THE RELATIVE VALUE OF DIGITALINE PREPARATIONS IN HEART FAILURE WITH AURICULAR FIBRILLATION

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At the present time there are at least six digitaline preparations in use in this country. Digitaline, first isolated by Nativelle (1869), consists of digitoxin with traces of other glucosides and impurities. In the *British Pharmaceutical Codex* (1934) the only standards stipulated for the drug are a melting point not below 240°C ., and a loss of not more than 1 per cent at 100°C . Although the drug is not a pure substance there is no obligation for a manufacturer to carry out a biological assay of the preparation, and it may be dispensed by weight. Methods of manufacture vary slightly from one firm to another and the exact processes remain a secret in some instances. The use of digitaline has been recently advocated by Gold and his associates (Gold *et al.*, 1942; Gold *et al.*, 1944) on the grounds of its ready and almost complete absorption from the intestinal tract (Eggleston and Wyckoff, 1922; Gold and Travell, 1941). For this reason they regard it as particularly appropriate for rapid digitalization by a single adequate dose given by mouth. For maintained digitalization it is a satisfactory preparation, but there are good grounds for preferring digitalis leaf for routine use (Evans, 1940). Gold, Kwit, and Cattell (1940) found that 3 cat units of Nativelle's digitaline by mouth was equivalent to 25 cat units of digitalis leaf. As Cushny (1925) pointed out, the cat method is only useful to compare different samples of the same drug and to estimate their probable effect in man, and is of little value for the comparison of different preparations of digitalis given in treatment. Gold *et al.* (1940) found that Nativelle's digitaline by weight was two hundred times more potent than digitalis leaf standardized by the cat and frog methods, but was one thousand eight hundred times more potent in man when given by mouth. This difference is largely explained by the better absorption of digitaline. Evans (1940) found that 1/600 grain (0.25 mg.) of Nativelle's digitaline was

equivalent to 1 grain of the powdered digitalis leaf, a finding in agreement with the observations of Campbell (1938). Digitaline (Allen and Hanbury), however, supplied in granules similar in appearance and dosage to Nativelle's digitaline, was not found to be so effective in a dosage of 1/240 grain, as was Nativelle's preparation in a dose of 1/600 grain (Evans, 1940).

The present work was undertaken to ascertain whether there was any variation in the value of six commercial preparations of digitaline when dispensed to patients with heart failure and auricular fibrillation. The method for this clinical assay was the same as that described by Evans (1940). The preparations tested, marketed by six different firms, were designated A, B, C, D, E, and F.

Thirteen patients, all of whom had been under observation for some time, were chosen for the clinical trial. Three failed to complete the course, two owing to irregular attendance and the third owing to admission to hospital with an exacerbation of heart failure, leaving 10 in the series; six were men and four women. Their ages varied from 24 to 63. Auricular fibrillation and heart failure were present in all, associated with hypertension in two and with mitral stenosis in the remaining eight. They were all treated as out-patients and they led their usual lives, the majority being at work. With one exception they had been receiving powdered digitalis leaf for prolonged periods before the tests. The patients attended each fortnight; their statement on progress was recorded at each visit, and after a short rest the apical rate was counted over three successive half-minute periods, and the average rate was taken. They were examined clinically and by cardioscopy at intervals according to need. At each attendance they were given a different digitaline preparation for the following test period of 14 days, thus ensuring that by the end of the period each patient had been fully under the influence of the fresh preparation for

a few days at least. One grain of powdered digitalis leaf and one pill (1/600 grain) of each digitaline preparation were given as single doses, while the number of doses a day was different for different patients according to their habitual requirements before the clinical trials were started, and it was kept constant for each patient throughout the investigation. The order in which the preparations were given was deliberately varied in each case. The following is an account of one case.

Male, aged 45, with mitral stenosis, aortic incompetence, auricular fibrillation, and heart failure

At the age of 11 the patient had rheumatic fever. He was prevented from playing games at school as a consequence of this, and was rejected from the army during the 1914-18 war on account of his heart. Twenty years ago he had a small hæmoptysis and a larger one thirteen years later. Dyspnœa had been present for seven years and recently this had become worse and was present at rest. In the last five weeks he had been unable to work. Hæmoptysis recurred a week before. He had been receiving digitalis for the last three months from his doctor who sent him to the Cardiac Department for treatment.

He was breathless when examined and showed slight cyanosis and venous congestion in the neck. The pulse was 80 and was irregular from auricular fibrillation. The blood pressure was 160/55. There was no œdema. The apex beat was displaced outwards to the anterior axillary line. Systolic and mid-diastolic murmurs were heard in the mitral area, as well as aortic, systolic, and diastolic murmurs. Fine crepitations were found at both bases and the liver was distended and tender. The urine was normal. Cardioscopy showed great cardiac enlargement, involving the left ventricle, left auricle, right auricle and the conus and pulmonary artery; there was moderate pulmonary congestion. He was admitted to hospital the same day and responded readily to treatment with rest, restricted fluids, digitalis and two injections of neptal. He was discharged four weeks later, with only slight pulmonary congestion, and he continued to take 1 grain of digitalis leaf twice daily. He was included in the present series on August 13, 1946, and his progress during the clinical trials is set out below in tabulated form.

Date	Medicine during previous 14 days	Digitalis dose (given twice daily)	Heart rate a minute	Patient's statement on progress
13 Aug.	Digitalis leaf	1 grain	68	Well
27 Aug.	Drug E	1/600 „	78	Well
10 Sep.	Drug C	1/600 „	65	Very well
24 Sep.	Drug A	1/600 „	81	Well
8 Oct.	Drug D	1/600 „	57	Very Well
22 Oct.	Drug F	1/600 „	87	Well
5 Nov.	Drug B	1/600 „	65	Well

Clinical signs of heart failure did not increase during the period of trials, and the urinary output was satisfactory.

The results for all six digitaline preparations are summarized in Table I.

TABLE I
HEART RATE IN TEN PATIENTS WITH AURICULAR FIBRILLATION AFTER TREATMENT WITH SIX DIFFERENT KINDS OF DIGITALINE

Case No.	Age	Sex	Weight in lb.	No. of doses daily	Drug A	Drug B	Drug C	Drug D	Drug E	Drug F	Average
1	24	F	149	3	109	85	87	85	91	87	91
2	58	M	180	2	83	68	85	73	76	63	75
3	44	M	144	2	103	82	85	84	79	77	85
4	47	M	132	2	82	70	73	79	82	89	79
5	59	M	127	2	97	81	73	99	82	108	90
6	48	M	146	2	109	95	102	80	81	101	95
7	63	M	201	2	114	104	79	84	80	113	96
8	45	M	126	2	81	65	65	57	78	87	72
9	27	F	101	2	53	65	61	51	58	52	57
10	56	M	140	2	87	79	77	79	87	81	82
			Average		92	79	79	77	79	86	

The results were examined statistically by the analysis of variance method (Fisher, 1937). There was found to be a significant difference between the effect of the drugs, due to the high heart rates obtained with drug A, and the probability of this difference occurring by chance was less than 1 in 100.

In order to check these findings another series of trials was carried out with the same digitaline preparations on twelve other patients with auricular fibrillation and heart failure. Three patients had to be excluded from the series owing to irregular attendance, and two on account of an increase in the severity of the heart failure necessitating admission to hospital. In the seven remaining patients mitral stenosis was the underlying cause of the heart failure in four and hypertension in three. The same procedure was followed in carrying out the trials but the order in which the drugs were given was decided by drawing lots. The results are summarized in Table II.

Applying the same statistical method to the results in Table II, Drug A is again found to be significantly inferior to the remaining five preparations, the probability of such a result arising by chance being about 1 in 21.

It is apparent from these two series of trials that

TABLE II
HEART RATE IN SEVEN PATIENTS WITH AURICULAR
FIBRILLATION AFTER TREATMENT WITH SIX DIFFERENT
KINDS OF DIGITALINE AND WITH POWDERED DIGITALIS
LEAF

Case No.	Age	Sex	Weight in lb.	No. of doses daily	Drug A	Drug B	Drug C	Drug D	Drug E	Drug F	Digitalis leaf	Average
1	64	M	201	2	101	70	85	77	91	83	81	84
2	54	M	126	2	102	97	87	90	87	90	89	92
3	67	F	115	2	91	89	97	101	80	91	81	90
4	42	F	154	2	85	82	86	39	87	91	67	82
5	36	M	143	2	113	69	73	81	77	72	70	79
6	45	M	126	1	74	60	66	71	69	65	71	68
7	54	F	132	1	79	81	70	83	83	87	89	81
Average					92	78	81	83	82	83	78	
Average for first series					92	79	79	77	79	86		

Drug A is not as efficacious as the remaining preparations. There was no significant difference between the effects of the other drugs. It is now recognized that the dosage of digitalis necessary to produce an adequate clinical effect in any given patient lies within a fairly wide range, particularly when there is only slight or moderate heart failure present (Gold and De Graff, 1930), and it is probable that the inferiority of Drug A demonstrated in these two series of trials represents a fairly considerable difference of potency. It is unsatisfactory that preparations with the same or similar names, but differing in clinical potency, should be marketed by different firms. A practitioner prescribing digitaline cannot be certain that his patient will always receive a preparation of the same potency, and undesirable

toxic effects may be produced by one drug, while another may have an inadequate effect. There is no obligation on the manufacturers to standardize their products by biological assay, nor is it certain to what extent this would result in a greater uniformity of digitaline preparations. The explanation of the inconsistent results obtained with digitaline preparations may lie in the method of manufacture. In some instances certain stages of the procedure are a closely guarded commercial secret, and there is no certainty that the final products are identical with the different processes used, thus rendering the standardization of different digitaline preparations by biological assay of less value. Digitalis leaf has been found to produce consistent clinical results by many observers. Its method of preparation is known to all and is simple, and its standardization by biological assay is adequate for clinical purposes. It is suggested that if a standard method of preparation were laid down for digitaline, as it is for digitalis leaf, and biological assay of the product were compulsory, variations in potency might be reduced. At the present time powdered digitalis leaf would appear to be preferable for maintained digitalization.

SUMMARY

The effect of six different commercial preparations of digitaline has been tried in two series of ten and seven patients with heart failure and auricular fibrillation. One preparation was much less effective than the other five in both trials. It is suggested that a standardized procedure for the manufacture of digitaline should be introduced, and that biological assay should be made compulsory. The variability in the potency of digitaline preparations suggests the advisability of using digitalis leaf for continuous digitalization at the present time.

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