THE USE OF DIGIPURATUM IN HEART-DISEASE

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Digitalis leaf preparations from different localities show great differences in pharmacologic strength. This variation in pharmacologic efficiency is due to the fact that there are a number of factors, variations in which will modify the amount of the active substances contained in the leaves. Among these factors are the soil, the gathering season, the methods of collecting and drying the leaves and the methods used in preserving the dried product. Carefully trained apothecaries may render the conditions fairly constant for one locality, but even then the leaves themselves are found to vary greatly from year to year. This variation in strength will of course be found also in the Galenic preparations made from the dried leaves.

In 1902 Fraenkel¹ studied the strength of *digitalis* and *strophanthus* preparations obtainable in Heidelberg and the surrounding towns, that is, the leaf and seed preparations of practically one section. His material consisted of samples of the tincture and infusion of *digitalis* and the tincture of *strophanthus* from six different sources. As his unit of strength he used the minimum amount of each preparation which was necessary to produce systolic stoppage of the heart in 100 gm. of frog in one hour. As a result of his tests Fraenkel found that the samples of the infusion of *digitalis* varied from 100 to 275 per cent. in strength, the samples of the tincture of *digitalis* varied from 100 to 400 per cent. and those of the tincture of *strophanthus* showed variations in strength of from 100 to 6,000 per cent.

What these figures mean is best shown by a table giving the total weight of frog in which the maximal daily dose for the human adult, of the strongest and the weakest preparation respectively, will produce systolic standstill of the heart in one hour.

Buehrer² studied the fluidextract of *digitalis* obtainable throughout one section of Switzerland and found the preparations to vary from 100 to 400 per cent. He also tested the fluidextract of two successive years from one apothecary and found the two preparations to show a difference of 200 per cent. in strength, both extracts being tested within a few days of their preparation.

1. Fraenkel: *Therap. d. Gegenw.*, 1902, iv, 106.

2. Buehrer: *Corr.-Bl. f. schweiz. Aerzte*, 1900, xxx, 617.

TOTAL WEIGHT OF FROG IN WHICH MAXIMAL DAILY DOSE FOR THE HUMAN ADULT, OF STRONGEST AND WEAKEST PREPARATION RESPECTIVELY, WILL PRODUCE SYSTOLIC STANDSTILL OF THE HEART IN ONE HOUR

Maximal dose for twenty-four hours		Systolic standstill of heart in weight of frog from	
		weakest prep.	strongest prep.
	c.c.	gm.	gm.
Tinct. digit.....	5.0	200	830
Infus. digit.....	100.0 (1 gm. powd. leaves)	1.450	4,000
Tinct. stroph.....	1.5	150	10,000

Since the German apothecary is probably the most carefully trained apothecary in the world, these figures represent about the best results obtainable under the old system of unstandardized preparations. They will serve to explain in a great measure the almost proverbial uncertainty of digitalis medication in the past. This variation in strength of digitalis

Chart 1.—Case 1 (Hosp. No. 165,337). Man, aged 39; mitral and aortic regurgitation, enlarged liver, marked brawny edema of legs, no dyspnea, mild break in compensation. In this and the following charts, the line of dashes represents the urinary output in ounces.

preparations, particularly of the tincture, which is undoubtedly the most reliable Galenic preparation, makes systematic treatment with unstandardized preparations an impossibility. The physician is obliged to feel his way, to test the strength of his preparation on the patient himself, as it were. If he is cautious his results may be negative, or at least unsatisfactory; if, on the other hand, the physician, relying on former experience, “pushes” the drug he may be suddenly confronted with a case of pronounced digitalis intoxication.

The use of the pure active principles of the digitalis group makes exact dosage possible, and therefore many French physicians, following

the lead of Huchard, use pure crystalline digitoxin (digitaline Nativelle). In Germany, too, digitoxin (Schmiedeberg) and digitalin (digitalinum verum, Kiliani) are used to a limited extent. The therapeutic value of the active principles as compared with that of the leaf extracts was fully discussed at the nineteenth congress for internal medicine (Wiesbaden, 1901). At this congress many prominent clinicians spoke strongly in favor of the leaf extracts. They asserted that neither digitalin nor digitoxin alone could produce the true digitalis effect obtainable from the leaf preparations. In a recent paper by one of us³ the properties of digitalin and digitoxin are discussed at some length, and it is shown that stro-

Chart 2.—Case 2 (Hosp. No. 165,545). Man, aged 38. Myocardial weakness, broken compensation, general anasarca, dry pericarditis and pleuritis. The effect on the pulse was prompt. The first digipuratum cure had little effect on the diuresis; the pronounced diuresis which began on the tenth day was probably started by the fluidextract of apocynum and continued by the second digipuratum treatment.

phanthin is probably a better substitute for digitalis leaf preparations than either of the digitalis bodies. But strophanthin is specially suited for intravenous application; it is not adapted for long-continued digitalis medication. In his lectures on digitalis Schmiedeberg himself warns his

3. Boos: Boston Med. and Surg. Jour., 1909, clxi, 589.

pupils against the use of pure digitoxin, on account of the insolubility and the great toxicity of this drug.

These facts all show that the need of leaf preparations of known strength is very great, and the introduction of physiologically standardized preparations of the tincture and fluidextract was therefore a decided step in advance. But these preparations are reliable only if they have been recently standardized, since it seems to be very difficult to render liquid preparations of digitalis permanent in point of pharmacologic strength. That is why German physicians prefer to use the powdered leaves, preparations of these being considered more nearly permanent.

Chart 3.—Case 3 (Hosp. No. 166,588). Man, aged 67. Senile heart, failing compensation for six months. Had not slept in bed for two weeks. At entrance: cyanosis, urgent dyspnea, edema of lungs, enlarged, tender liver, massive brawny edema of legs and genitals, general anasarca. Blood-pressure 150 mm. Hg. Fifth day after entrance, striking improvement. Patient sleeping well at night without morphin; color good, edema very slight.

Focke⁴ made a special study of these leaf-powders. His experience was that leaf-powders, which he obtained from various reliable German druggists, deteriorated in some cases more rapidly than the fluid preparations. The cause of this deterioration he found to be an excessive moisture con-

4. Focke: Therap. d. Gegenw., 1904, xlv, 250.

tent of the powdered leaves. As a result of his tests Focke concludes that the deterioration in strength which occurs in the course of one year is proportional to the amount of moisture above 3 per cent. which is contained in the leaf-powder. Some powders which contained as much as 8 per cent. moisture showed a loss in strength of over 60 per cent. Focke prepared permanent leaf-powders in the following manner: he dried the leaves quickly with artificial heat at a temperature just below 100 C. until the moisture content was below 1.5 per cent.; he then removed the thick stems, coarsely powdered the leaves and preserved them in air-tight tins. All the samples of leaf-powder prepared and preserved in this manner showed no diminution in strength after one year.

Chart 4.—Case 4. (Hosp. No. 165,693). Man aged 47. Myocardial insufficiency, mitral regurgitation (relative), broken compensation, edema of lungs, enlarged liver, edema of legs, infarct of lung involving whole right lower lobe. Marked general improvement and efficient diuresis with second digipuratum cure. Discharged with fair compensation.

Standardized leaf-powders prepared according to Focke's method may therefore be used for accurate dosage. There is, however, another factor which often renders digitalis medication difficult and at times even impossible, namely, the tendency of leaf preparations to produce in many patients gastro-enteric disturbances. Such disturbances are due, no doubt,

in dilute alkalies, a property which insures their ready absorption from the intestine. The yellow fluid is standardized physiologically and is then taken up with sugar of milk to form a powder. The powder obtained is further diluted with sugar of milk until the resulting product has a definite and constant pharmacologic strength. In his physiologic tests Gottlieb uses *Rana temporaria* (the German field frog), obtained during the months of July to October and kept in captivity as short a time as possible before use. His unit of strength is the minimum amount of the extract which in thirty minutes will cause systolic stoppage of the heart of a frog weighing 30 gm. This quantity Gottlieb calls a "frog

Chart 6.—Case 6 (Hosp. No. 166,029). Man, aged 44. Chronic glomerulonephritis, hypertrophy and dilatation of the heart, broken cardiac compensation, old syphilis. Blood-pressure 190 mm. Hg; very large ascites; extremely firm edema of legs; edema of lungs; pleural anasarca; Cheyne-Stokes respiration; very severe break in compensation. Tapping of ascites gave marked relief. The early diuresis was probably due to the tapping; it cannot possibly be attributed to the digipuratum because only two tablets of the drug had been taken when it began. The digipuratum diuresis began on the fourth day of the medication.

unit." By standardizing a large number of the best leaf-powders obtainable, Gottlieb found that the ordinary dose of the powdered leaves, 0.1 gm., varied in strength in the different samples from 4 frog units to 12. Eight frog units being the average, Gottlieb chose this strength for his

purified extract. Digipuratum is therefore prepared as a powder having the constant strength of 8 frog units to each 0.1 gm. of the powder, corresponding to the average strength of a single dose (0.1 gm.) of the crude powdered leaves. For greater convenience of dosage digipuratum is usually dispensed in tablet form, each tablet containing 0.1 gm. of the powder. These tablets have an agreeable vanilla flavor and are taken readily by all patients.

The very favorable results obtained with digipuratum by Hoepfner,⁵ Mueller,⁶ Tissot,⁷ Clemens⁸ and others encouraged us to try the preparation in the medical services of the Massachusetts General Hospital.

Chart 7.—Case 7 (Hosp. No. 166,254). Man, aged 49. Chronic glomerulonephritis (blood-pressure 240 mm. Hg), hypertrophy and dilation of heart, broken cardiac compensation (rather acute, very severe break in compensation), edema of lungs, right hydrothorax, slight ascites, enlarged liver, marked brawny edema of legs, general anasarca. Venesection at entrance gave immediate relief to subjective symptoms. On the fifth day after entrance the edema of legs was practically gone.

5. Hoepfner: München. med. Wehnschr., 1908, lv, 1774.

6. Mueller: München. med. Wehnschr., 1908, lv, 2651.

7. Tissot: Folia Serol., 1909, iii, 1.

8. Clemens: Fortschr. d. Med., 1908, xxvi, 1057.

In the treatment of broken cardiac compensation we gave the drug as suggested by the clinicians mentioned, namely, in the form of so-called treatments; that is to say, we employed the ideal digitalis medication, giving large doses in as short a time as possible. We were enabled in this way to determine if the drug, when it is given in sufficient quantity rapidly to produce its physiologic effect, is really free from the irritating substances which usually make similar dosage of the crude drug an impossibility, and to determine if under these circumstances this drug exhibits a lesser tendency to produce cumulation than the crude preparations. We gave digipuratum as a rule in treatments of twelve tablets in four days; four tablets the first day, three the second day, three the third and two the fourth day (that is, 1.2 gm. or 18 grains in four days).

Chart 8.—Case 8 (Hosp. No. 166,451). Man, aged 36. Aortic insufficiency, aortic roughening, Cheyne-Stokes respiration, acutely dilated heart. Venesection, rest, digipuratum. Discharged, with compensation, in fifteen days.

In many of the more serious cases we were obliged, of course, to continue the drug in doses of one or two tablets for a longer or shorter period.

In order to show in a purely objective way what the drug will do, we shall report in brief (see charts and legends) eight cases taken from the first fifteen cases of heart disease treated at the hospital with digipuratum. The cases which we reported were chosen with a view to illustrating the action of digipuratum alone, as well as in combination with other therapeutic measures. To make the picture more graphic we reproduce the charts with as little text as possible.

Each of the eight cases shows interesting features. The diuresis is efficient in all the cases. In Case 3 the diuretin probably played little or no part in producing the phenomenal urinary output. Cases 1, 2, 5 and 8 show the marked effect of digipuratum on the pulse-rate. Case 5 is perhaps the most remarkable case of all. This patient was sent into the hospital in a moribund condition and we felt but little hope of her life. She reacted very quickly to digipuratum, however, and compensation was established in a week. The patient has been under the care of one of us since leaving the hospital. At first she needed two tablets of digipuratum daily for several months; after that the dose could be gradually diminished until now, after one year, she takes on the average only four or five tablets a week. At times she goes a week or ten days without the drug. She is comfortable, looks after her household duties and makes many visits, although she lives up one flight of stairs. The physical signs are the same as when she left the hospital.

In some of the cases the first digipuratum treatment gave little or no result, while the second was very efficient. Cases 2, 6, 7 and 8 illustrate the good results which may often be obtained by combining digipuratum medication with venesection or the removal of fluid from the body by tapping. In Case 2 the efficient diuresis which began on the tenth day was due to a combination of digipuratum with the fluidextract of apocynum. The blood-pressure was rarely affected. There was no vomiting or diarrhea in any of the cases.

Digipuratum has now been in use at the Massachusetts General Hospital for over a year and more than 180 cases of primary heart disease or secondary cardiac involvement have been treated with it. The effect on the urinary output has been very prompt in most instances. There was not a single case of vomiting or diarrhea; in fact, the vomiting of a number of cardiac patients at entrance was promptly stopped by digipuratum. Cumulative poisoning has never been observed. One of the early patients, a boy of 16, was given 106 tablets in six weeks; at no time was there any suggestion of digitalis poisoning. In one or two instances the house officers were made uneasy by sudden drops of forty or more beats in the pulse-rate, but no disagreeable consequences followed in any case. It must be borne in mind, however, that digipuratum is a digitalis preparation, and that as such it must necessarily have a tendency to produce poisoning by cumulation. In the case of digipuratum this tendency is merely much diminished, so that it is possible by means of this drug to push digitalis therapy in a manner heretofore unknown.

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