A COMPARATIVE STUDY ON SOME PHARMACOLOGICAL EFFECTS OF DIGITOXIN, ACETYLDIGITOXIN AND GITALIN (AMORPHOUS) IN CATS

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Received February 17, 1958

The lethal doses of digitoxin, acetyldigitoxin and gitalin were determined in cats. Electrocardiograms were recorded intermittently during the course of the repeated injections of these glycosides. Their relative lethal activities in cats were found to be similar to the reported relative therapeutic activities in man. Gitalin was found to be significantly more liable to cause cardiac arrhythmias than the other two glycosides.

IT is generally known that the therapeutic indices of various cardiac glycosides are essentially identical although the absolute activities are different[1–4]. More recently, however, a number of investigators[5,6] have reached the conclusion from clinical experience that gitalin (amorphous) has a greater therapeutic index than the other cardiac glycosides. Whether this reported difference in the therapeutic index can be demonstrated in experimental animals, was herein examined.

METHODS

The lethal doses of digitoxin, acetyldigitoxin and gitalin were determined in adult healthy cats weighing 1·8 to 3·5 kg. The procedure was similar to the assay for digitoxin described in the U.S. Pharmacopoeia XIII. In brief, the glycoside, in solution, was given intravenously at a rate of 1 ml./kg. every 5 minutes. The concentration of the solution was such that the cat would die after receiving 13 to 19 injections of the glycoside. A total of 14 cats were used for each glycoside. During the course of the experiments, electrocardiograms (Lead II) of these cats were recorded before each injection. The digitoxin was a sample of the U.S.P. Reference Standard, and the acetyldigitoxin and gitalin were supplied by Sandoz Ltd., and White Laboratories, respectively.

RESULTS

The mean lethal dose in mg./kg. and its standard error were calculated for each glycoside from the concentration of the solution and the number of injections used. The results are listed in Table I. The figures in parentheses are quoted from Rothlin and others[7]. The relative lethal activities were computed from the mean lethal doses, the activities of acetyldigitoxin and gitalin being expressed in percentages in terms of digitoxin. While the lethal doses of digitoxin and acetyldigitoxin determined by Rothlin and others appear to be appreciably smaller than our figures, the relative activities of these two glycosides ascertained from their data are in good agreement with ours.

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For comparative purposes, the relative therapeutic activities of these glycosides are also listed in Table I. According to the data of Willems[8], acetyldigitoxin has 80 or 93 per cent of the activity of digitoxin depending on the rate of digitalization, and from Batterman and others[5] gitalin has 42·8 per cent of the activity of digitoxin. The relative lethal activities of

TABLE I

THE RELATIVE ACTIVITY OF SOME CARDIAC GLYCOSIDES

Glycoside	Lethal dose*	Relative lethal activity in cats per cent	Relative therapeutic activity in man per cent
Digitoxin	0·463 ± 0·014 (0·386)	100·0	100·0
Acetyl-digitoxin	0·556 ± 0·015 (0·447)	82·2 (86·4)	80·0† 93·0†
Gitalin	1·154 ± 0·033	39·6	42·8‡

Figures in parentheses are quoted from Rothlin and others[7].

* Mean ± S.E., in mg./kg.
† From data reported by Willems[8].
‡ From data reported by Batterman and others[5].

these three glycosides in cats are similar to their relative therapeutic activities in man.

As expected, a variety of changes was observed in the ECG. Since the control heart rates of the cats differed considerably, in order to increase the precision of the result, the chronotropic effects of these glycosides were expressed as changes in heart rate. The means and standard errors of the changes in heart rate after the cats had received approximately

TABLE II

THE CHRONOTROPIC EFFECTS OF SOME CARDIAC GLYCOSIDES IN CATS

Glycoside	After 25 per cent of LD	After 40 per cent of LD	After 55 per cent of LD	After 70 per cent of LD	After 85 per cent of LD
Digitoxin ..	97·2 ± 1·5	100·5 ± 3·1	97·1 ± 3·3	115·8 ± 5·5	133·1 ± 8·5
Acetyldigitoxin	97·4 ± 1·5	95·7 ± 2·6	100·4 ± 6·8	101·3 ± 3·6	118·4 ± 5·5
Gitalin ..	92·5 ± 2·2	96·0 ± 4·6	101·0 ± 6·3	113·9 ± 6·3	121·7 ± 6·2

The figures are mean ± S.E. of heart rates expressed as percentages of the control value in each cat.

25, 40, 55, 70 and 85 per cent of the lethal doses of these glycosides are listed in Table II. It may be seen that the negative chronotropic effects of these glycosides, on the average, were not marked. But definite bradycardia (a reduction in heart rate of 15 per cent or more) did occur in about one third of the cats in each group and prolongation of the PR interval appeared only in these animals. Furthermore, in all the cats that had bradycardia, the minimum heart rate was recorded after they had received approximately 60 per cent of the lethal dose of the glycoside. Figure 1 shows the ECG of the cat that had the most marked bradycardia. This cat died after receiving 17 injections of gitalin. Immediately before the eleventh injection the heart beat was reduced from a control of 148 to 70 per minute, and simultaneously the PR interval increased from 0·10 sec.

to 0·16 sec. A delayed increase in heart rate was seen in every cat, as shown in Table II.

In addition to the chronotropic effects of the glycosides, many other changes were noted in the ECG. The most consistent were cardiac arrhythmias. Extra systoles were usually seen at low dosages. At

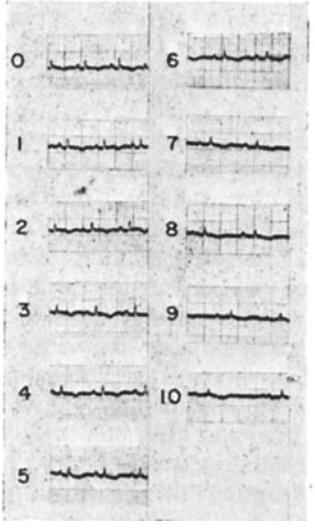

FIG. 1. The ECG of a cat showing marked bradycardia and prolongation of the PR interval. The cat died after receiving 17 injections of gitalin The control heart rate was 148 per. minute and the PR interval, 0·10 sec. Five minutes after the tenth injection, these changed to 70 per minute and 0·16 second respectively.

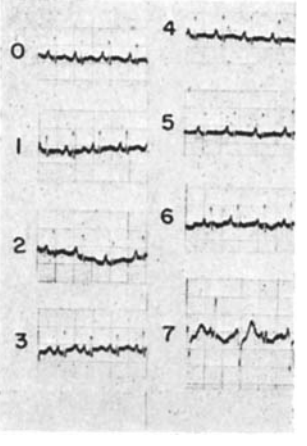

FIG. 2. The ECG of a cat which died after receiving 15 injections of digitoxin. There was no definite bradycardia or prolongation of the PR interval. Extrasystoles appeared after the seventh injection.

higher dosages, there were pulsus bigeminus, pulsus trigeminus, and various types of tachycardia. The dose that induced the first sign of arrhythmia, expressed as a percentage of the lethal dose for each cat, was determined. For each glycoside the mean and standard error of this dose

TABLE III

DOSES OF GLYCOSIDES INDUCING CARDIAC ARRHYTHMIAS AND CHANGES IN T WAVE, EXPRESSED AS THE LETHAL DOSES PER CENT IN CATS. (MEAN ± S.E.)

Glycoside	Cardiac arrhythmia (lethal dose, per cent)	Changes in T wave (lethal dose, per cent)
Digitoxin ..	67·9 ± 5·2	38·3 ± 3·1
Acetyldigitoxin	70·9 ± 2·5	46·1 ± 4·1
Gitalin ..	44·3 ± 4·0	34·4 ± 2·4

in all 14 cats are listed in Table III. With digitoxin and acetyldigitoxin, cardiac arrhythmias occurred only after two thirds of the lethal dose was given, whereas with gitalin these occured before one half of the lethal dose

was given. Heart block was usually seen shortly after the onset of arrhythmias. Bundle branch block in most cases appeared after A–V block. The T wave became bisphasic or inverted in many cats. The doses that caused changes in the T wave, expressed as percentages of the lethal doses of these glycosides, are also summarized in Table III.

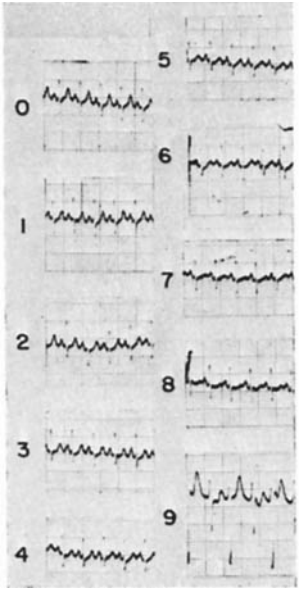

FIG. 3. The ECG of a cat which died after receiving 13 injections of acetyldigitoxin. There was no definite bradycardia or prolongation of the PR interval. Extrasystoles appeared after the ninth injection.

Other ECG changes such as lowering of the P wave and the QRS complex and shortening of the QT interval were inconsistent. Depression of the ST segment occurred in 7 of the cats which had received, on the average, 52·1 per cent of the lethal dose of gitalin. Elevation, instead of depression, of the ST segment was observed in 9 of the cats receiving acetyldigitoxin and in only 3 of the cats receiving digitoxin. With acetyldigitoxin, ST elevation occurred after 49·0 per cent of the lethal dose was given. This is not significantly different from gitalin. Figures 2 and 3 illustrate the absence of a negative chronotropic effect. Figure 4 exemplifies the earlier appearance of extra systoles in cats receiving gitalin in contrast to those receiving digitoxin and acetyldigitoxin (cf. Fig. 2 and 3).

The therapeutic ratio for these glycosides, as reported in the literature, are given in Table IV. These figures show that gitalin has a wider margin of safety than the other two glycosides. In cats, if it may be assumed that

TABLE IV

THE "THERAPEUTIC RATIOS" OF SOME CARDIAC GLYCOSIDES

Glycoside	"Therapeutic ratio" in cats per cent	"Therapeutic ratio" in man per cent
Digitoxin ..	49·1	58·0*
Acetyldigitoxin	47·0	53·0†
Gitalin ..	76·9	36·9* 42‡

* Figures from Batterman and others[5].
† Figure from Loeffler and others[12].
‡ Figure from Weiss and Steigmann[6].

the therapeutic dose corresponds to one third of the lethal dose as suggested by Walton[9], the ratio of this "therapeutic dose" to the arrhythmia dose presents an exactly opposite picture. In other words, gitalin is more liable to cause cardiac arrhythmias than the other two glycosides.

Discussion

While the lethal doses and the cardiac arrhythmia doses of these glycosides in cats were determined with satisfactory precision, a suitable criterion for therapeutic doses was not observed. The lack of a consistent bradycardiac effect of these glycosides in our experiments agrees with the findings of Gold and others[10]. Prolongation of the PR interval, shortening of the QT interval and lowering of the P wave and the QRS complex, which have been considered as signs of the therapeutic phase[7], were noted in less than 50 per cent of the cats in our experiments. This, however, does not indicate that there was no increase in contractility of the myocardium in the other cats, since it has been established that increased contractility may occur in the absence of any change in the ECG.[3]

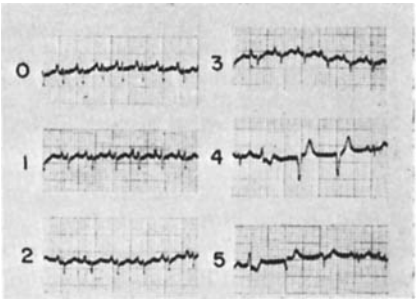

FIG. 4. The ECG of a cat showing an early occurrence of extrasystoles. The cat died after receiving 16 injections of gitalin. Extrasystoles appeared after the fourth injection.

It is not certain why gitalin seems to have a smaller margin of safety in the cat while clinically it has been reported to be superior to the other two glycosides. However, since clinically the end point of toxic doses was the occurrence of any sign or symptom of toxicity, it is possible that digitoxin and acetyldigitoxin are more prone to cause minor toxic signs and symptoms while cardiac arrhythmias are seen more frequently with gitalin administration. It is also possible that gitalin has a greater therapeutic activity than that indicated by the lethal dose; that cardiac glycosides may have a greater margin between the therapeutic and the lethal dose has recently been reported[11].

Acknowledgement. The authors wish to acknowledge the valuable technical assistance of Mr. A. F. Peterkin.

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