

The progress from diuresis to oliguria following intravenous injection of successive doses of digitalis is a useful index of the development of toxic activity of the drug, and thus serves as a guide to the frequency and amount of its administration.

Cats showed wide individual variations in their susceptibility to digitalis, and their value in the assay of this drug appears questionable since in practice only a few animals are used.

Results of frog and guinea-pig assays agreed more closely with each other than with those of the cat method.

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THE RECTAL ABSORPTION OF DIGITALIS IN CATS.*

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INTRODUCTION.

Digitalis and its preparations, when administered by mouth, frequently cause nausea and vomiting. To overcome this untoward effect, Eichhorst, first (3), and later, other investigators have suggested administration by rectum. Therefore, digitalis preparations intended for rectal administration in suppository form and in solution have been offered to the medical profession within the last few years.

The available clinical reports on the administration of digitalis by rectum are favorable. It, therefore, seemed desirable to determine the preparation best suited for rectal use. With this objective in view, two preliminary experiments were conducted to determine whether or not digitalis is absorbed from the cat rectum. Large

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doses of a dealcoholized fluidextract were administered and positive absorption was noted. A comparative study was then made of the rectal absorption of digitalis from different vehicles.

EXPERIMENTAL.

A fluidextract of digitalis accurately standardized as to potency was dealcoholized by evaporation at a low temperature. Two anesthetized cats were then given approximately 20 M. L. D. and 10 M. L. D. of this solution by rectum. Difficulty was encountered in keeping the digitalis solution in the rectum due to the severity of the irritation produced. However, the cats received sufficient digitalis to cause death in from 3 to 3¹/₂ hours. These results show that digitalis is absorbed when given rectally.

For the purpose of obtaining comparative data on the rate of absorption of different preparations of digitalis when given by rectum, 5 additional series of experiments were conducted. In the first series, 5 separate experiments were carried out and in each of the remaining series, from 9 to 15 experiments. In all cases, the cats were anesthetized and kept under light anesthesia throughout the experiments by means of intraperitoneal injections of one of the barbiturates and, in some cases, ether was used as a supplement. Expulsion of the digitalis preparations was prevented by the application of anal clamps. About 5 hours after the administration of the rectal preparation, an amount of standardized digitalis solution sufficient to cause death was introduced intravenously.

SERIES NO. 1.

Suppositories were prepared, each containing the following:

Powdered Digitalis	0.3 Gm. (3 cat units)
Cacao Butter	1 Gm.

The results of the experiments with these suppositories are shown in Table I.

TABLE I.—ABSORPTION OF DIGITALIS POWDER IN CACAO BUTTER SUPPOSITORIES ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs. and Min.		Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
1	1.93	3	1.55	6	7	20.0
2	1.91	3	1.57	4	44	24.1
3	1.77	3	1.69	5	3	22.5
4	1.72	3	1.74	5	43	10.0	0.72	0.42
5	1.15	3	2.60	6	38	8.8	0.27	0.23

Since cats Nos. 1, 2 and 3 showed no absorption and cats Nos. 4 and 5 showed very slight absorption, the amount of digitalis given was increased in the next series of experiments.

SERIES NO. 2.

Each suppository used in this series contained:

Extract of Digitalis	0.375 Gm. (15 Cat units)
Cacao Butter, sufficient to make	2 Gm.

An extract of digitalis, 4 times the strength of the powdered digitalis used in the previous series, was used because the incorporation of an equivalent amount of powdered digitalis would have been impractical due to its bulk.

TABLE II.—ABSORPTION OF EXTRACT OF DIGITALIS IN CACAO BUTTER SUPPOSITORIES ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs. and Min.		Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
6	3.15	15	4.76	6	20	33.7
7	2.80	15	5.35	See below		..	2.80	1.00
8	2.80	15	5.35	5	50	26.5	0.15	0.05
9	2.75	15	5.45	5	53	32.5
10	2.73	15	5.49	5	6	17.2	1.01	0.37
11	2.56	15	5.85	6	10	31.6
12	2.54	15	5.90	4	12	25.2	0.02	0.01
13	2.47	15	6.07	5	19	11.0	1.37	0.55
14	2.45	15	6.12	5	47	20.6	0.39	0.16
15	2.43	15	6.17	5	24	11.6	1.27	0.52
16	2.35	15	6.38	5	10	20.3	0.32	0.14
17	2.27	15	6.60	3	38	17.2	0.55	0.24
18	2.25	15	6.66	5	56	16.7	0.58	0.26
19	1.89	15	7.93	5	27	17.0	0.19	0.10

Cat No. 7 died about 3 hours after insertion of the suppository. An autopsy revealed that the heart was in systole which is an indication of digitalis poisoning. However, the cat may have been abnormal and may have died from other causes. Cats Nos. 6, 9 and 11 showed no rectal absorption and actually required more solution intravenously than should have been needed theoretically had no digitalis been given rectally.

TABLE III.—ABSORPTION OF EXTRACT OF DIGITALIS IN GLYCERINATED GELATIN SUPPOSITORIES ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs. and Min.		Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
20	3.93	15	3.82	5	26	33.3	0.60	0.15
21	3.12	15	4.81	5	20	27.3	0.39	0.13
22	2.85	15	5.26	4	55	21.0	0.75	0.26
23	2.73	13.65	5.00	5	33	30.0
24	2.72	16.5	6.07	5	40	17.0	1.02	0.38
25	2.70	15	5.56	5	16	10.5	1.65	0.61
26	2.67	15	5.62	4	18	22.0	0.47	0.18
27	2.65	13.25	5.00	4	54	23.5	0.30	0.11
28	2.60	15	5.77	5	45	35.0
29	2.57	15	5.84	5	5	10.2	1.55	0.60
30	2.42	16.5	6.82	5	31	18.7	0.55	0.23
31	2.33	12.5	5.36	6	3	9.0	1.43	0.61
32	2.30	15	6.52	5	32	17.7	0.53	0.23
33	2.23	11.2	5.02	5	4	16.0	0.63	0.28
34	1.55	15	9.68	5	59	14.3	0.12	0.08

SERIES NO 3.

The base for the suppositories which were given throughout this series of experiments was Glycerinated Gelatin, U. S. P. X. Extract of Digitalis of the same lot as that employed in Series No. 2 was again used. The suppositories were prepared on two different occasions by the formulas which follow.

Lot No. 1	Extract of Digitalis	0.225 Gm. (9 cat units)
	Glycerinated Gelatin, sufficient to make	2.4 Gm.
Lot No. 2	Extract of Digitalis	0.375 Gm. (15 cat units)
	Glycerinated Gelatin, sufficient to make	2.4 Gm.

In both cases, the extract was thoroughly incorporated with the fused glycerinated gelatin after the source of heat had been removed from the base. This procedure prevented prolonged heating of the extract which would inactivate the digitalis principles.

In those cases in which the suppositories containing 9 cat units of digitalis were used, it was necessary to administer a fraction more than one suppository to approximate the dosage desired.

SERIES NO. 4.

The results obtained in the preceding experiments indicate relatively poor absorption when cacao butter or glycerinated gelatin are used as suppository bases. It was, therefore, inferred that, perhaps, the absorption was retarded by these bases. To determine the correctness of this observation, a series of experiments was run in which gelatin alone was used as the base and in which the proportion of the latter was reduced to a minimum. This was accomplished by administering No. 1 hard gelatin capsules into which 0.375 Gm. (15 cat units) of extract of digitalis was packed. Prior to insertion of the capsules, water, in an amount equal to about 10 cc., was injected into the rectum to aid the dissolution of the capsule material.

TABLE IV.—ABSORPTION OF EXTRACT OF DIGITALIS IN HARD GELATIN CAPSULES ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs. and Min.		Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
35	3.80	15	3.95	5	4	34.9	0.31	0.08
36	3.15	15	4.76	5	13	30.7	0.08	0.03
37	3.10	15	4.84	5	17	15.0	1.51	0.52
38	3.05	15	4.92	5	21	29.6	0.09	0.03
39	3.00	15	5.00	5	33	14.9	1.51	0.50
40	2.87	15	5.23	5	47	23.0	0.57	0.20
41	2.85	15	5.26	5	38	25.8	0.27	0.09
42	2.85	15	5.26	5	20	25.0	0.35	0.12
43	2.40	15	6.25	5	0	21.6	0.24	0.10
44	2.23	15	6.73	6	21	23.3
45	2.13	15	7.04	5	39	16.3	0.50	0.23
46	1.80	15	8.33	5	19	10.5	0.75	0.42
47	1.80	15	8.33	5	7	14.5	0.35	0.19
48	1.70	15	8.82	5	46	14.0	0.30	0.18

The heart beat of cat No. 37 was weak and irregular throughout the experiment. After death, the heart was examined and found to be in diastole which throws doubt upon the probability of death from digitalis.

SERIES NO. 5.

In the experiments which follow, the possible influence of any extraneous matter was eliminated completely by injecting a dealcoholized tincture of digitalis. The tincture was prepared by the U. S. P. X method and the alcohol was removed by heating to about 50° C. in an open vessel, over which a current of warm air was passed until all of the alcohol had evaporated. The solution was injected by means of a rectal tube attached to a hypodermic syringe.

TABLE V.—ABSORPTION OF DEALCOHOLIZED TINCTURE OF DIGITALIS ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs. and Min.		Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
49	3.80	19	5	5	40	14.5	2.35	0.62
50	3.35	16.75	5	5	28	35.5
51	3.30	16.5	5	5	33	31.0	0.20	0.06
52	3.02	15.1	5	4	53	19.6	1.06	0.35
53	2.85	14.25	5	4	17	19.5	0.90	0.32
54	2.38	11.9	5	5	40	6.5	1.73	0.73
55	2.35	11.75	5	See below		..	2.35	1.00
56	2.02	4.04	2	4	21	17.0	0.32	0.16
57	1.87	9.35	5	5	46	16.3	0.24	0.13

Cat No. 55 died about three hours after receiving the rectal digitalis solution. It is believed that digitalis was the cause of death because the usual symptoms of digitalis poisoning were noted.

CONTROL EXPERIMENTS.

During the course of the experiments, the problem arose as to whether or not the prolonged anesthesia and the clamping of the anus materially affected the results obtained. To solve this problem, control experiments were run as follows:

Two cats were anesthetized in the manner employed throughout this work. As soon as anesthesia was induced, the ani were clamped to simulate the conditions when digitalis was administered rectally. After about six hours, digitalis solution was introduced intravenously in an amount sufficient to kill the cats. This amount was found to be within 10% of the calculated minimum lethal dose in both cases.

DISCUSSION.

The available published clinical reports highly recommend rectal digitalis therapy (2, 3, 4, 5, 6, 7, 8 and 9), citing several advantages for it over the oral method, and suggest it as a substitute for intravenous and subcutaneous administration. The results of the investigations upon which the findings reported in this paper are based do not confirm those reported by clinicians. While it is true that in the experiments from which these results were obtained the test animals used were cats and the drug was administered under abnormal conditions, *i. e.*, prolonged anesthesia and clamping of the anus, it has been shown by control experiments that these abnormalities caused no perceptible effect on the susceptibility of the cats to the drug. It is possible, however, that the application of anal clamps may have either hastened or retarded absorption.

The absorption of digitalis from the rectum was found to be very slow and small in amount considering the large doses which were administered. Nausea and emesis occurred in the interval elapsing between the rectal administration and the intravenous administration of the drug in approximately half of the experiments. This may have been caused by the anesthetic since emesis was observed in one of the controls. The digitalis was observed to be quite irritating to the rectum since it was necessary to clamp the anus to prevent expulsion of the drug and since autopsies disclosed considerable inflammation, even in the recta of those cats on which anal clamps were not used. The rate of absorption from the rectum was also found to be irregular and inconsistent as evidenced by the large variations in the amounts which were absorbed by different cats.

Scrutiny of the preceding tables shows that digitalis is more rapidly absorbed from the rectum when administered in the form of the dealcoholized tincture than in the other forms which were employed. Following, in the order of rapidity of absorption, are glycerinated gelatin suppositories, cacao butter suppositories and finally, hard gelatin capsules.

Since available clinical results indicate rapid rectal absorption, it is evident that either the procedure of study which has been followed does not reflect accurately the absorption in the human, or, it is possible that the means by which other workers made their observations are not sufficiently dependable. Whether or not the procedure used in this work reflects the absorption rate in humans, it is believed that a comparative study of rectal, oral and subcutaneous absorption using this technique, will provide reliable information on the relative absorption rate through the above three avenues of administration in humans. However, future work is contemplated to compare relatively these three means of administration.

In view of the foregoing work, it appears that the rectal mode of giving digitalis may be a good one when digitalization is to be maintained over a rather lengthy period and when a prompt action is not essential.

CONCLUSIONS.

1. Digitalis is absorbed from the rectum.
2. The rectal absorption in cats is very slow, irregular and erratic.
3. Considerable irritation and inflammation was found to be produced in the rectum as a result of rectal administration of digitalis.
4. The most rapid absorption by rectum was observed when a dealcoholized tincture of digitalis was given.
5. The actual significance of these results will not become evident until the absorption rate following oral administration has been determined in the same manner.
6. The rectal method for administering digitalis should be subjected to more investigation before it be accepted as conventional.

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