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THE EFFECTS OF DIGOXIN AND OUABAIN ON THE HEART-LUNG PREPARATION OF THE DOG

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From the beginning of experimental pharmacology in the nineteenth century, much attention has been paid to the action of the digitalis glycosides by observers such as Schmiedeberg, Gottlieb, and Cushny, in an endeavour to determine their action in heart failure. They agreed that all digitalis glycosides act on the heart itself, and in consequence they called them cardiac glycosides. Since the work of Harrison and Leonard in 1926 a series of observations has been made which has been taken to indicate that the main action of digitalis is not on the heart but elsewhere in the body. This action is such that a fall in pressure occurs in the right auricle believed to be due to diminished venous return. This, it has been suggested, would produce beneficial effects in a manner similar to venesection. McMichael has been a notable exponent of this view, he and his colleagues having made many observations in man by the method of right heart catheterization. In a lecture given two years ago (McMichael, 1948) he described observations on the effect of *g*-strophanthin, or ouabain, which differed from those he had previously made when using digoxin. He concluded from these that ouabain in fact exerted "a direct stimulating action on the human heart in certain cases of failure," which "can be seen in some instances to be independent of any significant venous-pressure-reducing effect." He considered, however, that "so far as digoxin is concerned it is the venous-pressure-reducing effect which predominates," and that a direct stimulant action on the heart plays a much less important part.

When previous work is consulted, it is found that experimental observations on cardiac output have been made with ouabain, and none have been made with digoxin. In pharmacological teaching it has been usual to assume that both substances act alike, and to say that, because ouabain can stimulate cardiac muscle, digoxin can do the same. In view of McMichael's work we felt that it was right to investigate whether the assumption was justified, and we therefore undertook the investigation now to be described. We have used the Starling heart-lung preparation of the dog and have investigated the effect of ouabain and digoxin when the heart was failing, taking as an indication of failure a steady fall in the cardiac output. One series of experiments was performed in which ouabain was injected and a second series was performed in which digoxin was injected.

METHODS

Heart-lung preparations were made in the usual way under chloralose anaesthesia, heparin being used as the anticoagulant. The mixture for artificial respiration consisted of 95 per cent O_2 and 5 per cent CO_2; 0.05 unit insulin and 100 mg. glucose were added to the circulating blood at 20 minute intervals throughout the course of each experiment. In some experiments the right auricular pressure was recorded by a water manometer attached to a cannula inserted into the inferior vena cava. In others the outflow from the coronary sinus was obtained by means of a Morawitz cannula. The way in which the heart was damaged varied. In some experiments thiopentone or pentobarbitone was added to the blood in the venous reservoir. This addition was continuous until the end of the experiment, so that any improvement observed after the glycoside injection must have been due to the injection and not to a lessening of the barbiturate effect. In other experiments the preparation was allowed to deteriorate spontaneously, the process usually being accelerated by providing a high peripheral resistance or by raising the venous reservoir, within which the level of blood was kept constant by an overflow tube and pump, as in the work of Bülbring, Burn, and Walker (1949). Doses of digoxin or ouabain were injected into the rubber tube leading to the superior vena cava.

RESULTS

Experiments with ouabain.—The result of an experiment with ouabain is shown graphically in Fig. 1. The upper record is that of the cardiac output directly

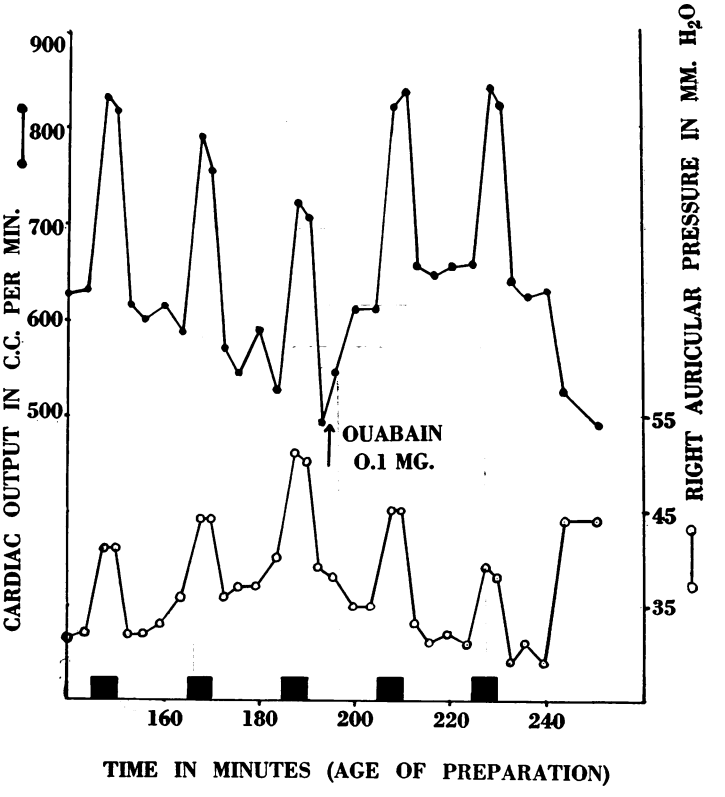

FIG. 1 (Exp. 5).—Upper graph shows cardiac output in c.c./min. changing with the age of the preparation. Lower graph shows the right auricular pressure in mm. H_2O. Thiopentone was added to the venous reservoir at a uniform rate throughout the experiment. The venous reservoir was raised during the periods shown by the black squares. Note the steady fall in output and rise in right auricular pressure before the injection of 0.1 mg. ouabain. Note the increase of output and fall in right auricular pressure after the injection of ouabain.

measured in 10 second periods and the lower record is that of the right auricular pressure in mm. H_2O, both records beginning when the preparation had already been working for 2 hours 20 minutes. For periods of 5 minutes, indicated by the black squares along the abscissa, the venous reservoir was raised by 3 cm., so that there was increased venous inflow to the heart and in consequence a rise in cardiac output. Failure was produced in this experiment by the addition of thiopentone (Pentothal) to the venous reservoir at a uniform rate. A total of 66 mg. was added during 96 minutes previous to the injection of ouabain, and the addition continued at the same rate during the remainder of the experiment. In consequence the cardiac output (as measured with the venous reservoir in the lower position) fell from 625 c.c. per minute at the beginning of Fig. 1 to 492 c.c. per minute at a time 49 minutes later. Ouabain was injected in the amount of 0.1 mg., and since the volume of blood in circulation was one litre the injection was equivalent to the injection of 0.5 mg. ouabain into a man with five litres of blood.

The effect of the ouabain in increasing the cardiac output and decreasing the right auricular pressure is clearly shown in the Figure; with the venous reservoir in the lower position, the cardiac output rose from 492 to 650 c.c. per minute in 20 minutes and was maintained at about this level for a further 20 minutes. During this 40 minute period the right auricular pressure fell from 39 to 29 mm. Likewise if the cardiac output is considered when the venous reservoir was in the higher position, the maximum output was 702 c.c. per minute before the injection of ouabain, and 840 c.c. after the injection.

These figures, however, do not represent the whole effect of the ouabain. As can be seen by careful inspection of Fig. 1, the cardiac output was falling steadily during the 40 minutes prior to the injection. If the injection had not been given

TABLE I

RESULTS WITH OUABAIN

Exp.	Dose (mg.)	Output c.c./min. increased		Time after injection (min.)	Per cent increase	Mean increase
		From	To			
1	0.15	225	430	18	91	91
2	0.15	395	540	10	36	28
		320	390	24	21	
3	0.1	305	375	4	23	37
		235	355	19	51	
4	0.1	320	350	14	9	9
5	0.1	425	655	20	54	73
		385	665	30	73	
		330	630	46	91	
6	0.1	375	470	25	25	25
7	0.1	520	605	12	16	14
		495	535	24	8	
		460	540	33	17	
8	0.1	240	300	6	25	25
9	0.1	453	530	5	17	17
10	0.2	366	485	15	32	35
		325	450	24	38	
11	0.1	450	560	28	24	24
12	0.1	710	790	3	11	11

it is reasonable to assume that the output would have continued to fall at a rate not less than that before injection ; since thiopentone was accumulating in the blood it is probable that the rate of fall would have been greater. However, assuming the same rate of fall, it is possible to obtain an approximate estimate of what the output would have been without the injection of ouabain by drawing a line through the points for the output before the injection (taking those when the venous reservoir was in the lower position) and continuing it to the right. By extrapolating in this way through the points in Fig. 1 recorded during 33 minutes before the injection an output of 330 c.c./min. is obtained 46 minutes after the injection, when the output actually observed was 630 c.c./min. Thus at that point it can be said that the output was 91 per cent greater than if ouabain had not been given.

Results for all the experiments with ouabain have been calculated in this way and are given in Table I. For many of the experiments more than one calculation has been made at different times after the injection. The percentage increase in the output is shown for each calculation, and the mean increase for each experiment is shown in the last column. It is clear that the quantitative expression of the action of ouabain thus obtained can be only approximate because of the uncertainty inherent in extrapolation. However, in no experiment either with ouabain or with digoxin was there doubt of the direction of the extrapolation. Thus it was possible to obtain figures for the effects of ouabain and for those of digoxin in order to see if they were of a similar order of magnitude.

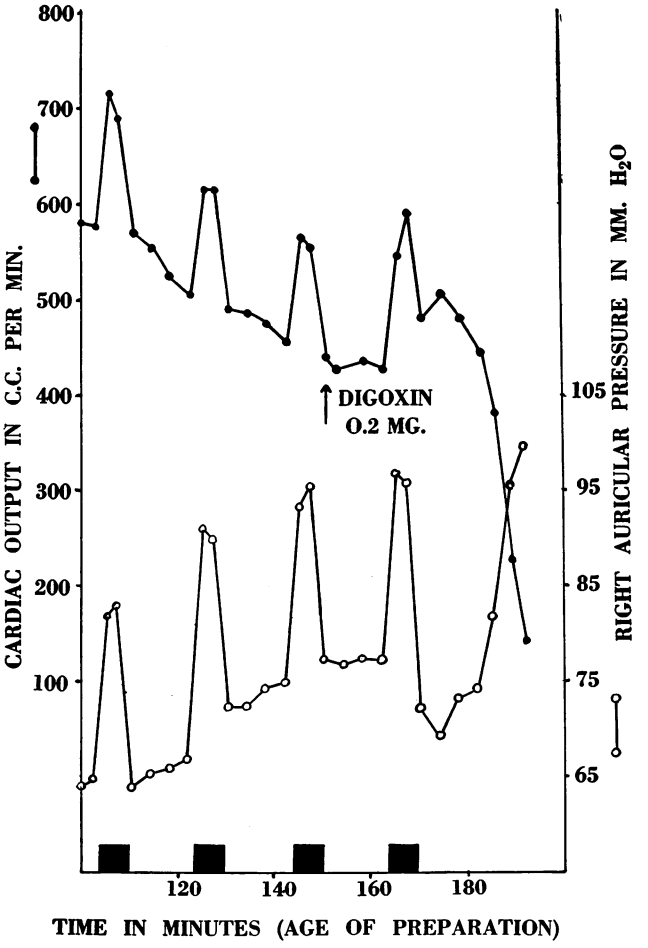

FIG. 2 (Exp. 20).—A similar record to that in Fig. 1 showing the effect of digoxin in increasing the output and reducing the right auricular pressure. The dose of digoxin was equivalent to only half that of ouabain used in Fig. 1.

Experiments with digoxin.—Experiments were carried out in a precisely similar manner with digoxin, and on the whole similar results were obtained. The dose of digoxin injected was 0.2 mg. in all save one experiment, and in comparison with the dose of ouabain used this was too small, as will be discussed later. Fig. 2 is a record of an experiment similar to that of Fig. 1, though the effect of the digoxin was less prolonged than that of the ouabain. At the beginning of the record the preparation had been working for 100 minutes, and the cardiac output was falling because of the addition of thiopentone to the venous reservoir. During 123 minutes before the injection of digoxin, 44 mg. thiopentone was added. As Fig. 2 shows, the cardiac output (measured with the venous reservoir in the lower position) fell from 580 c.c./min. to 438 c.c./min. at an almost uniform rate during 47 minutes. When digoxin was injected the output slowly rose to a figure of 504 c.c./min. 24 minutes later. Similarly, the right auricular pressure, which had been steadily rising in the 47 minutes before injection from 64 to 78 mm. H_2O, fell after injection to 69 mm. at the point of maximum output. The injection of digoxin maintained the output above the value at the time of injection for 35 minutes, after which the preparation failed rapidly, owing to the thiopentone which was still being added to the reservoir.

Other examples of the effect of digoxin in increasing the cardiac output are shown in Figs. 3 and 4. In both of these the venous reservoir had been raised to such a height that the cardiac output at the beginning of the two records was 1,000 c.c. and 1,100 c.c. per minute respectively. With thiopentone infusion this output at first fell steeply and then less steeply, the rate of fall becoming approximately linear. Digoxin was then injected in a dose of 0.2 mg., after which the output rose and was

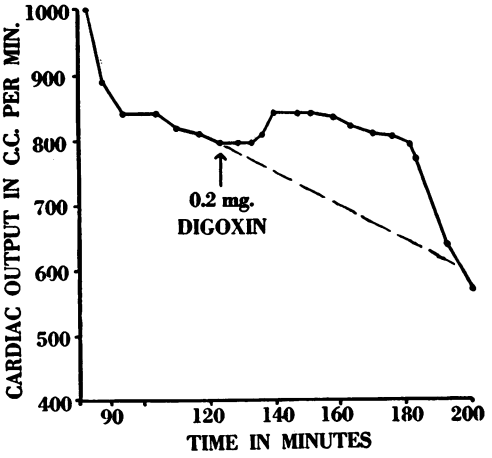

FIG. 3 (Exp. 13).—Cardiac output c.c./min. falling as time goes on under the influence of thiopentone infusion. The venous reservoir was previously raised so that the output was high, but it fell rapidly at first and then more slowly. 0.2 mg. digoxin was then injected.

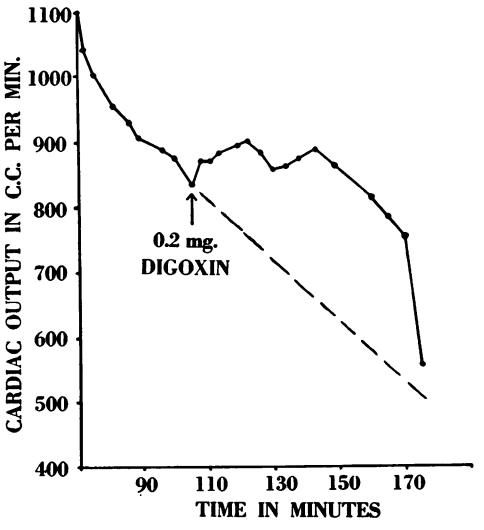

FIG. 4 (Exp. 16).—Another experiment similar to that in Fig. 3.

TABLE II

RESULTS WITH DIGOXIN

Exp.	Dose (mg.)	Output c.c./min. increased		Time after injection (min.)	Per cent increase	Mean increase
		From	To			
13	0.2	750	840	16	12	17
		653	795	58	22	
15	0.2	894	906	8	1	1
16	0.2	745	900	16	21	38
		635	885	37	39	
		490	755	64	54	
17	0.2	630	890	4	41	41
18	0.2	1,055	1,165	14	10	9
		1,040	1,122	23	8	
19	0.2	683	755	8	10	11
		630	705	15	12	
20	0.2	365	505	23	38	36
		350	470	28	34	
21	0.4	150	270	18	80	80
22	0.2	335	372	16	11	11

maintained above the level at injection for one hour in Fig. 3 and for 45 minutes in Fig. 4. The effect of the injection on the cardiac output is shown by the difference between the recorded output and the dotted line showing the expected output in the absence of digoxin.

The results in the experiments with digoxin are set out in Table II, drawn up in the same way as Table I, and they resemble the results in Table I quite closely. Of the nine experiments in Table II, four show that digoxin produced a good increase in output, and four that it produced a moderate increase of about 10 per cent. The results indicate that the effect of digoxin on the cardiac output was substantially similar to that of ouabain, and that both exerted a stimulant action on the heart muscle.

TABLE III

DURATION OF EFFECT (MIN.)

Ouabain		Digoxin	
Exp. 1	52	Exp. 13	58
2	26	15	10
3	more than 23	16	65
4	19	17	9
5	more than 71	18	34
6	40	19	15
7	44	20	33
8	more than 23	21	more than 40
9	15	22	20
10	60		
11	more than 46		
12	6		
Mean	35	Mean	31

Duration of effect.—Table III shows the duration of the action in minutes of the ouabain or digoxin given in each experiment. The period was calculated from the injection to the point on the output record at which a rapid drop set in. Thus in the experiments shown in Figs. 1–4, the duration was taken as (1) more than 71 minutes, (2) 33 minutes, (3) 58 minutes, and (4) 65 minutes. The mean duration for ouabain was 35 minutes and 31 minutes for digoxin, but the results for ouabain include four of which it can only be said that the duration of action exceeded a certain time, and therefore the actual duration of the ouabain effect probably exceeded that of the digoxin effect by more than the difference in the means.

Discussion

Observations on the heart-lung preparation with digitalis or its glycosides have been made by Bodo (1928), Gremels (1933), and Cohn and Steele (1932). Bodo did not record the changes in output, but instead he recorded the changes in cardiac volume. He found that the addition of digitalis tincture or of digitalis infusion to the system diminished the cardiac volume, but without altering the difference between the diastolic and systolic volumes. From this observation he concluded that digitalis exerted a tonic effect on the ventricles, so that they worked at a shorter length of fibre, but maintained the same output per beat.

Gremels investigated the action of lanadigin, which like digoxin is a pure glycoside from *Digitalis lanata.* He observed that in a heart-lung preparation which was spontaneously deteriorating, the addition of lanadigin diminished the oxygen uptake while the output rose slightly ; thus lanadigin increased the efficiency, since more work was done with a smaller expenditure of energy.

Cohn and Steele (1932) determined the effect of digitan on the output in 23 heart-lung preparations. Using a dose of 0.02 g./kg. they observed an increase in output in 16 experiments. In one experiment the output rose from 230 to 360 c.c./min. within 10 minutes, and then to 620 c.c./min. after 10 minutes more ; after another 20 minutes, the output fell to 500 c.c./min. They observed corresponding changes in the right auricular pressure, which fell when the output rose.

In the experiments described in this paper, digoxin acted like ouabain and caused an increase in the output of the failing heart. The effects observed were of the same order of magnitude, although the doses were dissimilar, namely, 0.2 mg. for digoxin and 0.1 mg. for ouabain. In B.P. 1948 the maximum intravenous dose of ouabain is 0.25 mg. and the corresponding dose of digoxin is 1.0 mg. Moreover, White (1934) found that in both the frog and the cat the toxicity of ouabain was four times as great as that of digoxin. Therefore we might well have used twice the dose of digoxin. Since the blood volume was always about 1 litre, the injection of 0.2 mg. digoxin may be regarded as equivalent to the injection of 1 mg. in man. Since 0.25 mg. ouabain is injected in man, the corresponding dose for the heart-lung preparation would have been 0.05 mg. In spite of the relatively low dose of digoxin there was evidence in almost every experiment that the cardiac muscle was stimulated with the result that the output rose. Hence the conclusion can be drawn that there is no more reason to suspect an extra-cardiac site of action for digoxin than there is for ouabain.

What is then to be said of McMichael's different conclusion that while the main effect of ouabain is on the heart, that of digoxin is due to a reduction of venous pressure by an extra-cardiac action ? In his lecture (McMichael, 1948) he illustrates the effect of ouabain by a record from a patient who received 1 mg. by intravenous injection, and the effect of digoxin by two records in each of which 1.5 mg. was given. It is certainly true that the dose of digoxin was too small for a proper comparison of the two drugs. It is fair to suggest that had McMichael used 4 mg. digoxin as a single dose, he might have observed just as striking an effect on cardiac output and work as he did with 1 mg. ouabain.

In discussing the action of digoxin, McMichael divides patients with heart failure into two classes—those with high output, e.g., patients with anaemia and emphysema, and those with a low output as in valvular disease. Several patients with heart failure in lung disease have been investigated by Howarth, McMichael, and Sharpey-Schafer (1948). In five of these the intravenous injection of digoxin resulted in a fall of right auricular pressure; the cardiac output rose in two of these, and fell in the other three. Fig. 2 of their paper records the effect of digoxin in one patient with heart failure due to emphysema in whom the cardiac output fell from 6.46 to 4.2 litres per minute in 7 minutes after the injection. So rapid and so great a fall is most difficult to understand, and we are led to wonder whether the method of determining the cardiac output is reliable in such a case. In using the Fick equation Bayliss and McMichael (1950) say that the measurement of oxygen uptake is not made simultaneously with the withdrawal of the mixed venous sample of blood, but that it is done at the beginning of the observations, and they state that this is justified because when the oxygen uptake is redetermined at the end of the experiment the coefficient of variation has been found to be ± 5 per cent. This may be true for normal subjects, but it may not be true for patients in heart failure due to emphysema. We are therefore inclined to doubt whether the fall in cardiac output of over 2 litres per minute, which the method indicated to have occurred 7 minutes after injection, actually took place.

Recently Wood and Paulett (1949) have investigated the action of digoxin, by methods similar to those used by McMichael, in four patients with congestive heart failure with normal rhythm, and in twelve patients in whom the venous pressure was raised because of anaemia, thyrotoxicosis, acute nephritis, artificial hydraemia, and chronic constrictive pericarditis. In the patients with heart failure the injection of 1.5 mg. digoxin caused a fall in right auricular pressure and a rise in output, but in the other patients who had no heart failure the injection had no effect on the right auricular pressure in 40 minutes. In some the cardiac output fell, but this was attributed to the fall in pulse rate. Wood and Paulett conclude that digoxin in doses of 1.5 mg. intravenously does not primarily lower the venous pressure and suggest that its effect on the venous pressure in congestive heart failure " may yet depend upon its direct action on the heart, as originally believed."

We have now shown in experiments on the failing heart of the heart-lung preparation that digoxin does stimulate the heart in the same manner as ouabain. It therefore appears to us reasonable to suppose that digoxin acts in heart failure as the digitalis glycosides have long been considered to act, namely, as direct stimulants of heart muscle.

SUMMARY

A comparison has been made of the effects of ouabain and digoxin in the heart-lung preparation of the dog. The work was undertaken because of the conclusions reached by some workers that, while ouabain acts as a direct cardiac stimulant, the effect of digoxin is different. It has been suggested that the action of digoxin is not on the heart, but is primarily concerned with a reduction of venous pressure. Hitherto no observations have been published with digoxin in the heart-lung preparation, and indeed very few observations have been made with any digitalis preparation. We have compared digoxin and ouabain and have observed in the failing heart-lung preparation that both these glycosides stimulate the heart and raise the cardiac output in a similar way.

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