NOTES ON SOME NEW SUBSTITUTES FOR THE GALENICAL PREPARATIONS OF DIGITALIS

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The experiments, which form the basis of this paper, were undertaken with the object of comparing the actions of Digalen*, Digipuratum† and Digitalone‡, all recently put on the market as substitutes for Digitalis preparations in therapeutics.

Digalen is an aqueous solution containing 25 per cent. of glycerine: it was first prepared by Cloetta², and is an amorphous powder, soluble in water. Its exact chemical composition appears to be somewhat doubtful. Dixon³ states that it bears a certain chemical and physiological resemblance to Digitoxin; and he points out that it is not identical with the product of Schmiedeberg and Killiani, which is crystalline and insoluble in water. Killiani¹⁰ believes that it consists chiefly of Digitaleïn. Cloetta states that, whilst it is quite as good a therapeutic agent as Digitoxin, it is less toxic. The latter statement is confirmed by Neave¹⁴, Hale⁷, Hatcher⁸, Symes¹⁶ and Moore¹². There is great variation in the reports on the clinical value of this product.

It has been stated that Digalen is more rapid in its action than the Galenical preparations of Digitalis, though the results of Fränkel⁵, Müller and others show that it is not absorbed any more rapidly than Digitalis. Digalen, whilst it is probably less irritant to the stomach than Digitoxin, appears to be a violent irritant when used subcutaneously, and not devoid of irritant power when injected intramuscularly (Dixon⁴).

Digipuratum is prepared by treating Digitalis leaves with alcohol and ether, the preparation being in the form of a powder, which is insoluble in water, though soluble in dilute alkaline solutions. It is said to contain about 95 per cent. of the active principles of Digitalis leaves, though 85 per cent. of the saponins and inert matter are excluded (Gottlieb)⁶. Schüttler¹⁵ states that Digipuratum is about 50 per cent. less toxic than Digitalis leaves: it is also said to be free from irritant effect on the stomach.

* Digalen, Hoffmann La Roche.

† Digipuratum, Knoll.

‡ Digitalone, Parke Davis & Co.

NOTE.—The tincture of digitalis used as a control was the product of Ferris & Co. physiologically standardised.

Höpffner⁹ reports favourably on its action: Müller¹³ states that gastric disturbance is rarely caused by it, though Szinnyei¹⁷ records nausea and vomiting as following its use.

Digitalone is an alcohol-free solution containing 0·6 per cent. of chloretone, and is said to contain all the active principles of *Digitalis* leaves. It is said to be less irritant than Digitoxin or Digitalin, though subcutaneous injections are by no means free from pain.

My experiments divide themselves naturally into two parts, the first part consisting of a series of perfusion experiments on the isolated mammalian heart, in an endeavour to ascertain the relative stimulating powers and toxicities of these preparations, whilst the second part is confined to an attempt to establish their relative rates of absorption from the intestinal tract and their irritant properties.

PERFUSION EXPERIMENTS

Equivalent doses of these three preparations were taken, and of these, solutions of 1 in 2,500 were prepared as required in freshly oxygenated Ringer's solution made up with special glass-distilled water. Rabbits of medium size (averaging 1·8 kilograms) were used in all these experiments: these were decerebrated, their hearts immediately excised and perfused by the method of Langendorff, using the apparatus described by Brodie. By this means the hearts were perfused through the coronary vessels, and maintained at a steady temperature of 37° C. A silk thread was attached by an entomological hook to the apex of the heart, and connected with a suitably placed counterbalanced recording lever, the writing point of which recorded the cardiac movements on a revolving drum. The perfusion fluid was placed in two glass jars at a suitable height above the suspended heart, one jar containing Ringer's solution and the other a 1 in 2,500 solution of the drug in Ringer's solution. By means of a Y-tube junction-piece either solution could be made to supply the perfusion fluid at will.

In all, twenty experiments were performed, the results of which may be given under six heads:—

1. Alteration in rate of heart-beat.
2. Alteration in amplitude of heart-beat.
3. Toxicity.
4. Alteration in rate of coronary flow.
5. Alteration in height of mean tonus.
6. Incidental remarks.

1. *Alteration in rate of heart-beat.*

In this particular Digipuratum had by far the strongest action, the average alteration being a slowing of 33 per cent. in 30 minutes. In one experiment the beat was slowed from 90 to 48 per minute, nearly 50 per cent. Between Digalen and Digitalone there was but little difference, both being far less potent than Digipuratum: Digalen produced a slowing of 7.6 per cent. and Digitalone of 6.2 per cent. The greatest degree of slowing produced by these drugs in any experiment was from 81 to 69 per minute by Digalen, and from 96 to 82 by Digitalone. These results are shown graphically in Fig. 1.

2. *Alteration in amplitude of heart-beat.*

Digipuratum again showed the most powerful action, very closely followed in this case by Digalen; the average figures being an increase of 97 per cent. for Digipuratum, 90.9 per cent. for Digalen and 22.7 per cent. for Digitalone; but, whereas the Digipuratum effect was produced in 10 minutes, that of Digitalone did not reach its maximum under 30 minutes. Digitalone also required 30 minutes for the production of its maximum effect. Corresponding experiments with Tincture of Digitalis showed an increase in amplitude of 88.9 per cent., produced in 30 minutes. It should be stated, however, that the increase in amplitude produced by Digipuratum is not so well maintained as is that produced by Digalen and Digitalone, as shown in Fig. 2.

3. *Toxicity.*

The relative toxicities of these preparations were measured by the times elapsing between the moment at which the drugs were first put into the perfusion fluid, and the time at which the heart finally ceased beating in systole. The average results are as follows:—

Digitalone	...	...	...	260 minutes.
Digalen	...	...	...	235 minutes.
Tincture of Digitalis	...	...	...	165 minutes.
Digipuratum	...	...	...	160 minutes.

Their ratios of toxicity may then be put at: Digitalone 0·63, Digalen 0·70, Tincture of Digitalis 1·00 and Digipuratum 1·03. These results are shown graphically in Fig. 3.

Professor W. E. Dixon very kindly undertook to perform a series of injection experiments on frogs, and by his courtesy I am able to publish the results of these in confirmation of the above toxicity figures. The frogs were injected with varying doses diluted with an equal quantity of saline solution, the injections being made with a fine hypodermic needle into the dorsal lymph-sac.

Briefly stated, these four drugs showed exactly the same order of toxicity as in the perfusion experiments: 2·5 minims of Digipuratum killed a frog of 20 grams in 1½ hours, a frog of the same weight was killed by 2·6 minims of Tincture of Digitalis in 3 hours, whilst 4·5 minims of Digalen were necessary to kill a 20 grams frog in 3 hours, and 5 minims of Digitalone failed to kill a frog of 22 grams in 3 hours.

If we compare the ratios of toxicity given above with similar figures obtained from the results of alteration in amplitude of heart-beat, in each case putting Tincture of Digitalis at 1·00, we obtain the following table:—

					Ratio of increase in amplitude		Ratio of toxicity
Tincture of digitalis	...	...	...	...	1·00	...	1·00
Digipuratum	...	...	...	...	1·09	...	1·03
Digalen	...	...	...	...	1·02	...	0·70
Digitalone	...	...	...	...	0·25	...	0·63

From these figures it is evident that, taking Tincture of Digitalis as a standard, both Digipuratum and Digalen are pharmacologically relatively more potent than toxic, whilst Digitalone is both less potent, pharmacologically, and also less toxic than the Tincture; but, whereas its toxicity is 37 per cent. less than that of Tincture of Digitalis, its pharmacological activity, as judged by its power of increasing the amplitude of the heart-beat, is as much as 75 per cent. less.

FIG. 2. Variation in Amplitude of Heart Beat.

FIG. 3. Relative Toxicities to the Isolated Heart.

4. *Alteration in Rate of Coronary Flow.*

Digipuratum has a far more powerful action than the other preparations, the rate of coronary flow sinking from 5 c.c. in 60 seconds to 5 c.c. in 201 seconds. Digalen comes next with a fall of from 5 c.c. in 55 seconds to 5 c.c. in 90 seconds. Digitalone produced a fall of from 5 c.c. in 42 seconds to 5 c.c. in 65 seconds. This gives the following table of percentage diminution in rate of coronary flow:—

Digipuratum	...	...	...	...	233.0 %
Digalen	...	...	...	...	63.6 %
Digitalone	...	...	...	...	54.8 %
Tincture of digitalis	...	...	...	...	40.0 %

The results are shown graphically in Fig. 4. It will be noticed that Digipuratum produces its maximum effect in 10 minutes, whilst that of Digalen is not reached till 45 minutes after the drug was first admitted to the perfusing fluid.

FIG. 4. Variation in Rate of Coronary Flow in the Isolated Heart.

5. *Variation in Height of Mean Tonus.*

These results were obtained by measuring the height of the middle point of the curve above the base-line at certain times. It was found that, starting from an average height of 23 mm., Digalen produced an increase in tonus to 28 mm. in 10 minutes, after which followed a gradual

fall. Digipuratum, from an initial average height of 49 mm. above the base-line, caused a rise to a maximum of 53 mm., 60 minutes after the introduction of the drug. Digitalone and the Tincture of Digitalis produced no increase in mean tonus until the final rise of approaching death in systole. Reducing these results to percentages we can express them graphically, as in Fig. 5.

FIG. 5. Variation in Height of Mean Tonus.

Reading these results in conjunction with the results of variation in total amplitude of heart-beat, it is noted that Digipuratum in the first 10 minutes produces an increase of nearly 100 per cent. in amplitude without altering the tonus, so that when the amplitude of the beat is greatest the tonus is unaltered. At the end of an hour after the introduction of this drug, when the total amplitude of the beat is nearly 15 per cent. less than the normal, the mean tonus is nearly 10 per cent.

higher than the initial figure. In the case of Digipuratum the heart has by this time commenced its final rise of tonus towards its approaching death in extreme systole. Digalen, on the other hand, shows two almost parallel curves, in that, 20 minutes after the introduction of the drug, the amplitude of heart-beat has increased by 80 per cent., and the mean tonus has risen 20 per cent. At this time each curve often shows a slight fall.

Thus, in the therapeutic stage, Digipuratum increases the amplitude of the beat without increase of tonus, whilst Digalen produces an increase in tonus coincident with the increase in amplitude of heart-beat.

6. *Incidental Remarks.*

Under this heading I have grouped such occurrences as variation in rhythm, partial heart-block and extra-systole, merely wishing to direct attention thereto, owing to the prominence given to such features of cardiac action by Mackenzie¹¹ and others.

Variation in rhythm was noticed once only, and that in a heart under the influence of Tincture of Digitalis, the change being to a 3 : 1 rhythm, and occurring 105 minutes after the commencement of perfusion with that drug.

Partial heart-block was produced once by Digipuratum, once by Digalen, twice by Digitalone, and not at all in this series of experiments by Tincture of Digitalis. (Fig. 6.)

FIG. 6. Shows partial Heart Block produced by Digalen 190 minutes after introduction of drug.

FIG. 7. Shows extra-Systole produced by Digipuratum 30 minutes after introduction of drug.

Extra-systole was noticed but once, Digipuratum being the drug which produced it: it occurred 30 minutes after the introduction of the drug into the perfusion fluid. (Fig. 7.)

Figs. 8, 9, 10, 11 show typical tracings of the action of Digalen, Digipuratum, Digitalone and Tincture of Digitalis, respectively, when perfused through the isolated heart.

FIG. 8. Rabbit's Heart perfused with Ringer's Solution At 11.0, 1 in 2,500 Digitalis was admitted into the perfusion fluid.
Time in seconds.

FIG. 9. Rabbit's Heart perfused with Ringer's Solution. At 11.0, 1 in 2,500 Digipuratum was admitted into the perfusion fluid. Time in seconds.

FIG. 10. Rabbit's Heart perfused with Ringer's Solution. At 2.55, 1 in 2,500 Digitalone was admitted into the perfusion fluid. Time in seconds.

Fig. 11. Rabbit's Heart perfused with Ringer's Solution. At 11.30, 1 in 2,500 Tincture of Digitalis was admitted into the perfusion fluid. Time in seconds.

RATE OF ABSORPTION FROM THE ALIMENTARY CANAL

Cats of medium size were used in these experiments (weighing circa 2 kilo.). They were anaesthetised with ether, followed by urethane intraperitoneally; tracheotomy was performed and a respiration tube tied in the trachea. The animals were then decerebrated, and the carotid artery of one side put into connection with a mercurial manometer. The abdomen was then opened in the middle line, and the duodenum brought forward in readiness to receive the drug. When the blood-pressure had reached a constant level—usually in about 15 minutes—the drug was injected into the lumen of the duodenum by means of a fine hypodermic needle; the bowel was immediately replaced in the abdomen, which was stitched up. Doses equivalent to 16 c.c of the Tincture of Digitalis were used in all cases, and diluted up to a total volume of 20 c.c

The average results of these experiments may be given with advantage in tabular form:—

	Digipuratum	Digalen	Digitalone	Tincture of Digitalis
Variation in blood pressure	Slight rise after 70 minutes	Slight rise after 50 minutes	No appreciable rise in 5 hours	No appreciable rise
Condition of heart at end of experiments	Still beating after 6½ hours	Death 2 hours 20 minutes after introduction of drug	Still beating 5 hours after introduction of drug	Death 2½ hours after introduction of drug
Condition of duodenal mucous membrane	Very slight injection	Slight injection	No sign of injection	Considerable inflammation
Evidence of absorption	Yes	Yes	No	Yes

In order to obtain further information as to the irritant properties of these drugs a further experiment was performed: a rabbit, as large as could be obtained, was anaesthetised with ether, followed by urethane intraperitoneally; the abdominal wall was then cleaned of fur by means of a depilatory, and washed. Four skin areas was then mapped out, and a hypodermic injection of one drug was made with due aseptic precautions into each area. Doses equivalent to 1 minim of the Tincture of Digitalis were used. The animal was then wrapped up and kept on a warm stage and examined from time to time.

Little or no change was noticed in the condition of the skin around the areas of injection for more than 4 hours—after which time the following changes were noted:—

				5½ hours after injection	6½ hours after injection
Digalen	...	...	...	Distinct redness	Oedema, definite inflammation, hot
Digipuratum	...	...	...	Slight injection	As before
Digitalone	...	...	...	No change	No change
Tincture of digitalis	...	...	...	Discoloration and slight injection	As before

CONCLUSIONS

In comparing these three preparations with the Tincture of Digitalis, Digitalone may be at once discarded as a useful therapeutic agent, since its cardiac action is in every respect inferior to that of the Tincture of Digitalis; and when this drug was administered by way of the alimentary canal no evidence was obtained that it exerted any physiological action on the circulatory system.

Digalen has the advantage over the Tincture of Digitalis that it is less toxic when directly perfused through the heart, though, when it is administered by way of the alimentary canal, this difference is not evident: it increases the amplitude of the heart-beat to about the same extent as the Tincture of Digitalis. It is, however, inferior to the Tincture, in that it does not slow the beat so much; indeed this effect on the vagus is extremely small. The mean tonus of the heart is raised, producing a condition which involves a large expenditure of energy (Barcroft and Dixon¹) it may be of a useless kind. It is conceivable that, in certain conditions such as acute dilatation of the heart, this might be advantageous, but if the mean tonus of the heart is normal it could hardly be other than a harmful effect. Injected subcutaneously, Digalen produces more irritation than any other preparation. Moreover, Digalen has not the merit of cheapness.

Digipuratum is, if anything, more toxic than Tincture of Digitalis, when perfused through the isolated heart; but it has the disadvantage of

very markedly diminishing the rate of coronary flow. It slows the heart rather more than does Tincture of Digitalis: between it and the Tincture there is but little to choose in the matter of increase in amplitude. It acts quite well when administered by the alimentary canal; and is much less irritant than Digalen when injected subcutaneously, though quite as irritant, when given in this way, as the Tincture.

All things considered, it appears that not one of these new preparations has made a successful bid for superiority to the Tincture of Digitalis.

It gives me great pleasure to record my thanks to Professor W. E. Dixon for his continued help and advice.

BIBLIOGRAPHY

1. Barcroft and Dixon, *Journ. of Physiol.*, XXXV, pp. 3, 182, 1907.
2. Cloetta, *Münch. med. Woch.*, LI, p. 1446, 1904.
3. Dixon, *Quart. Journ. of Medicine*, V, pp. 18, 297, 1912.
4. Dixon, *loc. cit.*
5. Fränkel, *Arch. f. Exp. Path. u. Pharm.*, Leipzig, LVII, p. 131, 1907.
6. Gottlieb, *Münch. med. Woch.*, LVIII, p. 10, 1911.
7. Hale, *U.S. Hygien. Lab. Bull.*, p. 74, 1911.
8. Hatcher, *Amer. Journ. Pharm.*, LXXXIII, p. 360, 1910.
9. Höpfner, *Münch. med. Woch.*, LV, p. 1774, 1908.
10. Killiani, *Münch. med. Woch.*, LIV, pp. 886, 1112, 1907.
11. Mackenzie, *Heart*, II, p. 4, Aug., 1911.
12. Moore, *Brit. Med. Journ.*, p. 60, Jan. 13th, 1912.
13. Müller, *Münch. med. Woch.*, LV, p. 2651, 1908.
14. Neave, *Scot. Med. and Surg. Journ.*, Edinb., XX, p. 390, 1907.
15. Schüttler, *Dissertation*, Berlin, 1909.
16. Symes, *Brit. Med. Journ.*, II, p. 1346, 1911.
17. Szinnyei, *Therap. Monatsh.*, XXIV, p. 427, 1910.