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THE EFFECTS OF SYNTHETIC ELEDOISIN ON THE SYSTEMIC AND CORONARY HAEMODYNAMICS AND METABOLISM OF THE INTACT DOG

BY

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Cardiac output and coronary blood flow were measured before and after intravenous injection of eledoisin into anaesthetized dogs. The following changes, statistically significant at the 5% level, were found: increase of heart rate, and decreases in systemic and pulmonary arterial blood pressure, cardiac output, stroke volume, and in right and left ventricular work. Coronary flow decreased, cardiac oxygen extraction increased, and cardiac efficiency decreased. Many of these effects are similar to those caused by bacterial endotoxin.

Eledoisin, a polypeptide derived from the salivary glands of a Mediterranean octopus (Erspamer, 1949), causes a fall of arterial pressure in mammals. This compound has been synthesized (Sandrin & Boissonnas, 1962). Eledoisin has been administered to unanaesthetized dogs (Olmsted & Page, 1962) and to man (Sicuteri, Fanciullacci, Franchi & Michelacci, 1963) and is said to dilate the coronary arteries (Bergamaschi & Glässer, 1963). However, no detailed examination of its effect upon the systemic and coronary vascular system has been made. This paper presents the results of experiments in which the effects of synthetic eledoisin were investigated in dogs.

METHODS

Eleven apparently healthy dogs weighing from 9 to 25 kg were given morphine sulphate (3 mg/kg, subcutaneously). After 1 hr, a mixture of pentobarbitone (12.5 mg/kg), allobarbitone (12.5 mg/kg), monoethylthiourea (50 mg/kg) and urethane (50 mg/kg) was injected intravenously. A cuffed tube was placed in the trachea.

The superficial neck veins were isolated and standard cardiac catheters placed therein; under fluoroscopic control, one catheter tip was placed in a main branch of the pulmonary artery, and another in the coronary sinus. The position of the latter was verified by its characteristic X-ray silhouette, and by aspiration through it of blood which was much reduced in oxygen content compared to a sample from the pulmonary artery. A Cournand needle was inserted percutaneously into each femoral artery. Catheters and needles were connected to a manifold system which allowed pressures to be measured, and blood samples taken.

One hour after administration of the intravenous anaesthetic, cardiac output was calculated by the Fick principle from measurements of gas exchange and blood gas concentrations. Expired air was collected from the endotracheal tube into a Tissot spirometer, whence the minute volume was determined. The gas was collected for 5 min, and appropriate blood samples were taken at the midpoint of the collection.

Immediately after the determination of cardiac output, coronary flow was measured by the nitrous oxide saturation method; during this period the animal breathed a gas mixture containing nitrous oxide (15%), oxygen (21%) and nitrogen (64%). Mean coronary flow was estimated over a 10 min period.

Pressures were measured in the pulmonary artery and femoral artery twice during the cardiac output and coronary flow determinations; mean pressures were electrically derived from the strain gauge outputs, and recorded on a direct-writing instrument. Expired air samples were analysed for oxygen and carbon oxide in a Scholander apparatus. Blood samples were analysed for nitrous oxide, oxygen and carbon dioxide in a manometric Van Slyke apparatus: *p*H was measured in a Cambridge instrument. Blood sugar was measured by the glucose oxidase method (Huggett & Nixon, 1957), lactate, pyruvate, and α-ketoglutarate were measured by enzymatic methods (Horn & Bruna, 1956), and sodium and potassium in a flame-photometer. After 30 min from the control measurements of cardiac output and coronary flow, the effect of synthetic eledoisin was examined. Eledoisin (100 μg) was dissolved in 20 ml. of 0.9% saline; sufficient of this solution was injected into a catheter in the superior vena cava to lower the systemic arterial blood pressure to 60% of the control level. The systemic arterial pressure was constantly monitored, and a steady state of hypotension maintained by the intermittent infusion of the eledoisin solution during the measurement of cardiac output and coronary flow; the average total dose was found to be 2 to 3 μg/kg of body weight. The volume of infusate was always less than 20 ml. Initially gasping respirations were seen, so that cardiac output was not measured until 3 min after the initial injection. Thus each animal acted as its own control for each of the parameters measured. The reproducibility of the general methods used has been previously reported (Maxwell, Castillo, Crumpton, Clifford & Rowe, 1959).

TABLE 1

THE EFFECT OF INTRAVENOUS INJECTIONS OF ELEDOISIN ON THE METABOLISM AND HAEMODYNAMICS OF ANAESTHETIZED DOGS

Values are means with standard deviations. Gas volumes are S.P.T.D.

Parameter	Control	During infusion of eledoisin	*P*
Minute volume (l./min)	2·1±0·7	2·6±0·5	<0·05
Respiratory rate (breaths/min)	21±8	23±7	<0·6>0·5
Oxygen consumption (ml./min)	87±24	82±25	<0·3>0·2
Carbon dioxide production (ml./min)	71±7	68±10	<0·5>0·4
Arterial-mixed venous oxygen difference (ml./100 ml.)	3·2±0·7	4·2±1·7	<0·1>0·05
Mixed venous-arterial carbon dioxide difference (ml./100 ml.)	2·5±1·2	3·4±1·4	<0·2>0·1
Cardiac output (l./min)	2·7±0·7	2·0±1·0	<0·05>0·02
Heart rate (beats/min)	93±8	144±33	<0·001
Femoral arterial pressure (mean, mm Hg)	108±11	79±4	<0·001
Pulmonary arterial pressure (mean, mm Hg)	11±3	8·5±1·5	<0·01
Left ventricular work (kg.m/min)	3·9±1·1	2·1±1·4	<0·01
Right ventricular work (kg.m/min)	0·40±0·19	0·23±0·15	<0·01
Total peripheral resistance (c.g.s. units)	3,196±754	3,157±808	<0·3>0·2
Total pulmonary resistance (c.g.s. units)	325±70	339±77	<0·2>0·1

RESULTS

These are presented as group means with standard deviations. Statistical analysis was carried out using Student's *t*-test, and statistical significance was accepted at the 5% level.

Table 1 shows the results for general metabolism and haemodynamics. In addition to the values given, the haemoglobin concentration was increased. This was paralleled by a significant rise in arterial oxygen content (14.2 ± 1.8 to 16.0 ± 2.0 ml./100 ml.), so that arterial saturation was unchanged. The oxygen content of the mixed venous blood did not vary significantly (11 ± 2.0 to 11.8 ± 2.8 ml./100 ml.). The mixed venous carbon dioxide content decreased significantly (56.1 ± 4.5 to 52.5 ± 5.0 ml./100 ml.), as did the arterial carbon dioxide content (53.6 ± 4.1 to 49.1 ± 4.6 ml./100 ml.). It is clear that stroke volume decreased (29 ± 9 to 14 ± 10 ml.) significantly. There was no measurable change in *p*H, or sodium or potassium concentrations. The arterial blood sugar increased significantly (114 ± 30 to 133 ± 46 mg/100 ml.), as did arterial lactate values (6.9 ± 1.5 to 13.2 ± 4.5 mg/100 ml.). The values for arterial pyruvate and α-ketoglutarate were unchanged.

The results for coronary haemodynamics and cardiac oxygen and carbon dioxide exchange are presented in Table 2.

TABLE 2

THE EFFECT OF INTRAVENOUS INJECTIONS OF ELEDOISIN ON THE MYOCARDIAL CIRCULATION AND OXYGEN AND CARBON DIOXIDE EXCHANGE

Values are means with standard deviations. Gas volumes are S.P.T.D. The " index of efficiency " is the ratio of left ventricular work to the cardiac oxygen consumption

Parameter	Control	During infusion of eledoisin	*P*
Coronary blood flow (ml./100 g heart/min)	93±20	72±21	<0·05>0·02
Coronary flow per beat (ml.)	1·0±0·4	0·5±0·3	<0·01
Coronary vascular resistance (arbitrary units)	1·1±0·3	1·1±0·4	<0·6>0·5
Arterial oxygen content (ml./100 ml.)	13·9±2·2	15·7±2·2	<0·02
Coronary sinus oxygen content (ml./100 ml.)	5·7±2·8	4·1±2·2	<0·05
Arterial-coronary sinus oxygen difference (ml./100 ml.)	8·2±2·3	11·6±2·6	<0·01
Coronary sinus carbon dioxide content (ml./100 ml.)	60·7±5·7	56·4±5·4	<0·01
Arterial carbon dioxide content (ml./100 ml.)	53·1±4·4	46·5±4·7	<0·01
Coronary sinus-arterial carbon dioxide difference (ml./100 ml.)	7·6±1·7	9·9±4·3	<0·1>0·05
Cardiac respiratory exchange ratio	0·92±0·02	0·93±0·08	<0·4>0·3
Cardiac oxygen consumption (ml./100 g heart/min)	7·6±1·7	8·3±3·6	<0·4>0·3
Cardiac carbon dioxide output (ml./100 g heart/min)	7·0±2·4	7·2±2·8	<0·4>0·3
" Index of efficiency "	0·54±0·3	0·25±0·20	<0·01

DISCUSSION

In these experiments there was no evidence of the prolonged respiratory stimulation reported in humans given eledoisin (Sicuteri *et al.*, 1963). Olmsted & Page (1962), in another study of conscious dogs, do not comment upon hyperventilation. Accordingly, there appears to be a species difference in this aspect of the activity of eledoisin.

In the present study, the increase in systemic arterial—mixed venous oxygen content difference is the main mathematical determinant of the decrease in cardiac output. The cause of the increase in haemoglobin concentration is not obvious, but the increase may have been due to splenic contraction. The decrease in cardiac output and stroke volume and the hypotension are similar to those found by Olmsted & Page (1962) in conscious dogs given relatively larger doses of eledoisin.

The present discussion then probably relates to a relatively high dosage, although the one employed was chosen only to obtain a steady level of hypotension. The systemic hypotension accords with the findings of authors already cited ; in the present study, there is also a decrease in mean pulmonary arterial pressure.

There is a clear-cut decrease in the work of both ventricles, due as much to the fall in output as to the fall in pressure. These same changes maintain vascular resistance at control values in the greater and lesser circuits. Olmsted & Page (1962) observed a considerable decrease in peripheral resistance in the conscious dog. This result is not greatly in conflict with the present study, as perusal of their results shows a return of peripheral resistance to the control value while cardiac output and systemic blood pressure were still reduced.

The mean coronary flow was reduced. It is felt that this change is physiologically as well as statistically significant. It should, however, be recalled that the present method of measuring coronary blood flow gives results as mean flow/100 g of left heart over a period of 10 min ; during this time a reasonably " steady-state " must be present. It was considered that such a steady state occurred in the present study. It is clear that the method may not always detect rapid changes in coronary flow. It has, however, been shown to parallel other methods of estimating coronary flow, and is the only one which is applicable to the intact animal (Bing, Hellems & Regan, 1960). With these reservations it is still felt that the 22% average reduction in coronary flow cannot be ignored, although this observation could be at variance with the report of coronary vasodilatation by Bergamaschi & Glässer (1963). These authors did their study in an artificially ventilated " open-chest " animal and, while finding coronary vasodilatation, also noted a decrease in coronary flow after intra-arterial injections of large doses of eledoisin.

In the present study the fall in blood pressure parallels the decrease in coronary flow, as in the general systemic circuit, so that calculated coronary vascular resistance was unchanged. The increased cardiac oxygen extraction is balanced by the decrease in coronary blood flow, so that the cardiac metabolic rate for oxygen did not change significantly. Similar observations may be made for cardiac carbon dioxide metabolism. The " index of cardiac efficiency " shown in Table 2 avoids weighing the left ventricle. It does, however, bear a reasonable relationship to " mechanical efficiency " as derived by Joule's law (see Maxwell, Elliott & Kneebone, 1962).

Many pharmacological similarities exist between eledoisin and bradykinin (Stürmer & Berde, 1963). The present study suggests that these are not maintained in the cardiovascular system of the intact dog. Thus, in similarly prepared animals, Maxwell *et al.* (1962) showed that bradykinin increased cardiac output, coronary flow and coronary sinus oxygen content. Bradykinin caused hypotension and tachycardia, but cardiac efficiency was well maintained. These results contrast with those of the present study.

Bacterial endotoxins are, like eledoisin, powerful hypotensive agents. The present results are similar to the effects of endotoxin from *Serratia marcescens* given to similarly prepared dogs (Maxwell, Castillo, Crumpton, Afonso, Clifford & Rowe, 1960). Both agents cause tachycardia, decreased cardiac output and stroke volume, and reduce systemic and pulmonary blood pressure, ventricular works, coronary flow, coronary sinus oxygen content and cardiac efficiency. These similarities seem too numerous to be coincidental. The increase in glucose and lactate noted here may imply interference with cellular metabolism, as occurs with the endotoxin. The evidence on this point is not, however, conclusive.

This investigation offers no evidence that eledoisin is a worth-while coronary vasodilator: its depressant effects, as shown by the present method, are such that it should be used in man with great caution, if at all.

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