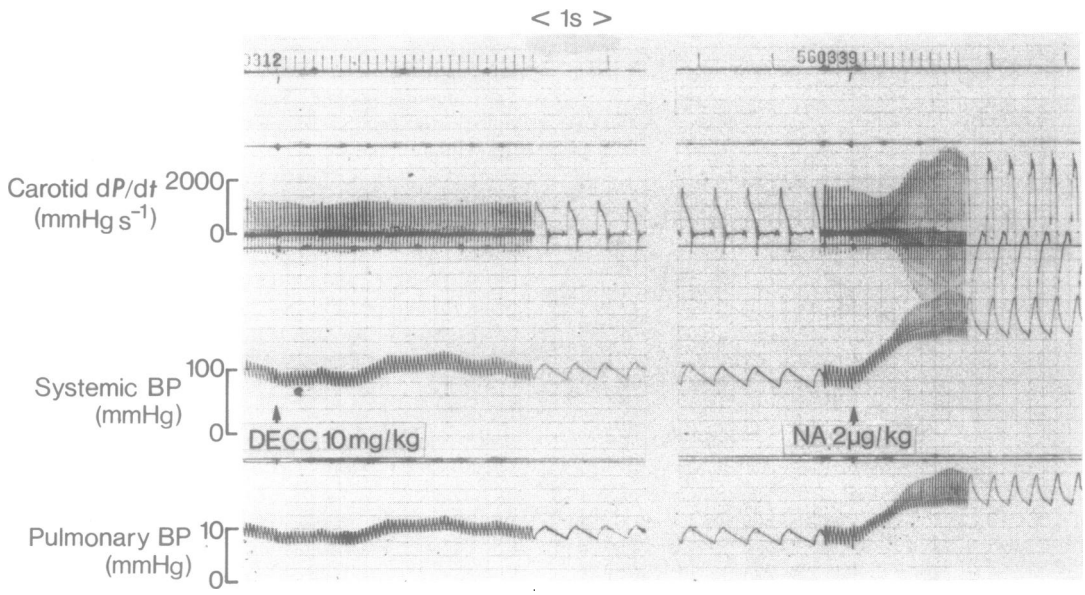

Figure 3 Cardiovascular effects of diethylcarbamazine citrate (DECC, 10 mg/kg i.v.) in an anaesthetized cat after the administration of hexamethonium (0.5 mg/kg). The systemic and pulmonary vascular effects (Figure 1) were almost completely inhibited; responses to noradrenaline (NA, 2 μg/kg i.v.) were unaffected.

+ 0.2 ± 0.1 mmHg (+ 3.3%), + 0.3 ± 0.1 mmHg (+ 5%) and + 0.7 ± 0.1 mmHg respectively (7 observations at each dose level). It is possible that these changes were mediated through reflex vagal activity. In view of the observation that DECC antagonizes the effect of prostaglandins E_2 and $F_{2\alpha}$ on isolated bovine pulmonary venous strips (Burka & Eyre, 1974), and in view of the claimed efficacy of DECC in asthma (for references see introductory section), experiments were performed to investigate the effect of the drug on prostaglandin-induced changes in pulmonary compliance. A single dose of prostaglandin $F_{2\alpha}$ was chosen (2.5 μg/kg, i.v.) and this increased intratracheal pressure by 2.4 ± 0.3 mmHg (from the control pressure of 7.8 ± 0.4 mmHg (i.e. by 30%); increases in mean pulmonary artery pressure (from 16 ± 1 to 26 ± 1 mmHg) were also observed with this dose of prostaglandin F_2 (Figure 4). DECC, in doses up to 10 mg/kg administered intravenously 30 s before prostaglandin $F_{2\alpha}$, had no effect on this pulmonary vascular response (16 ± 1 mmHg before prostaglandin $F_{2\alpha}$ and 28 ± 1 mmHg after) but, at the higher dose levels (5 and 10 mg/kg) it did reduce the prostaglandin-induced increase in intratracheal

Table 3 Cardiovascular effects of diethylcarbamazine citrate (DECC, 5 and 10 mg/kg i.v.) before, and 1 h after, the intravenous administration of bethanidine (3 mg/kg)

	Before bethanidine			*After bethanidine*		
	Control	*Change induced by DECC*		*Control*	*Change induced by DECC*	
		5 mg/kg	*10 mg/kg*		*5 mg/kg*	*10 mg/kg*
Systolic blood pressure (mmHg)	115 ± 15	+ 50 ± 5	+ 130 ± 20	97 ± 10	+ 19 ± 5*	+ 33 ± 13*
Diastolic blood pressure (mmHg)	88 ± 14	+ 48 ± 6	+ 96 ± 14	59 ± 9	+ 17 ± 5*	+ 29 ± 10*
Heart rate (beats/min)	207 ± 23	+ 6 ± 4	+ 29 ± 27	221 ± 17	− 5 ± 2	− 6 ± 13
Pulmonary artery pressure	16 ± 1	+ 3.2 ± 0.7	+ 13 ± 4.1	17 ± 1	+ 1.7 ± 0.5	+ 3.0 ± 1.2**

Values are means of five experiments ± s.e. of the mean.
* $P < 0.01$; ** $P < 0.05$ compared with change before bethanidine.

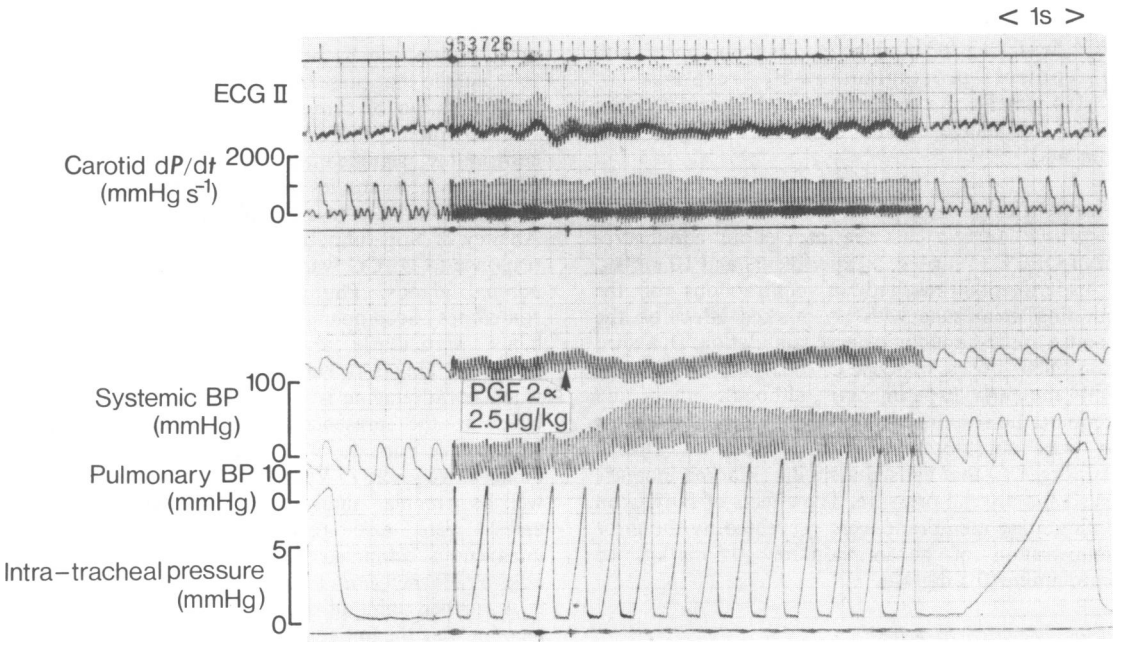

Figure 4 The effects of an intravenous injection of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 2.5 µg/kg) on the E.C.G., carotid arterial d*P*/d*t* and pressure, pulmonary artery pressure and intra-tracheal pressure, of a cat anaesthetized with pentobarbitone. The most pronounced effects of prostaglandin $F_{2\alpha}$ were increases in pulmonary artery pressure and in intra-tracheal pressure (from 8.8 to 11.6 mmHg at the end of inspiration, i.e. + 32%).

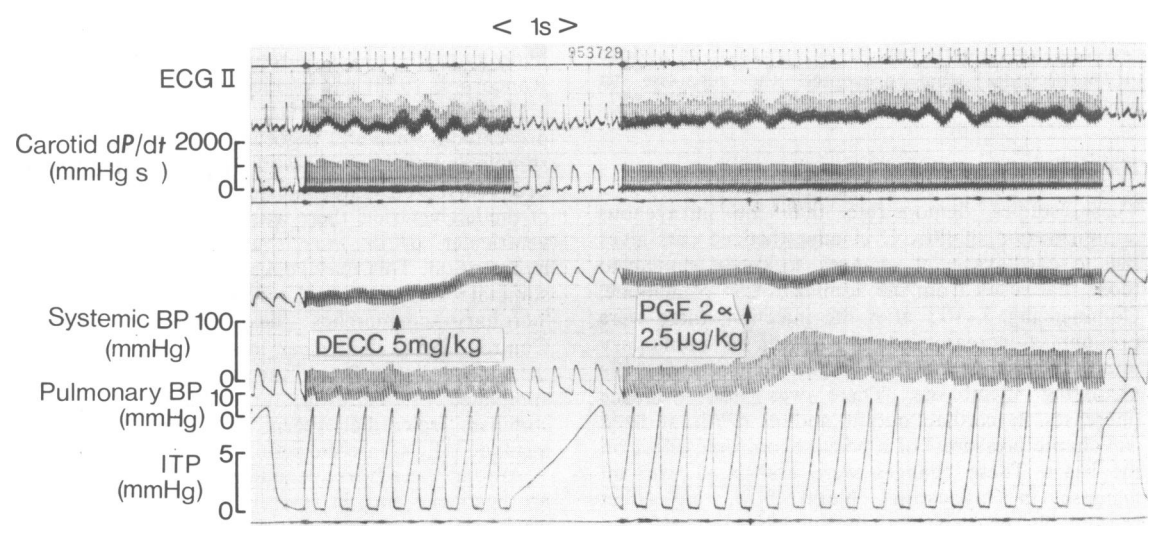

Figure 5 Same experiment as Figure 4. Modification of the effects of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) on intratracheal pressure by the prior administration of diethylcarbamazine citrate (DECC, 5 mg/kg). The increase in intratracheal pressure (ITP) was from 8.8 to 10.0 mmHg at the end of inspiration (i.e. + 14%) compared with + 32% in the control situation (Figure 4).

pressure (Figure 5). Thus the change after 5 mg/kg DECC was 1.4 ± 0.3 mmHg ($P < 0.05$ compared with the control prostaglandin F_2 response of 2.4 ± 0.4 mmHg; 5 experiments) and after 10 mg/kg DECC the increase was only 0.7 mmHg (2 experiments).

Effects of diethylcarbamazine citrate on the nictitating membrane In two cats the intravenous administration of DECC (5 mg/kg, 3 experiments and 10 mg/kg, 15 experiments) resulted in contractions of the nictitating membrane with no marked effect on the response to pre-ganglionic nerve stimulation. In a third cat, similar doses of DECC did not contract the membrane (4 experiments) although they did potentiate the response to nerve stimulation, an effect that was not observed with a dose of DMPP (30 μg/kg, i.v.) that caused a similar, marked increase in systemic arterial pressure. The effects of DECC on the nictitating membrane were prevented by the prior administration of hexamethonium (0.5 mg/kg) or phentolamine (0.5 mg/kg).

Isolated coronary arteries

In view of the increases in local myocardial blood flow observed when DECC was administered to anaesthetized cats, experiments were performed to see whether the drug relaxed isolated coronary arteries *in vitro*. In concentrations of 2.6×10^{-2} M to 2.0 mM, DECC caused dose-dependent relaxations of pig coronary artery strips contracted with potassium (10 to 20 mM); the ED_{50} was 2.0 mM (compared with isoprenaline on the same preparations, $ED_{50} = 5 \times 10^{-5}$ mM; 11 estimations). The DECC response was unaffected by propranolol in a dose (1.7×10^{-3} mM) that prevented the response to isoprenaline.

Discussion

These studies demonstrate that the intravenous administration of DECC in anaesthetized cats gives rise to cardiovascular changes strikingly similar to those that result from the administration of nicotine. Commencing 5–10 s after the injection, there were pronounced increases in both systemic and pulmonary arterial pressures and there was a contraction of the nictitating membrane. There was also evidence (increases in cardiac output and in dP/dt at fixed isovolumic pressures) of a positive inotropic effect on the heart. These changes were associated with an increase in myocardial blood flow, an effect presumably secondary to the increases in perfusion pressure and in cardiac work; only in high concentrations does DECC relax coronary arteries *in vitro*. Since the hypertensive effect was markedly reduced by phentolamine, and since both the systemic hypertension and the increases in myocardial contractility and blood flow were reduced by hexamethonium and by bethanidine, it seems reasonable to conclude that these effects of DECC are secondary to stimulation of sympathetic ganglia. It is doubtful whether direct stimulation of the adrenal medulla contributes significantly to these haemodynamic effects since, in studies designed to examine the effect of DECC on the soleus and tibialis muscles of the cat, Abaitey & Nott (unpublished) found that the pressure response to DECC was unaffected by removal of the adrenal glands. The cardiovascular changes were sometimes accompanied by ventricular premature beats, particularly at the height of the pressure response. This is rather similar to the effect obtained when noradrenaline is infused intravenously (particularly in the presence of myocardial ischaemia; Marshall & Parratt, 1973) and was not observed after bilateral vagotomy. Ventricular premature beats, as well as irregular sinus rhythm and periods of sinus arrest were also reported following the rapid intravenous administration of DECC in conscious dogs by Harned *et al.* (1948).

A further point of similarity between DECC and nicotine was the initial bradycardia and the reductions in systemic and pulmonary artery pressures and in left ventricular and carotid artery dP/dt *max*. These effects occurred within the initial 4–5 s of an intravenous injection and were more pronounced, and more rapid in onset, following injection into the pulmonary artery. In close-chest, spontaneously breathing, cats there was also inhibition of respiration lasting 7–10 seconds. This combination of apnoea, bradycardia and hypotension is similar to the response to the intravenous administration of diguanides and isothiourea derivatives (Dawes & Fastier, 1950), of 5-hydroxytryptamine (Comroe, Van Lingen, Stroud & Roncoroni, 1953) and of nicotine itself (Armitage & Hall, 1969) and the fact that the effects were prevented by bilateral vagotomy suggests that DECC stimulates vagal receptors in the pulmonary vascular bed. When DECC was injected directly into the lumen of the left ventricle there was a slight decrease in left ventricular dP/dt *max*. but almost no systemic hypotension. This may suggest that DECC does not stimulate receptors in the coronary circulation (the 'coronary chemoreflex' described by Dawes & Comroe, 1954). It is clear that receptors situated at the endocardial surface of the left ventricle are also not stimulated by the drug; no attempt was made to stimulate epicardial receptors (Sleight, 1964) by instilling DECC into the pericardial sac.

Among the adverse reactions attributed to DECC are headache and, in severely debilitated patients, a weak pulse, respiratory distress and coma (for references see introductory section). The headaches may be associated with increased systemic pressure. To our knowledge, blood pressure has not been measured in man following the intramuscular or oral administration of DECC but the recommended

clinical dose (6–16 mg/kg in single or divided doses in the treatment of *Wuchereria bancrofti* and *Loa loa* and 10 mg/kg in the treatment of asthma) is clearly within the range of that used in the present studies. There was no evidence for a direct depressant effect of DECC on the myocardium, even when injected in a high concentration directly into the lumen of the left ventricle. However, it must be recognized that these were essentially normal cats and it would not be valid to draw the conclusion from these experiments alone that DECC has no depressant effect on the myocardium already damaged by ischaemia or disease.

The use of DECC in intractable asthma (i.e. asthma usually unresponsive to standard bronchodilators) was first suggested by Mallen in 1965. He observed excellent results in an asthmatic patient who was given DECC to treat tropical eosinophilia. This observation led to its successful use in other asthmatic patients (Mallen, 1965; Srinivas & Antani, 1971) and, more recently, it has been demonstrated that DECC protects against exercise-induced airway obstruction in asthmatic children (Sly & Matzen, 1974). DECC is itself without bronchodilator activity (Sly & Matzen, 1974 and present paper). One possible explanation for the apparent effectiveness of DECC in asthma is its ability to inhibit the release of slow reacting substance-A (Orange, Valentine & Austen, 1968) but the recent observation by Burka & Eyre (1974) that it antagonizes prostaglandin $F_{2\alpha}$-induced contractions of bovine pulmonary veins, prompted us to examine its effect against the pulmonary responses to this prostaglandin *in vivo*. When given just before prostaglandin F_2, DECC reduced the changes that occurred in pulmonary compliance without influencing the pulmonary vascular response. This does not necessarily imply the presence of two receptor types for prostaglandin F_2; DECC-induced release of catecholamines would be another, simpler explanation. Clearly, however, this is a promising area for further experimental study.

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