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A COMPARATIVE STUDY BETWEEN THE CARDIOVASCULAR EFFECTS OF CETIEDIL, A NEW VASODILATOR, AND PAPAVERINE AND AMINOPHYLLINE

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ABSTRACT

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The cardiovascular effects of progressively increasing infusions of papaverine hydrochloride, aminophylline and cetiedil, a new vasodilator, were studied and compared in the anesthetized intact dog preparations. Papaverine and aminophylline had qualitatively the same effects on the various parameters, but in general the maximal effects of papaverine were of a greater order of magnitude. Cetiedil exhibited a different pattern of cardiovascular activity characterized by initial decrease in mean pulmonary arterial flow of 16% accompanied by an increase in systemic vascular resistance of 28% and in pulmonary vascular resistance of 19%, a stage of restoration of mean pulmonary arterial flow to control level accompanied by decrease in *dp/dt* of 25% and increase in pulmonary vascular resistance of 27% and a final stage of decrease in mean pulmonary arterial flow, representing toxic effects and accompanied by decrease in mean aortic pressure of 26%, *dp/dt* of 54% and heart rate of 27%, and an increase in pulmonary vascular resistance of 84%. These results indicate that cetiedil is devoid of cardiac stimulant activity. In another group of experiments devoted to measurement of vascular resistance of the hind limb, the results indicate that cetiedil, like papaverine and aminophylline, increased femoral blood flow through a decrease in resistance of the hind limb vasculature. This increase in flow could have been brought about only by redistribution of the cardiac output through differential effects on different vascular beds, since unlike papaverine and aminophylline, cetiedil does not increase cardiac output. The lesser maximal increase in femoral blood flow following cetiedil as compared to that following papaverine is probably referable to the relatively limited capacity of redistribution of the cardiac output to augment femoral blood flow. Superimposition of cetiedil and aminophylline on maximal effects of papaverine led to an additional decrease in mean femoral perfusion pressure, probably implying differences in basic mechanisms by which the three agents bring about their smooth muscle relaxant action.

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Notwithstanding serious limitations in the use of vasodilators in the treatment of peripheral vascular diseases, partly because of the limited efficacy of available drugs and partly because of the nature of the organic changes which are at the basis of these diseases (Hamilton and Wilson, 1952; Gillespie, 1959; Coffman and Mannick, 1972), the search for newer vasodilators continues. More recently cetiedil, the citrate of α-cyclohexyl-3-thiopheneacetic acid, 2-(hexahydro-1H-azepinlyl) ethyl ester, was synthesized by Robba and LeGuen (1967) and introduced in France for the symptomatic relief of intermittent claudication and pain of the lower extremities caused by arteriosclerosis obliterans, diabetogenic arteriosclerosis and Raynaud's disease (Linquette *et al.*, 1973). Cetiedil is purported to possess the following pharmacological attributes: relaxant action on vascular smooth muscle, inhibition of phosphodiesterase with consequent increase in 3',5'-adenosine monophosphate (cyclic AMP), blocking action on the effects of bradykinin and serotonin, interference with perception of ischemic pain and inhibition of platelet aggregation. The present investigations were undertaken to study the cardiovascular effects of cetiedil and compare them with those of the two classical vasodilators, papaverine and aminophylline. For this purpose, two preparations were used: the intact anesthetized dog for measurement of cardiac output and total systemic vascular resistance, and the anesthetized dog with perfused hind limb for measurement of femoral vascular resistance.

Methods

Cardiac output and total systemic vascular resistance. Experiments were performed on 21 mongrel dogs of either sex, weighing between 14 and 25 kg (average 19 kg), anesthetized with pentobarbital sodium (30 to 35 mg/kg). After artificial respiration was instituted through a tracheostomy with a Starling Ideal respirator, a left thoracotomy was performed *via* the fourth intercostal space. The pulmonary artery was dissected free from the arch of the aorta and a Statham electromagnetic flow probe, smaller in diameter by approximately 10%, was fitted around the artery shortly before its bifurcation. The probe was connected to a Statham SP 2202 electromagnetic flowmeter. Catheters were then placed in the left atrium through the auricular appendage and in the pulmonary artery of the left lower lobe, to measure left atrial and pulmonary arterial pressures. The cardiac apex was then exposed through a right-sided thoracotomy in the sixth intercostal space and a catheter was passed to the left ventricular lumen to measure left ventricular pressure. Aortic pressure was measured by cannulating the right carotid artery. All pressures were measured with P23 AA Statham pressure transducers. Recordings were made on a six-channel Sanborn 7700 recorder. Following a period of 15 to 20 minutes, during which the preparations were allowed to stabilize, an infusion of either papaverine hydrochloride, aminophylline or cetiedil was started. The drugs were dissolved in normal saline solution and their concentrations as well as the rate at which they were infused were adjusted so that the doses administered in mg/kg/min for intervals of 5 minutes each, were 0.1, 0.15, 0.2, 0.375, 0.5, 1.0, 1.5, 2.0 and 3.75. Papaverine hydrochloride was administered to eight preparations, aminophylline to six preparations and cetiedil to seven preparations. For papaverine and aminophylline, the data were pooled at the control state (C), when cardiac output started increasing (In St), when the increase became maximal (In Max) and when it started decreasing (Dec). For cetiedil, the data were pooled at the control state, when cardiac output started decreasing (Dec St), when the decrease became maximal (Dec Max), when cardiac output started increasing (In St), when the increase became maximal (In Max) and when it started decreasing (Dec). Data were analyzed by paired comparisons, the criterion for significance being $P < .02$.

Hind limb vascular resistance. Experiments were performed on 10 mongrel dogs of either sex weighing between 16 to 26 kg (average 20 kg). The experimental preparations were designed to study the effect of cetiedil, papaverine and aminophylline on the circulation of the hind limb, through perfusion of the femoral artery. The perfusion system consisted of a rubber tubing 0.6 cm in internal diameter passed through a peristaltic pump and attached at its sucking end to a rigid rubber catheter and at its perfusing end to a glass cannula. A catheter inserted close to the perfusing end was connected to a P23 AA Statham pressure transducer to measure perfusion pressure. Prior to cannulation, the system was filled with a 10% solution of dextran 40 in normal saline (Rheomacrodex, Pharmacia Laboratories). The dogs were anesthetized with pentobarbital sodium (30–35 mg/kg) administered intravenously. After artificial respiration was instituted, the sucking end of the perfusion system was inserted into the left atrium *via* the auricular appendage, through a left-sided thoracotomy. All the branches of the terminal aorta supplying the left hind limb were ligated through a suprapubic laparotomy and the distal end of the femoral artery was connected to the perfusing system. Aortic pressure was measured through a catheter in the carotid artery. All pressure measurements were made with

P23 AA Statham pressure transducers. Contralateral femoral arterial flow was measured with a Statham SP 2202 electromagnetic flowmeter. Recordings were made on a Sanborn 7700 recorder. Before limb perfusion was started, heparin sodium (400 U/kg) was injected intravenously. The speed of the pump was adjusted to give a mean perfusion pressure close to the mean aortic pressure. This speed and, consequently, the volume of blood delivered by the pump per unit of time, remained constant throughout the experiment, so that any changes in perfusion pressure reflected changes in vascular resistance of the perfused limb. Following a period of 15 to 20 minutes allowed for stabilization, increasing concentrations of cetiedil, papaverine hydrochloride and aminophylline were injected intravenously through a catheter in the jugular vein. Drugs were dissolved in normal saline solution. In some experiments at maximal and steady effect of a papaverine infusion, either aminophylline or cetiedil (4 mg/kg) was injected to observe whether additional changes could be detected. The data were analyzed by paired comparisons, the criterion for significance being $P < .02$.

Calculations and abbreviations. MPAP: mean pulmonary arterial pressure in cm H_2O, measured from the pulmonary artery of the left lower lobe; MLAP: mean left atrial pressure in cm H_2O, measured from the left atrium; LVP: left ventricular pressure in mm Hg, measured from a catheter in the left ventricular cavity inserted through the cardiac apex; *dp/dt:* maximal rate of rise of left ventricular pressure in mm Hg/sec, derived from the left ventricular pressure with a derivative computer; MAP: mean aortic pressure in mm Hg, measured from a catheter inserted through a carotid artery; MPAF: mean pulmonary arterial flow in ml/min, measured with a Statham electromagnetic flow probe around the main pulmonary artery, using a Statham electromagnetic flowmeter; HR: heart rate, in beats/min, computed from the aortic pressure waves, taken at a paper speed of 50 mm/sec; SVR: systemic vascular resistance in dynes·sec/cm^5, the quotient of the mean aortic pressure minus left ventricular end-diastolic pressure in dynes/cm^2 and the mean pulmonary arterial flow in ml/sec; PVR: pulmonary vascular resistance in dynes·sec/cm^5, the quotient of mean pulmonary arterial pressure minus mean left atrial pressure in dynes/cm^2 and of mean pulmonary arterial flow in ml/sec; MFAF: mean femoral arterial flow in mm Hg; MPP: mean perfusion pressure of hind limb in mm Hg.

Results

As these experiments were being started, it became apparent that the vasodilators could not be investigated in one group of experiments but in several devoted to cardiac function and the special vascular beds, such as the femoral, splanchnic, renal, coronary, cerebral and pulmonary. It was anticipated that the vascular beds had to be examined in the intact state, *i.e.*, supplied by the animal's own heart as well as by perfusion by a pump to control blood flow. The practice of single bolus injection to obtain a dose-response curve could not be applied for measurements of myocardial metabolism, cerebral metabolism and renal function. A decision was made to administer the drug by continuous infusion, a technique that would assure a steady state for measurements of the functions of the heart, brain and kidney.

The preliminary experiments showed that at a certain minimal rate of infusion of a drug that would influence blood pressure or *dp/dt*, a steady effect on either parameter was attained within 5 minutes of infusion, and that the response could be maintained for at least 1 hour of infusion. Five minutes was, therefore, accepted as the time for measurement of the effect of a drug at a particular rate of dose, and the dose was increased at intervals of every 5 minutes. This was the schedule selected for the experiments reported below and will be used in the examination of other special vascular beds that will be reported in the future.

Cardiac Output and Total Systemic Vascular Resistance

Changes in response to a progressively increasing infusion of papaverine, aminophylline and cetiedil are summarized in table 1 and figure 1. The pharmacological activity of these three agents was divided into stages based on changes in cardiac output as reflected by mean pulmonary arterial flow. Data presented in the text are mean differences between control and experimental values ± S.E. of difference.

Infusion of papaverine. In response to an infusion of papaverine, three stages of hemodynamic activity were delineated. The *first stage* was characterized by a beginning increase in cardiac output. This stage occurred at a dose level of 1.55 mg/kg administered in 13 minutes. In addition to an increase in mean pulmonary arterial flow of 154 ± 35 ml/min above average control value, there was an increase in heart rate and a decrease in mean aortic pressure and in systemic vascular resistance of 14 ± 4.6 beats/min, 13 ± 4.6 mm Hg and 2285 ± 598 dynes·sec/cm^5 from average control values, respectively. The *second stage* was characterized

TABLE 1

Cardiovascular effects of progressively increasing infusions of papaverine, aminophylline and cetiedil

Data are expressed in order as mean ± S.E.M., mean difference from control ± S.E. of difference and P value. For abbreviations, see "Methods."

	Papaverine				Aminophylline				Cetiedil					
	C	In St	In Max	Dec	C	In St	In Max	Dec	C	Dec St	Dec Max	In St	In Max	Dec
		1.55[a] in 13 min	14.44 in 32 min	25.38 in 38 min		1.48 in 10 min	11.21 in 29 min	27.67 in 38 min		1.52 in 10 min	6.63 in 25 min	11.63 in 29 min	21.09 in 34 min	30.52 in 40 min
MPAP (cm H_2O)	48.2±7.9	48.2±8.0	52.3±9.2	47.6±9.2	45.8±3.4	46.5±3.9	46.3±4.3	43.0±4.1	49.8±6.7	49.5±6.9	49.8±7.3	50.8±7.0	54.1±6.7	52.4±6.7
		0±3.5	+4.1±2.0	−0.6±2.1		+0.7±0.9	+0.5±1.8	−2.8±1.9		−0.4±0.3	0±1.0	+1±0.9	+4.3±1.4	+4.2±2.1
		NS	NS	NS		NS	NS	NS		NS	NS	NS	.01	NS
MLAP (cm H_2O)	19.1±4.6	18.5±4.7	21.2±5.5	18.5±5.1	14.0±1.7	13.6±1.8	13.6±1.2	12.1±1.1	18.6±2.5	18.8±2.4	18.4±2.7	18.8±3.0	19.8±3.5	17.5±2.0
		−0.6±0.7	+2.1±1.1	−0.6±1		−0.4±1.2	−0.4±1.4	−1.9±1.9		+0.2±0.4	−0.2±0.6	+0.2±0.8	+1.2±1.6	−0.4±2.0
		NS	NS	NS		NS	NS	NS		NS	NS	NS	NS	NS
LVP (mm Hg)	136±10.6	134±14.3	156±10.9	114±15.8	146±12.3	153±12.2	161±13.9	140±19.8	141±5.9	141±5.6	144±5.1	146±5.8	138±6.1	108±6.9
		−2±4.5	+20±7.9	−22±12.4		+7±1.7	+15±6.8	−6±16		0±1.1	+3±2.4	+5±3.5	−3±4.3	−33±7.4
		NS	0.2	NS		.01	NS	NS		NS	NS	NS	NS	.001
dp/dt (mm Hg/sec)	2713±421	3319±498	5375±559	3250±569	4000±1023	4667±1136	6667±1511	5500±1449	2579±254	2471±222	2371±177	2179±170	1900±199	1292±187
		+606±285	+2662±608	+537±689		+667±125	+2667±944	+1500±973		−107±743	−208±107	−400±126	−679±152	−1500±129
		NS	.001	NS		.001	.02	NS		NS	NS	.01	.001	.001
MAP (mm Hg)	139±8.3	128±12.8	116±10.2	80±12.3	140±10.3	146±7.5	131±6.8	93±7.9	127±6.6	129±6.9	135±5.9	136±6.8	129±6.7	94±8.0
		−13±4.6	−23±5.8	−59±8.4		+6±1.4	−9±7.1	−47±8.4		+2±2.4	+8±3.9	+9±4.7	+2±5.0	−34±9.3
		.02	.01	.001		NS	NS	.001		NS	NS	NS	NS	.01
MPAF (ml/min)	1144±125	1298±146	2063±177	1414±192	1900±248	1992±254	2467±243	2267±239	1110±111	1030±105	936±103	1014±108	1102±143	795±36
		+154±35	+919±94	+350±202		+92±9	+567±96	+367±109		−80±10	−174±24	−96±30	−8±37	−234±79
		.001	.001	NS		.001	.001	.01		.001	.001	.01	NS	.01
HR (beats/min)	129±8	143±7	150±7	128±7	151±13.6	160±14.0	177±12.8	172±11.5	148±11	148±10	142±10	138±9	133±10	112±9
		+14±4.6	+22±7.7	1±9.1		+9±2.2	+26±6.5	+21±7.5		0±0.7	−6±2.9	−10±4.6	−15±6	−42±8.2
		.01	.02	NS		.01	.01	.02		NS	NS	NS	NS	.001
SVR (dynes·sec/cm^5)	9543±550	7258±394	4486±358	3590±461	6255±1043	6214±985	4360±549	3257±288	8951±1068	9774±1087	11238±1180	10409±1060	9059±873	8370±826
		−2285±598	−5057±392	−6142±699		−41±162	−1895±523	−2998±819		+823±153	+2287±487	+1458±497	+108±535	−1075±648
		.01	.001	.001		NS	.01	.01		.001	.001	.02	NS	NS
PVR (dynes·sec/cm^5)	1511±224	1322±188	856±120	1036±137	1042±128	1032±154	803±102	839±116	1662±307	1751±312	1956±346	1874±316	1924±320	2609±495
		−189±74	−655±129	−364±196		−10±38	−239±58	−203±28		+89±15	+295±60	+212±59	+262±92	+947±259
		NS	.001	NS		NS	.01	.001		.001	.001	.01	.02	.01

[a] Drug doses are given as milligrams per kilogram.

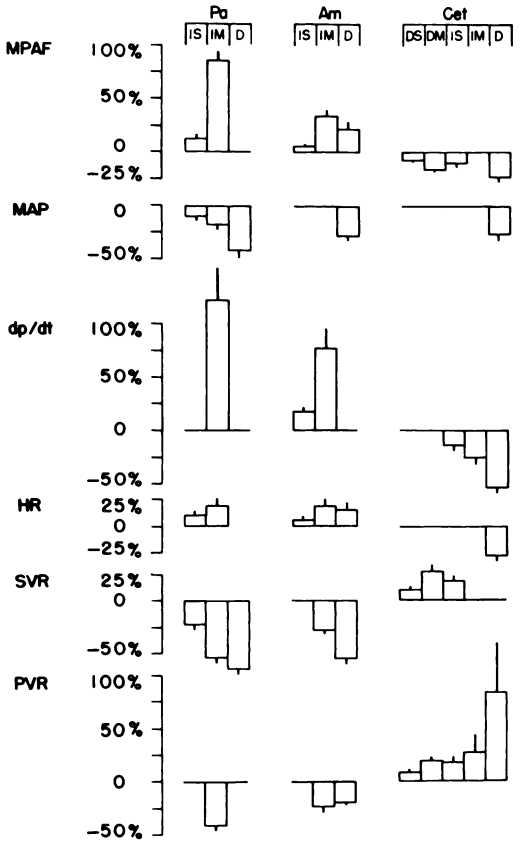

FIG. 1. Percentage changes from control in some cardiovascular parameters in response to infusions of papaverine (Pa), aminophylline (Am) and cetiedil (Cet). The effects were divided into stages based on changes in cardiac output as reflected by mean pulmonary arterial flow. IS, increase starts; IM, increase becomes maximal; D, decrease; DS, decrease starts; DM, decrease becomes maximal. For other abbreviations, see "Methods." Bars indicate S.E.M. Only the changes which were significantly different from control data were presented.

by maximal increase in mean pulmonary arterial flow of 919 ± 94 ml/min above average control value. It occurred at a dose level of 14.44 mg/kg, administered in 32 minutes. Changes in the remaining parameters at this stage included: an increase in peak left ventricular pressure, in maximal rate of rise of left ventricular pressure, *dp/dt*, and in heart rate of 20 ± 7.9 mm Hg, 2662 ± 608 mm Hg/sec and 22 ± 7.7 beats/min above average control values, respectively, and a decrease in mean aortic pressure of 23 ± 5.8 mm Hg in systemic and pulmonary vascular resistances of 5057 ± 392 dynes·sec/cm^5 and 655 ± 129 dynes·sec/cm^5 below average control values, respectively. The *third stage* was characterized by a decrease in mean pulmonary arterial flow from the maximal level attained earlier and its return to control level. This stage occurred at a dose level of 25.38 mg/kg, administered in 38 minutes. The changes included a decrease in mean aortic pressure of 59 ± 8.4 mm Hg and in systemic vascular resistance of 6142 ± 699 dynes·sec/cm^5 below average control values.

Infusion of aminophylline. In response to an infusion of aminophylline, again three stages of hemodynamic activity were noted. The *first stage* occurred at a dose level of 1.48 mg/kg administered in 10 minutes, and was characterized by an increase in mean pulmonary arterial flow, peak left ventricular pressure, *dp/dt* and heart rate of 92 ± 9 ml/min, 7 ± 1.7 mm Hg, 667 ± 125 mm Hg/sec and 9 ± 2.2 beats/min above average control values, respectively. The *second stage* occurred at an infusion level of 11.21 mg/kg, administered in 29 minutes, and was characterized by a maximal increase in mean pulmonary arterial flow of 567 ± 96 ml/min above average control value. In addition, *dp/dt* and heart rate increased by 2667 ± 944 mm Hg/sec and 26 ± 6.5 beats/min above average control values, respectively. The *third stage* occurred at an infusion level of 27.67 mg/kg, administered in 38 minutes, and was characterized by a decrease in mean pulmonary arterial flow from the maximal value attained during the second stage, although it remained higher than the average control value by 367 ± 109 ml/min. In addition, mean aortic pressure and systemic and pulmonary vascular resistances decreased below average control values by 47 ± 8.4 mm Hg, 2998 ± 819 dynes·sec/cm^5 and 203 ± 28 dynes·sec/cm^5, respectively. Heart rate increased by 21 ± 7.5 beats/min above average control value.

Infusion of cetiedil. In contradistinction to papaverine and aminophylline, five stages of hemodynamic activity, again based on changes in cardiac output as reflected by mean pulmonary arterial flow, were delineated with progression of the cetiedil infusion. The *first stage* was characterized by a starting decrease in mean pulmonary arterial flow averaging 80 ± 10 ml/min below average control value. This stage occurred at a dose level of 1.52 mg/kg, administered in 10 minutes. Other changes included an increase in systemic and pulmonary vascular resistances of 823 ± 153 dynes·sec/cm^5 and 89

± 15 dynes·sec/cm^5 above average control values, respectively. During the *second stage*, decrease in mean pulmonary arterial flow reached a maximum of 174 ± 24 ml/min below average control value. Systemic and pulmonary vascular resistances increased by 2287 ± 487 dynes·sec/cm^5 and 295 ± 60 dynes·sec/cm^5 above average control values, respectively. This stage occurred at a dose level of 6.63 mg/kg, administered in 25 minutes. The *third stage* occurred at a dose level of 11.63 mg/kg, administered in 29 minutes, and was characterized by a beginning increase in mean pulmonary arterial flow as compared to the maximal decrease noted earlier, but it remained lower than the average control value by 96 ± 30 ml/min. Other changes included a decrease in *dp/dt* of 400 ± 126 mm Hg/sec below average control value and an increase in systemic and pulmonary vascular resistances of 1458 ± 497 dynes·sec/cm^5 and 212 ± 59 dynes·sec/cm^5 above average control values, respectively. The *fourth stage* occurred at a dose level of 21.09 mg/kg, administered in 34 minutes, and was characterized by return of mean pulmonary arterial flow to control level. In addition, mean pulmonary arterial pressure and pulmonary vascular resistance increased by 4.3 ± 1.4 cm H_2O and 262 ± 92 dynes·sec/cm^5 above average control values, respectively, and *dp/dt* decreased by 679 ± 152 mm Hg/sec below average control value. The *fifth stage* occurred at a dose level of 30.52 mg/kg administered in 40 minutes, and was characterized by a decrease in mean pulmonary arterial flow of 234 ± 79 ml/min below control average in addition to a decrease in peak left ventricular pressure, *dp/dt*, mean aortic pressure and heart rate of 33 ± 7.4 mm Hg, 1500 ± 129 mm Hg/sec, 34 ± 9.3 mm Hg and 42 ± 8.2 beats/min below average control values, respectively. Pulmonary vascular resistance increased by 947 ± 259 dynes·sec/cm^5 above average control value.

Hind Limb Vascular Resistance

Changes in mean hind limb perfusion pressure, mean aortic pressure and mean femoral arterial flow in response to single injections of varying concentrations of papaverine hydrochloride, aminophylline and cetiedil are summarized in table 2 and figure 2. Data in the table and text are presented as mean differences from control ± S.E. of difference.

Separate injections of papaverine, aminophylline and cetiedil. A concentration of 0.5 mg/kg of papaverine hydrochloride, aminophylline and cetiedil decreased mean perfusion pressure by 41 ± 5.3 mm Hg, 25 ± 3.8 mm Hg and 20 ± 5.3 mm Hg below control averages, respectively. At this dose level, only papaverine decreased mean aortic pressure by 34 ± 2.6 mm Hg below control average and both papaverine and aminophylline, but not cetiedil, increased mean femoral arterial flow by 30 ± 7.0 ml/min and 26 ± 5.7 ml/min above average control values, respectively.

A maximal decrease in mean perfusion pressure below the average control value of 70 ± 10.1 mm Hg was obtained with papaverine at a dose of 4 mg/kg. Aminophylline decreased the same parameter maximally by 54 ± 6.5 mm Hg below average control value at a dose of 2 mg/kg and cetiedil by 69 ± 11.4 mm Hg below average control value at a dose of 4 mg/kg. A maximal decrease in mean aortic pressure of 34 ± 2.6 mm Hg below average control value was noted following a dose of papaverine of 0.5 mg/kg, of 22 ± 8.0 mm Hg below average control value following a dose of 3 mg/kg of aminophylline and of 46 ± 6.7 mm Hg below average control value following a dose of 4 mg/kg of cetiedil. Both papaverine and aminophylline produced a maximal increase in mean femoral arterial flow at a dose of 2 mg/kg, of 37 ± 5.1 ml/min and 42 ± 7.8 ml/min above average control values, respectively. Cetiedil, on the other hand, produced a maximal increase in the same parameter of 17 ± 2.9 ml/min above average control value at a dose of 1 mg/kg.

Aminophylline and cetiedil superimposed on maximal effects of papaverine. Progressively increasing infusions of papaverine were administered and, when maximal and steady decrease in mean perfusion pressure was observed, either aminophylline or cetiedil was injected intravenously in doses of 4 mg/kg. The data of table 3 show that the decrease in mean perfusion pressure and in mean aortic pressure were significantly lower after either aminophylline or cetiedil superimposed on papaverine than after papaverine alone.

Discussion

Cardiovascular effects of papaverine and aminophylline. The results of these experiments indicate that both papaverine and aminophylline share basically the same spectrum of

TABLE 2

Effect of increasing intravenous doses of papaverine (Pa), aminophylline (Am) and cetiedil (Cet) on some hemodynamic parameters

Data represent in order, mean control (C) and experimental (E), mean difference ± S.E. of difference and P value. For abbreviations, see "Methods."

	MPP (mm Hg)						MAP (mm Hg)						MFAF (ml/min)					
	Pa		Am		Cet		Pa		Am		Cet		Pa		Am		Cet	
	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
0.5 mg/kg	151	110	153	128	160	141	136	102	126	123	127	126	39	69	39	65	35	37
	−41 ± 5.3		−25 ± 3.8		−20 ± 5.3		−34 ± 2.6		−3 ± 1.3		−1 ± 0.6		+30 ± 7.0		+26 ± 5.7		+2 ± 1.3	
	.001		.001		.01		.001		NS		NS		.01		.001		NS	
1 mg/kg	158	97	159	128	163	124	129	93	128	129	126	114	35	64	33	64	32	49
	−61 ± 8.2		−31 ± 5.2		−39 ± 5.6		−36 ± 3.8		+1 ± 1.8		−12 ± 2.9		+29 ± 5.0		+31 ± 7.9		+17 ± 2.9	
	.001		.001		.001		.001		NS		.001		.001		.01		.001	
2 mg/kg	156	96	160	106	162	104	134	94	125	113	122	98	34	71	32	74	33	50
	−60 ± 6.6		−54 ± 6.5		−58 ± 7.6		−40 ± 5.8		−12 ± 7.6		−24 ± 2.7		+37 ± 5.1		+42 ± 7.8		+18 ± 3.6	
	.001		.001		.001		.001		NS		.001		.001		.001		.001	
3 mg/kg	147	82	149	89	154	92	119	76	118	96	124	86	31	64	33	79	32	49
	−65 ± 7.4		−60 ± 8.2		−62 ± 9.0		−43 ± 7.8		−72 ± 8.0		−38 ± 4.5		+33 ± 8.2		+46 ± 8.0		+17 ± 3.7	
	.001		.001		.001		.001		.02		.001		.01		.001		.001	
4 mg/kg	141	71	141	90	148	79	113	70	108	83	116	70	32	50	30	61	32	49
	−70 ± 10.1		−51 ± 9.4		−69 ± 11.4		−43 ± 5.9		−25 ± 9.4		−46 ± 6.7		+18 ± 4.6		+31 ± 8.0		+17 ± 4.8	
	.001		.001		.001		.001		.02		.001		.01		.01		.01	

hemodynamic activity while the activity of cetiedil is contrastingly different. However, although the effects of papaverine and aminophylline on the various measured and derived parameters are qualitatively identical, distinct quantitative differences prevail. Thus, whereas cardiac output, as reflected by mean pulmonary arterial flow, increased maximally by 85 ± 11% following administration of papaverine, it increased maximally by only 34 ± 7% following administration of aminophylline (fig. 1). Similarly, myocardial contractile force, as reflected by maximal rate of rise of left ventricular pressure, *dp/dt*, increased following papaverine administration to a maximal limit of 123 ± 29% whereas following aminophylline it increased by 78 ± 17%. In addition, papaverine led to a maximal decrease in mean aortic pressure, systemic vascular resistance and pulmonary vascular resistance of 43 ± 6%, 63 ± 5% and 41 ± 5%, respectively, whereas the same parameters decreased following treatment with aminophylline by 27 ± 4%, 45 ± 4% and 23 ± 5%, respectively. On the other hand, the effect on heart rate was identical in that both papaverine and aminophylline produced a maximal increase of 19 ± 7% and 19 ± 6%, respectively. The effects of papaverine and aminophylline were also qualitatively identical during what appears to be the "toxic" level of their action. At this stage, cardiac output, myocardial contractile force and heart rate decreased markedly as compared with their respective maximal average. It is readily evident from the data that in its effect on all cardiovascular parameters, with the exception of its effect on heart rate, papaverine was capable of producing maximal changes of a greater order of magnitude than maximal changes induced by aminophylline. Whereas the cardiac stimulant action of aminophylline is well known, that of papaverine is often neglected. The older literature is replete with reports of opposite opinions regarding the cardiac stimulant action of papaverine. The more recent literature has focused predominantly on the enzymatic effects of papaverine (Kukovetz and Poch, 1970). Our results are in agreement with those of Levy (1972) who reported a positive inotropic effect in isolated human atrial preparations following exposure to papaverine. Working on isolated cat papillary muscles, Pokorski (1973) reported depression in contractility in response to papaverine. When administered by the intracoronary route in the intact dog preparation, papaverine was found by Seta (1970) to decrease cardiac output. Our studies indicate that during the "toxic" phase, papaverine brings about cardiovascular depression. Thus, the biphasic effect of papaverine, stimulatory with "therapeutic" doses and depressant

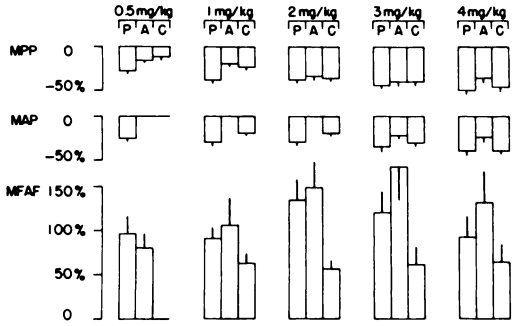

FIG. 2. Percentage changes ± S.E.M. in mean perfusion pressure (MPP), mean aortic pressure (MAP) and mean femoral arterial flow (MFAF) in response to varying intravenous doses of papaverine (P), aminophylline (A), and cetiedil (C). Only the changes which were significantly different from control data were presented.

TABLE 3

Percentage change from control in mean perfusion pressure (MPP) and mean aortic pressure (MAP) following maximal effects of papaverine and superimposed injections of aminophylline and cetiedil

Values represent in order means ± S.E.M., mean difference ± S.E. of difference, and P value.

	Papaverine	Papaverine and Aminophylline	Papaverine	Papaverine and Cetiedil
MPP	−31 ± 9.9	−49 ± 8.4	−30 ± 8.5	−55 ± 5.1
		+ 18 ± 5.3		+25 ± 7.3
		.01		.01
MAP	−26 ± 9.1	−42 ± 7.8	−22 ± 4.8	−42 ± 4.9
		+ 16 ± 4.0		+20 ± 4.7
		.01		.01

with "toxic" doses, can readily be overlooked when experimental preparations are used and routes of administration are resorted to, which do not permit clear delineation between therapeutic and toxic effects.

Cardiovascular effects of cetiedil. In contradistinction to the effects of papaverine and aminophylline, cetiedil exhibited a drastically different pattern of hemodynamic activity (fig. 1). In smaller doses, cardiac output decreased maximally by 16 ± 2.3%, whereas systemic vascular resistance and pulmonary vascular resistance increased maximally by 28 ± 5.5% and 19 ± 3%, respectively. Progression of the infusion led to restoration of the cardiac output to control level, but was associated with a decrease in *dp/dt* of 25 ± 6% and an increase in pulmonary vascular resistance of 27 ± 16%. Further infusion of cetiedil led to what appears to be a toxic effect, characterized by a drastic decrease in cardiac output, mean aortic pressure, *dp/dt* and heart rate of 21 ± 5%, 26 ± 7%, 54 ± 5% and 27 ± 4.5%, respectively, in addition to a marked elevation in pulmonary vascular resistance of 84 ± 47%. Insofar as cardiac output is concerned, therefore, cetiedil exhibited a triphasic effect, an initial decrease associated with insignificant change in myocardial contractile force, restoration to control level associated with moderate decrease in myocardial contractile force and a final decrease, representing effects outside the therapeutic range and associated with marked decrease in myocardial contractile force, mean aortic pressure and heart rate and a marked increase in pulmonary vascular resistance. Since the available data shed no light on the basic mechanisms involved in this triphasic mode of action, one can speculate that the changes in cardiac output following cetiedil represent vascular as well as cardiac loci of action. The initial phase of decrease in cardiac output could be due to effects on components of the peripheral vascular system in a manner which would favor a decrease in venous return and, consequently, a decrease in cardiac output. The second phase of restoration of the cardiac output to control level with progression of the infusion could be due to a shift in the differential actions of cetiedil, at this dose level, on the various components of the vascular system and possibly different effects on different vascular beds, such that the net action is an increase in venous return, thus favoring restoration of the cardiac output notwithstanding a moderate decrease in myocardial contractile force. It is evident that the stage of toxic activity is due to a combination of many factors including marked peripheral vascular dilatation, a decrease in myocardial contractility and a direct depressant action on the activity of the sinoatrial node.

Pulmonary vascular resistance. The effect of cetiedil on the pulmonary component of the cardiovascular system deserves comment. A progressive increase in pulmonary vascular resistance was noted starting with the least effective concentrations. During the stage of restoration of the cardiac output to control level, the increase in pulmonary vascular resistance was associated with an increase in mean pulmonary arterial pressure, but not in mean left atrial pressure. These observations suggest a pulmonary vasoconstrictor effect. That the decrease in cardiac output at constant mean pulmonary arterial pressure during the first three stages of the action of cetiedil was not the cause of the increase is proven by the fact that in an identical preparation, comparable decreases in cardiac output brought about by graded constriction of the inferior vena cava did not lead to an increase in pulmonary vascular resistance (table 4).

Hind limb vascular resistance. The results of perfusion experiments indicate that a dose of 0.5 mg/kg of papaverine, aminophylline and cetiedil, while hind limb mean perfusion pressure decreased by 27 ± 2.7%, 16 ± 2.4% and 11 ± 3.1%, respectively, there was an increase in mean blood flow in the contralateral femoral artery after papaverine and aminophylline of 96 ± 21% and 81 ± 16%, respectively, but not after cetiedil (fig. 2). The increase in mean femoral arterial flow following cetiedil became significantly higher than control and also maximal with a dose of 1 mg/kg. At this dose level, mean perfusion pressure and mean aortic pressure decreased by 24 ± 2.3% and 9 ± 2.4%, respectively. It is evident, therefore, from these data that cetiedil, like papaverine and aminophylline, can promote femoral arterial flow in the normal animal by promoting relaxation of the limb vasculature. However, close inspection of the data of table 2 reveals that major quantitative differences between the three pharmacological agents prevail. Although the same dose of papaverine and cetiedil decreased mean perfu-

TABLE 4

Percentage change from control ± S.E.M. in cardiovascular parameters following minimal (A), moderate (B) and severe (C) constriction of the inferior vena cava

Level of significance was assessed by paired comparisons of the absolute data. For abbreviations, see "Methods."

	MPAP	MLAP	MAP	dp/dt	MPAF	SVR	PVR
A	−9 ± 4.2	−2 ± 9.6	−9 ± 2.1	−4 ± 9.2	−12 ± 0.8	+6 ± 6.7	−5 ± 8.1
	NS	NS	NS	NS	.001	NS	NS
B	−29 ± 11.8	−23 ± 3.7	−25 ± 6.9	−20 ± 10.3	−27 ± 2.1	−1 ± 13.8	−9 ± 30.6
	NS	.01	.01	NS	.01	NS	NS
C	−35 ± 8.6	−38 ± 4.6	−45 ± 6.9	−47 ± 7.5	−46 ± 2.1	−4 ± 12.5	+25 ± 28.9
	.01	.01	.001	.001	.001	NS	NS

sion pressure maximally to comparable limits of 49 ± 4.9% and 45 ± 6%, respectively, cetiedil was maximally capable of increasing contralateral mean femoral arterial flow by 63 ± 13% as compared to a maximal increase of 134 ± 24% following papaverine. Aminophylline, on the other hand, decreased mean perfusion pressure maximally to a lesser extent than either cetiedil or papaverine (33 ± 3.9%) yet it produced the highest maximal increase in mean femoral arterial flow. This clearly indicates that the sum total of the underlying hemodynamic changes which is ultimately responsible for the increase in mean femoral arterial flow, is different in each instance. In the first group of experiments designed to compare the cardiac as well as the systemic and pulmonary vascular effects of cetiedil, papaverine and aminophylline, it became evident that, unlike papaverine and aminophylline, cetiedil was devoid of any cardiac stimulant activity and that its net cardiac and vascular actions did not lead to an increase in cardiac output (table 1). By contrast, a marked increase in cardiac output was noted with both papaverine and aminophylline. The conclusion was made that if cetiedil is to increase blood flow to skeletal muscle, it must do so by redistribution rather than augmentation of the cardiac output. The present study clearly shows that cetiedil does in fact increase femoral blood flow in the normal animal through preferential relaxation of the hind limb vasculature and possibly concomitant constriction of some other vascular beds, thus effecting a redistribution of the cardiac output. The limited maximal increase in femoral arterial flow produced by cetiedil as compared to that produced by papaverine and aminophylline is evidently due to the limited capacity of the mechanism of redistribution of the cardiac output to increase regional blood flow as opposed to the increase brought about by augmentation of the cardiac output in addition to regional vascular effects. The details of the effects of cetiedil on vascular beds other than those of skeletal muscles await further study. The fact that a much smaller maximal increase in femoral arterial flow of 63% was observed after cetiedil as compared to maximal values of 134% and 148% after papaverine and aminophylline, respectively, may not constitute a therapeutic disadvantage in that an increase of this order of magnitude may be all that is necessary for beneficial therapeutic purposes.

Mode of action. When either aminophylline or cetiedil was injected intravenously during an infusion of papaverine, which caused a maximal and steady decrease in mean perfusion pressure, an additional significant decrease in both mean perfusion pressure and mean aortic pressure was noted. While these experiments are too elementary to permit speculation on the possible mode of action of the three pharmacological agents, they show that preoccupation with the fact that inhibition of phosphodiesterase with consequent elevation of the concentration of cyclic AMP—a common accompaniment of the action of papaverine (Kukovetz and Poch, 1970), aminophylline (Butcher and Sutherland, 1962) and cetiedil (M. Aurousseau, 1974, personal communication)—should not preclude a search for additional mechanisms responsible for the observed relaxation of vascular smooth muscle. These will be reported in conjunction with the study of the effects of vasodilators on other special vascular beds.

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