# THE MARGIN OF SAFETY OF INTRAVENOUS DIGITALIS IN CATS *

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The medical profession has become greatly interested in intravenous therapy in recent years, and although no particular evidence of this enthusiasm has been reflected in the treatment of heart disorders, the work of Eggleston,[1] introducing the administration of large single doses of digitalis by mouth, might well lead others to try the effect of similar preparations intravenously. In the past, intravenous cardiac therapy has been essentially limited to preparations of strophanthin, which is generally considered to be a dangerous procedure. With this in mind, an attempt was made to determine whether the introduction into the blood stream of digitalis in its more complete and less potent form would prove to be a safe method for obtaining a therapeutic effect.

The margin of safety has been taken as the difference between the minimum lethal dose (M.L.D.) and the minimum toxic dose (M.T.D.). We introduce the concept of the margin of safety of digitalis preparations because in the practical use of the drug the therapeutic dose is very close to the toxic dose. Therefore, it is of great importance to know how far removed the lethal dose is from the toxic dose, and whether the margin is greater in some preparations than in others. The minimum lethal dose is that dose which is just required to cause standstill of the heart and death when the digitalis preparation is given in interrupted doses over a period of about one hour, similar to the method of Hatcher.[2] In a previous work by one of us [3] it was shown that the toxic and lethal doses are independent of the speed of administration of the drug from a period of fifteen minutes to four hours; and, therefore, in this work the injections were not given at any constant speed, sometimes producing the lethal effect in about one-half hour and sometimes in two hours or more. Some difference of opinion might exist as to the occurrence of the toxic effect. It is generally thought that the appearance of heart block, changing ventricular complexes, and extrasystoles indicate toxicity. The latter is the most common event in cats, and this was generally considered in timing the

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1. Eggleston, C.: Digitalis Dosage, Arch. Int. Med. **16**:1 (July) 1915.

2. Hatcher, R. A., and Brody, J. G.: A Biological Standardization of Drugs, Am. J. Pharmacy **82**:360, 1910.

3. Levine, S. A.: The Action of Strophanthin on the Living Cat's Heart, J. Exper. M. **29**:485, 1919.

toxic dose. This criterion has the added advantage that it is the most important clinical sign of toxicity, for heart block in itself rarely impairs the efficiency of the circulation, while extrasystoles indicate an increased irritability of the ventricles, and when numerous, certainly diminish the effective output of the heart. The minimum toxic dose, therefore, is calculated in these experiments as the smallest dose that is required to produce extraventricular systoles.

## METHOD OF PROCEDURE

Cats were used in preference to other laboratory animals because their reaction to digitalis is more like that of the human subject. The cat was etherized, placed on the animal board and the right front leg and left hind leg connected with the electrocardiograph. A canula was inserted in the right saphenous vein and attached by a small rubber tube to a 10 c.c. calibrated pipet which served as a buret. The normal electrocardiogram was taken, and the dose of the preparation to be used was then allowed to flow into the vein. One minute before each dose an electrocardiogram was taken, until a toxic effect was expected, previous experience having shown about where this was to occur. During the two critical periods, the beginning of toxic and lethal effects, the movements of the galvanometer string were watched carefully, and frequent tracings were taken to detect the earliest abnormality.

Various different digitalis preparations were used. The first was an aqueous extract of powdered digitalis (Marion, Virginia leaf) prepared according to Pratt;[4] the second was Squibb's powdered digitalis leaves prepared in the same way; the third was Squibb's tincture of digitalis, and finally, three different digitalis preparations in ampoules for subcutaneous and intramuscular use were tested. The details of the experiments are given in the accompanying table. In three experiments the average margin of safety (M.L.D. — M.T.D.) of intravenous aqueous extract of digitalis (Virginia leaf) was 50 per cent., that is, it required approximately half as much of the drug to produce extraventricular systoles as it did to cause standstill of the heart. An identical figure (50 per cent.) was obtained in the average of three experiments using the aqueous extract of Squibb's digitalis leaves. The average for Squibb's tincture of digitalis (five experiments) was 40 per cent.; for digifolin ampoules (one experiment) 50 per cent.; for digalen ampoules (one experiment) 56 per cent., and for digipuratum ampoules (one experiment) 64 per cent. It is evident that there are individual variations in different cats, both in the suscepti-

4. West, H. F., and Pratt, J. P.: Clinical Experience with a Standardized Aqueous Extract of Digitalis, J. A. M. A. **74**:1389 (May 15) 1920.

THE MINIMUM LETHAL DOSE AND MAXIMUM TOXIC DOSE OF VARIOUS DIGITALIS PREPARATIONS

| Cat Number | Weight in Kilos. | Drug | Speed of Administration | Toxic (M. T. D.) Dose | Lethal (M. L. D.) Dose | Per Cent. of M. L. D. that is Toxic | M. T. D. per Kilo. | M. L. D. per Kilo. | Margin of Safety M. L. D. minus M. T. D., per Cent. | M. L. D. per Kilo. in Gm. of Digitalis Leaves | Time for M. L. D. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2.2 | Aqueous extract of Virginia leaf | 0.5 c.c. every 6 min.[1] | 0.033 gm. | 0.06 gm. | 55 | 0.015 gm. | 0.027 gm. | 45 | 0.11 | 1 hr. 56 min. |
| 2 | 2.4 | Aqueous extract of Virginia leaf | 1.0 c.c. every 6 min. | 0.035 gm. | 0.07 gm. | 50 | 0.015 gm. | 0.029 gm. | 50 | 0.13 | 1 hr. 20 min. |
| 3 | 3.2 | Aqueous extract of Virginia leaf | 1.0 c.c. every 6 min. | 0.030 gm. | 0.065 gm. | 46 | 0.009 gm. | 0.020 gm. | 54 | 0.08 | 1 hr. 14 min. |
| 4 | 4.2 | Aqueous extract of Squibb's leaf | 1.5 c.c. every 24 min.[2] | 0.113 gm. | 0.188 gm. | 60 | 0.027 gm. | 0.045 gm. | 40 | 0.11 | 1 hr. 44 min. |
| 5 | 2.9 | Aqueous extract of Squibb's leaf | 0.3 c.c. every 6 min. | 0.038 gm. | 0.105 gm. | 36 | 0.013 gm. | 0.036 gm. | 64 | 0.09 | 1 hr. 10 min. |
| 6 | 2.6 | Aqueous extract of Squibb's leaf | 0.3 c.c. every 6 min. | 0.06 gm. | 0.113 gm. | 53 | 0.023 gm. | 0.042 gm. | 47 | 0.11 | 1 hr. 25 min. |
| 7 | 2.1 | Squibb's tincture digitalis | 0.2 c.c. every 12 min. | 0.1 gm. (1 c.c.) | 0.22 gm. (2.2 c.c.) | 45 | 0.048 gm. (0.48 c.c.) | 0.105 gm. (1.05 c.c.) | 55 | 0.105 | 2 hr. 1 min. |
| 8 | 3.2 | Squibb's tincture digitalis | 0.4 c.c. every 6 min. | 0.16 gm. (1.6 c.c.) | 0.28 gm. (2.8 c.c.) | 58 | 0.050 gm. (0.5 c.c.) | 0.088 gm. (0.88 c.c.) | 42 | 0.088 | 41 min. |
| 9 | 3.5 | Squibb's tincture digitalis | 0.2 c.c. every 6 min. | 0.2 gm. (2.0 c.c.) | 0.34 gm. (3.4 c.c.) | 59 | 0.057 gm. (0.57 c.c.) | 0.097 gm. (0.97 c.c.) | 41 | 0.097 | 1 hr. 44 min. |
| 10 | 3.4 | Squibb's tincture digitalis | 0.35 c.c. every 6 min. | 0.28 gm. (2.8 c.c.) | 0.385 gm. (3.85 c.c.) | 73 | 0.082 gm. (0.82 c.c.) | 0.11 gm. (1.1 c.c.) | 27 | 0.11 | 1 hr. 3 min. |
| 11 | 3.2 | Squibb's tincture digitalis | 0.5 c.c. every 24 min. | 0.30 gm. (3.0 c.c.) | 0.45 gm. (4.5 c.c.) | 67 | 0.094 gm. (0.94 c.c.) | 0.14 gm. (1.4 c.c.) | 33 | 0.14 | 3 hr. 30 min. |
| 12 | 2.3 | Digifoline ampoules[3] | 0.25 c.c. every 6 min. | 0.175 gm. (1.75 c.c.) | 0.35 gm. (3.5 c.c.) | 50 | 0.076 gm. (0.76 c.c.) | 0.152 gm. (1.52 c.c.) | 50 | .... | 1 hr. 19 min. |
| 13 | 3.1 | Digalen ampoules[4] | 0.25 c.c. every 6 min. | 0.83 mg. | 1.88 mg. | 44 | 0.27 mg. | 0.61 mg. | 56 | .... | 2 hr. 30 min. |
| 14 | 1.3 | Digiparatum ampoules[5] | 0.1 c.c. every 6 min. | 0.05 gm. (0.5 c.c.) | 0.14 gm. (1.4 c.c.) | 36 | 0.038 gm. | 0.11 gm. | 64 | .... | |

1. 100 gm. of Virginia leaf gave 24.5 gm. of aqueous extract. 1 c.c. = 0.005 gm. equeous extract.
2. 100 gm. of Squibb's powdered leaf gave 39.5 gm. of aqueous extract. 1 c.c. of solution = 0.025 gm. aqueous extract.
3. 1 c.c. = 0.1 gm. digitalis leaves; Society of Chemical Industry, Basle, Switzerland. (Ciba Co., New York).
4. 1 c.c. = 0.3 mg. amorphous digitoxin, Hoffmann, La Roche Chemical Works, N. Y. (Made in Switzerland).
5. 1 c.c. = 0.1 gm. of digipuratum powder, manufactured by Knoll & Co., Ludwigshafen. (Merck and Co., N. Y.).

bility to the drug and in the margin of safety, which varied from 27 to 73 per cent. Similar variations are found in the intravenous use of ouabain.[3] Undoubtedly, similar individual variations in susceptibility to digitalis are present in the human and should always be taken into account in practical therapy. The average margin of safety of all the experiments in this study was 48 per cent. This is identical with the result obtained with crystalline strophanthin or ouabain.[3]

The practical consideration that follows from these experiments is that although the various digitalis bodies, when given by mouth, are generally regarded as much safer than intravenous administration of strophanthin, when the entire digitalis glucosids (either the aqueous or alcoholic extracts) are given intravenously, the same risk is encountered as in using strophanthin. In fact, the rapidity with which the drugs act on the heart does not seem to differ very much no matter what preparation is put directly into the circulation. In one experiment, a single lethal dose was given and the toxic effect occurred in two minutes, and standstill in sixteen minutes. Large single doses of strophanthin produce death in from nine to thirty minutes.[3] In two experiments the interval between injections was purposely prolonged to twenty-four minutes to allow the opportunity of determining how soon after an injection the effect appears. It was found that the toxic effect occurred within three minutes after the injection. In experimenting with crystalline strophanthin, an interval of six minutes between injections was found sufficiently long to bring out any changes, that is, waiting from twelve to twenty-four minutes did not alter the results. Practically the same findings were observed using digitalis; i. e., if an effect is to occur at all with interrupted injections it will result within six minutes after the last one.

## CONCLUSIONS

1. The average margin of safety (the difference between the minimum lethal dose and the minimum toxic dose) of various digitalis preparations when given intravenously to cats was found to be 48 per cent.

2. The rapidity with which intravenous digitalis acts is similar to strophanthin, and does not differ appreciably no matter what preparation is put into the blood stream.

3. The risk in intravenous digitalis therapy appears from these experiments to be as great as in intravenous strophanthin.

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