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THE CENTRAL ACTION OF LIGNOCAINE AND ITS EFFECT ON CARDIAC OUTPUT

BY

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Fifty-nine tests were performed on twenty-four anaesthetized dogs in a study of the effects of lignocaine on circulatory and respiratory functions. In single-dog experiments, it was shown that lignocaine (1 to 2 mg./kg. body weight) increased ventilation somewhat, but had no effect on O_2 consumption. Cardiac output was increased due to a rise in both heart rate and stroke volume. There was an elevation of arterial blood pressure. The central blood volume was increased, but central venous pressure, total peripheral resistance and the ventilation-perfusion ratio were decreased. The increase in cardiac output after lignocaine was abolished both in decerebrate and in vagotomized dogs. In cross-circulation experiments with dogs, it was demonstrated that the primary site of action of lignocaine on cardiac output was central. The effect of lignocaine on cardiac output could be blocked by intravenous procaine.

Lignocaine increases the arterial blood pressure in man (Kimmey and Steinhaus, 1959) and in dogs (Carden and Steinhaus, 1956) when the dose is limited to 1 to 2 mg./kg. body weight. This effect differs from that of procaine, which decreases arterial blood pressure (Edmonds, Comer, Kennedy, and Taylor, 1949). How lignocaine produces this rise in blood pressure has not been explained. Possible mechanisms include: (1) a peripheral action on the heart or the blood vessels or both; and (2) a direct action on the brain, spinal cord or other elements of the nervous system. It was thought that these possible mechanisms might be analysed in decerebration experiments (in which central effects might be abolished) and in cross-circulation experiments (with central and peripheral effects isolated physiologically).

This paper is a report of an investigation of these possibilities. Special attention was paid to changes in cardiac output due to lignocaine.

METHODS

Fifty-nine experiments were performed on twenty-four mongrel dogs of both sexes, weighing 9 to 21 kg. and anaesthetized with either pentobarbitone sodium (30 mg./kg., body weight, intravenously) or a chloralose and urethane mixture (50 and 500 mg./kg. respectively). In decerebration experiments the midbrain was transected (Kao, Schlig, and Brooks, 1955) under thiopentone sodium (25 mg./kg.) anaesthesia.

For cross-circulation experiments, dogs of similar weight were selected. The head of the recipient dog was perfused exclusively by blood from a second dog, the donor. This preparation is depicted in Fig. 1. The technique and its validity have been discussed previously (Kao, 1956; Harmel, King, and Kao, 1958). In brief, the head of the recipient was supplied through its carotid arteries by blood (from the donor's common carotids) which was drained back to the donor by external jugular veins of the recipient. The vertebral arteries of the donor dog supplied its own head, but the vertebral arteries of the recipient dog were tied.

A tracheal cannula was inserted in each dog and connected to a Benedict-Roth spirometer which was filled with pure O_2 and arranged for continuous recording of tidal volume, respiratory rate and O_2 consumption.

In single-dog experiments, a catheter (internal diameter 0.085 in.; external diameter 0.128 in.) was inserted into one of the common carotid arteries and arterial blood pressure measured by means of a mercury manometer or a Statham strain-gauge. Pressure changes were monitored by a Sanborn Recorder. Usually in cross-circulation experiments the femoral arterial blood pressure of the donor dog was registered with a mercury manometer while femoral arterial blood pressure of the recipient dog was recorded by means of a transducer and the Sanborn Recorder. Heart rate was monitored continuously by a Lead I electrocardiogram.

Cardiac output was determined by the dye-dilution technique. Cardiogreen (2.13 mg.) was delivered through a BD 442T catheter to the right atrium and the dye concentration in the arterial blood was

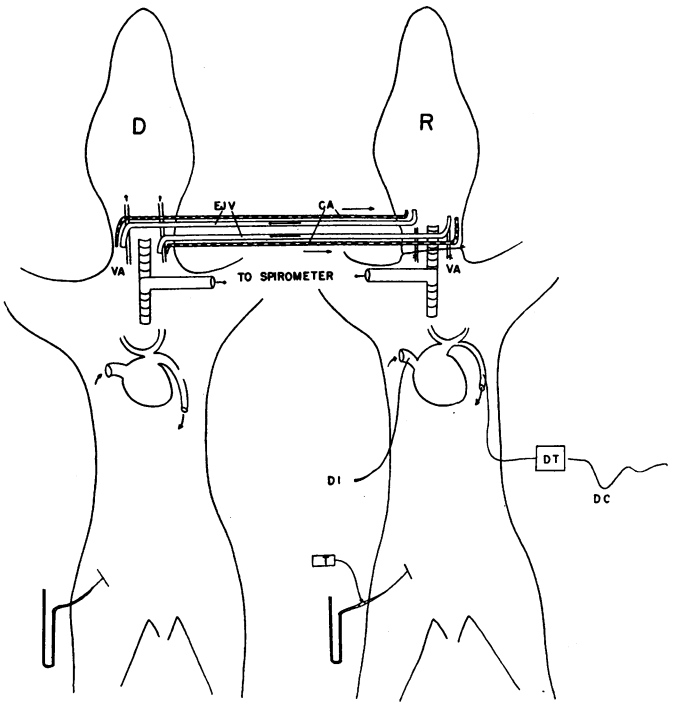

FIG. 1.—Diagram of the arrangement for cross-circulation experiments. D, donor dog; R, recipient dog. VA, vertebral artery; EJV, external jugular vein; CA, carotid artery; DI, site of dye injection; DT, densitometer; DC, dye curve; →, direction of blood flow.

continuously monitored through a Colson densitometer and recorded on a Sanborn Recorder. A catheter (internal diameter 0.106 in.; external diameter 0.138 in.) was introduced into the femoral artery and passed into the aortic arch for sampling the arterial dye concentration. In cross-circulation experiments only the cardiac output of the recipient dog was measured.

Additional experiments were performed in dogs with bilateral cervical vagotomy and in dogs after the administration of procaine (1 to 2 mg./kg.) to determine the effect of procaine alone and its blocking action on lignocaine.

Central blood volume was calculated by multiplying the circulation time in sec. and the cardiac output in ml./sec. The volume thus obtained is actually the blood volume by which the dye is diluted between the site of dye delivery and the site of dye sampling. This volume is somewhat greater than the true pulmonary blood volume. A change in central blood volume, however, reflects that of the pulmonary circulation, since any change in heart chamber volume is very small in comparison with the volume of the pulmonary vascular bed and since the amount of blood in the aortic arch can undergo no significant change.

The total peripheral resistance was calculated by employing the following conventional formula: total peripheral resistance = (arterial blood pressure − central venous pressure) × 1,332/cardiac output. Pressures were expressed in mm. Hg, and cardiac output in ml./sec. Total peripheral resistance was expressed in dyne-sec./cm.[5]

Biometrical analyses were as described by Snedecor (1946). All drugs were injected intravenously unless otherwise stated.

RESULTS

Effect of Lignocaine on Ventilation and O_2 Consumption

Since a change in O_2 consumption affects cardiac output (Kao and Ray, 1954) it seemed necessary to determine whether lignocaine increased O_2 consumption. O_2 consumption and ventilatory values before and after injection of lignocaine (1 mg./kg.) are shown in Table IA. The average increase in O_2 consumption (2.8 ml./min.) following lignocaine was not significant statistically; the total ventilation, however, increased from an average of 2.991 to 3.419 l./min. (difference, 0.422 l./min., $P<0.01$) though the change lasted only a few minutes. Maximal values were used for this part of the analysis.

Effect of Lignocaine on Cardiac Output and Peripheral Circulation

Cardiac output increased in the first minute after the injection of lignocaine. The maximal effect was attained within 10 min. and the increment lasted 40 min. Arterial blood pressure followed the same general course as the cardiac output, rising to a peak value during the first 10 min. and then declining gradually in the subsequent 30 min.

The various circulatory effects of lignocaine are shown in Table IB. In brief, lignocaine caused an increase in cardiac output by increasing both heart rate and stroke volume, but produced no change in O_2 consumption; thus the circulatory equivalent for O_2 (Kao and Ray, 1954) increased. This signifies that for each unit of O_2 demand made by body tissues, blood flow was available to supply this O_2. Arterial blood pressure was elevated by 11.3 mm. Hg, while the central venous pressure was not decreased significantly. The total peripheral resistance also decreased, which implied that there was a peripheral vasodilatation.

TABLE I

ACTIONS OF LIGNOCAINE (1·0 MG./KG., INTRAVENOUSLY)

The results are means of eight control and lignocaine-treated dogs (n=8). O_2 consumption is expressed at standard temperature and pressure, dry; tidal volume and total ventilation are expressed at body temperature and pressure, saturated.

Variables	Control	Lignocaine-treated	Mean Difference	t	P
A. O_2 consumption and ventilatory values					
O_2 consumption (ml./min.) ..	97·1	99·9	2·80	1·5873	<0·15
Respiration rate (breaths/min.) ..	15·5	18·4	2·9	1·0324	>0·30
Tidal vol. (ml.) ..	230·3	244·8	14·5	1·0469	>0·30
Total vent. (l./min.)	2·991	3·419	0·422	2·8691	<0·01
B. Circulatory responses					
Cardiac output (l./min.) ..	2·514	3·415	0·901	6·8854	<0.01
Heart rate (beats/min.) ..	139·5	158·1	18·6	3·2871	<0·01
Stroke vol. (ml.) ..	18·775	21·938	3·163	3·4117	<0·01
Arterial blood pressure (mm.Hg)	134·5	145·8	11·3	5·2055	<0·01
Central venous pressure (cm.H_2O)	4·88	4·63	−0·25	0·1517	>0·50
Total peripheral resistance (dyne-sec./cm.^{5})	4,368·8	3,442·5	−926·3	3·7651	<0·01
Central blood volume (ml.) ..	308·0	397·4	89·4	5·6312	<0·01
Ventilation-perfusion ratio	1·206	0·996	−0·210	4·2955	<0·01

It is interesting also to note that the central blood volume increased significantly, which means that a dilatation of the pulmonary vessels occurred, a process that is advantageous to the gas exchange in the lungs. Since the ventilation increased little compared to cardiac output, the ventilation-perfusion ratio (ventilation in l./min./cardiac output in l./min.) decreased.

Fig. 2 illustrates quantitatively the effect of lignocaine on cardiac output. The maximal response was obtained when the dose of lignocaine was about 1.5 mg./kg. Above this dosage, the rise in cardiac output was definitely smaller.

Lignocaine in Vagotomized Dogs

Eight experiments were performed on vagotomized dogs. Following bilateral cervical vagotomy, cardiac output increased in association with an elevation of arterial blood pressure to 145 to 180 mm. Hg and a rise in heart rate to 125 to 195 beats/min. When very small doses of lignocaine were given there was little further increment in cardiac output, and when the lignocaine dosage was increased cardiac output actually decreased (Fig. 3). This fall was due to a decrease in stroke volume since heart rate was increased significantly following all doses of lignocaine. Arterial blood pressure and the total peripheral resistance also decreased below the post-vagotomy level after large doses of lignocaine. Such falls did not follow similar doses of lignocaine before the vagi were cut.

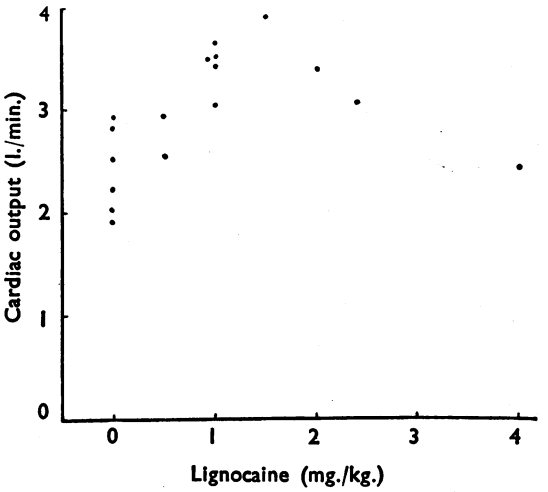

FIG. 2.—The relation between cardiac output and dose of lignocaine in intact dogs.

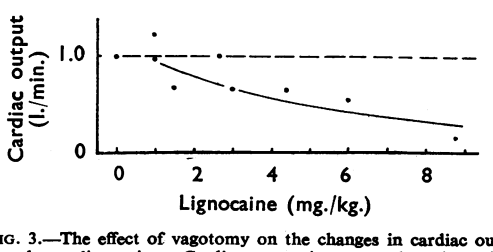

FIG. 3.—The effect of vagotomy on the changes in cardiac output due to lignocaine. Cardiac output is expressed as the ratio of values before and after various doses of lignocaine.

Lignocaine in Decerebrate Dogs

After midbrain transection, respiratory and circulatory adjustments are adequate even during muscular activity (Kao *et al.*, 1955). In the present series of experiments arterial blood pressure was sustained at a constant and usually a normal value following transection of the midbrain.

When lignocaine was given to these dogs even in small doses cardiac output was invariably decreased (Fig. 4). The fact that after midbrain transection and vagotomy lignocaine did not augment cardiac output suggests a central action of the drug. It was thought, however, that the drastic procedures employed might have masked any reaction. Therefore the cross-circulation technique was employed to test the hypothetical central action of the drug.

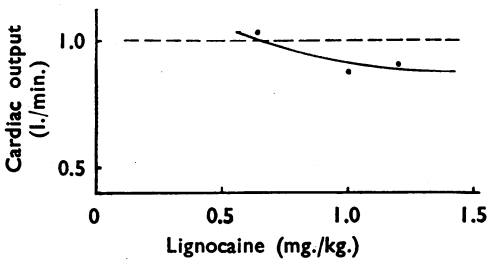

FIG. 4.—The effect of decerebration on changes in cardiac output due to lignocaine. Ordinate and abscissa as in Fig. 3.

Lignocaine in Cross-circulation Experiments

Twenty tests were carried out in four pairs of dogs with cross-circulations. When lignocaine was injected into the body of the recipient dog there was no change in cardiac output of the recipient dog (Fig. 5). This made it quite clear that lignocaine had no peripheral effect on the circulation. It is important to note that this finding constitutes further evidence that there was no appreciable blood supply to the head of the recipient dog from its own body. When lignocaine was injected into the blood supplying the recipient's head, the cardiac output of the recipient dog did increase. This effect was either markedly diminished or abolished after bilateral vagotomy in the recipient dog (Fig. 5).

Lignocaine in Procainized Dogs

Twenty tests were performed on six dogs into which various doses of procaine (0.3 to 2.0 mg./kg.) had first been injected. These doses of procaine had no observable effect on cardiac output or the peripheral circulation. But, when lignocaine (1 mg./kg.) was given to these dogs after treatment with procaine, the cardiac responses varied as a function of the amount of procaine employed. This is shown in Fig. 6. It can be seen that, when the procaine dose reached 1 mg./kg., the effect of lignocaine on cardiac output was abolished. After smaller doses of procaine lignocaine still caused some rise in cardiac output.

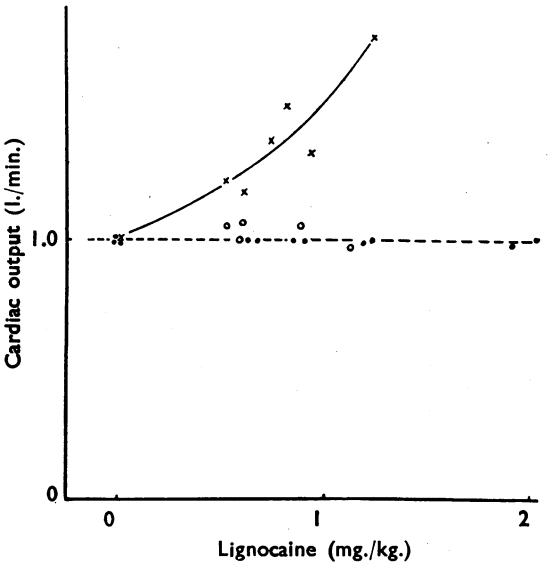

FIG. 5.—Cross-circulation experiments. The effects of lignocaine on the cardiac output of the recipient dog (expressed as in Fig. 3). Lignocaine was injected into the circulation of the recipient's head with vagi intact (X) and after vagotomy (O). There was no effect when lignocaine was injected into the recipient's body (●).

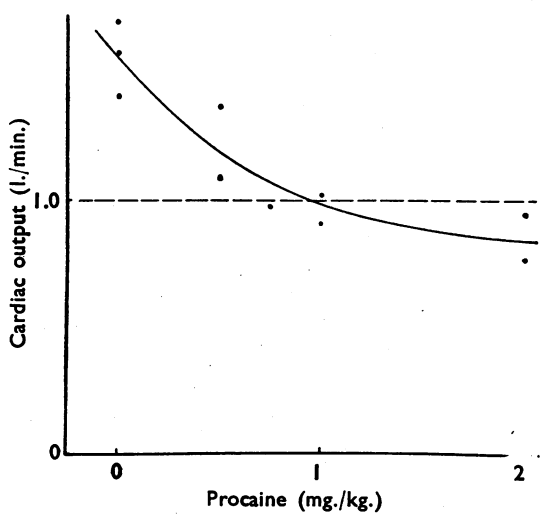

FIG. 6.—Effects of graded doses of procaine on the action of lignocaine (1 mg./kg.) on cardiac output (as expressed in Fig. 3).

DISCUSSION

Lignocaine possesses a variety of actions in mammals including man. Early studies were focused mainly on its local anaesthetic effect (Goldberg, 1949; Gordh, 1948; Wiedling, 1952). Kimmey and Steinhaus (1959) demonstrated that lignocaine raised the arterial blood pressure when

the intravenous dose was limited to 1 to 2 mg./kg. The mechanism of this effect was not explained. From the present study it seems clear that lignocaine has multiple effects on the circulation, and the elevation of arterial blood pressure is but one of them.

Lignocaine caused a peripheral vasodilatation, but the central venous pressure did not increase. This suggests that the increase in arterial blood pressure is due primarily to an increased contractile force of the heart or to an increased cardiac output not related to the peripheral vasodilatation. Our results show that lignocaine increases cardiac output by acting not on the heart directly but on the brain.

The exact site of this action in the brain has yet to be determined. It is evident, however, that both sympathetic and vagal pathways are involved. The rise in cardiac output is due to an increase both in stroke volume and heart rate. The increase in heart rate is probably due to sympathetic stimulation and the increment in stroke volume does not occur after vagotomy. It seems justifiable to state that lignocaine acts on autonomic areas in the central nervous system.

In view of the fact that lignocaine provokes a peripheral vasodilatation, a pulmonary vasodilatation and an increase in cardiac output, gas exchange in the body is enhanced. It may, therefore, be inferred that lignocaine might be useful in dealing with certain cardiac and circulatory disturbances.

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