The Cat and Dog Units of Digitalis

*By J. A. Bone, J. W. Elam and Philip Blickensdorfer**

Blickensdorfer and McGuigan, by the use of dogs, found the U. S. P. 1938 Digitalis Reference Powder to be 20 per cent stronger than labeled. Their results with cats were inconsistent and required more work before definite conclusions could be drawn regarding the dose for cats. The object of this work is to determine more accurately the cat dosage.

In their short series of experiments with cats, Blickensdorfer and McGuigan (Table III of their article, see page 103 of THIS JOURNAL) found that the dosage of the reference powder for the dog was 1.2 cc. per Kg. body weight. However, the results with cats showed too wide an individual variation to be acceptable. Part of this variation they think is due to the high concentration of the reference powder. In any biological standardization, an unaccountable variation of 10 per cent or more may occur. If the preparation is stronger than standard, the variations may be greater. When they used the factor 0.62 instead of 0.745, their dosage for cats was less than the dosage for dogs. However, the number of cats used (5) is insufficient to accept their results as the cat unit. In this work we have used enough cats to justify a comparison of the cat dosage with that for dogs.

EXPERIMENTAL

Method Used.—Cats were anesthetized with pentobarbital, 35 mg. per Kg. intraperitoneally. The tincture of digitalis was injected slowly into the femoral vein at the rate of 0.1 cc. per kilo every five minutes, until the heart stopped. Artificial respiration was used throughout. The tincture of digitalis was prepared by using the ratio of 0.62 Gm. of the reference powder, macerated for 24 hours, in 10 cc. of 70 per cent alcohol. The alcohol in this dose has little effect on the heart and kills by action on the respiratory center. By actual experiment we have found that at least four times the volume of alcohol is necessary to kill, and then by action on the respiratory center.

We used about an equal number of male and female animals, without noticeable difference in the results. The animals were all in an excellent state of health, and were not kept in captivity after bringing to the laboratory. We think incarceration except under rare conditions may mitigate against uniform results.

The following table shows the complete data:

Table I.—Results with a Tincture Prepared with U. S. P. Digitalis Reference Powder (0.62 Gm. in 10 Cc. 70% Alcohol)

Wt. of Cat, Kg.	No. of Injections	Total Dose, mg. per Kg. (Corrected)	Units per Kg.
3.3	10	100	1.00
3.4	13	130	1.3
3.0	$8^1/_2$	80	0.8
3.4	12	120	1.2
3.2	10	100	1.0
2.6	8	80	0.80
3.0	10	100	1.00
2.3	10	100	1.00
2.3	12	120	1.20
3.1	11	110	1.10
2.3	10	100	1.00
2.8	10	100	1.00
2.7	11	110	1.10
2.0	10	100	1.0
3.1	12	120	1.2
3.7	11	110	1.1
2.85	11	110	1.1
2.2	9	90	0.90
3.6	10	100	1.0
2.6	6	60	0.6
3.0	8	80	0.8
2.5	12	120	1.2
4.2	9	90	0.9
3.1	9	90	0.9
2.6	12	120	1.2
Average	10.16	101.6	1.016

Table II.—Results with a Tincture Prepared with the International Powder (0.8 Gm. in 10 cc. 70% Alcohol)

Wt. of Cat, Kg.	No. of Injections	Total Dose, mg. per Kg. (Corrected)	Units per Kg.
2.7	9	90	0.90
1.9	11	110	1.10
3.3	9	90	0.90
3.2	10	100	1.00
2.5	12	120	1.20
Average	10.2	102	1.02

SUMMARY AND CONCLUSIONS

The results with cats, as with dogs, support the opinion that the U. S. P. Digitalis Reference Powder is twenty per cent stronger than labeled. Instead of the factor of 0.745, the strength found is 0.62. Using this factor our results with cats are in harmony with previous workers and the average found is almost "ideal" for a dose of 1.00 cc. per Kg. weight of cat. Almost any sequence of five cats gives accurate results and within 10 per cent of the average dose. However, much of the idealism vanishes, when we note that the range varies between

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six and thirteen injections. Yet the average which must be taken is good, and the majority of the findings are close to the average. The method we present is simpler than that presented by others, in that the tincture may be used directly. The alcohol is not an interfering agent, since it kills, not by action on the heart but by action on the respiratory center, and several times the volume contained in the tincture is required to kill. Pentobarbital, as we have used it, is as good an anesthetic for cats, as for dogs.

In terms of the International Standard, the U. S. P. Reference Powder is 80/62 = 129% or 29 per cent stronger.

The experiments recorded in this paper and that by Blickensdorfer and McGuigan show:

1. That by the use of both dogs and cats, the U. S. P. Reference Powder is 20 per cent stronger than it is labeled. Instead of the factor 0.745, the factor 0.62 is more nearly correct.

2. When a tincture is prepared using 0.62 Gm. of the reference powder in 10 cc. alcohol, or 6.2 Gm. in 100 cc., the dose for dogs is 1.2 cc. per Kg. body weight. The dose for cats is 1.0 cc. per Kg.

3. The results are in harmony with the Hatcher dose for the cat, and agree closely with the results reported by other investigators using the frog method.

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The Action of Ephedrine on Halogenated Organic Compounds*

By Frank A. Steldt and K. K. Chen

The fact that ephedrine base reacts with chloroform to give ephedrine hydrochloride was first pointed out by Peterson in 1927 (1). To date no other organic compounds have been reported to have a similar reaction with ephedrine, although *a priori* it would seem possible. In order to test the validity of this idea, the present investigation was undertaken.

EXPERIMENTAL

A total of thirty-one halogenated organic compounds was examined. As shown in Tables I and II, twenty-three of the compounds reacted with ephedrine base to give the corresponding halide salt, and one, *o*-chlorobenzaldehyde, gave an addition product. The formation of the last substance is not surprising for ephedrine has been known to react with certain aldehydes, forming addition products in the proportion of one molecule of ephedrine to one molecule of aldehyde with the elimination of one

Table I.—Reaction with Ephedrine Base

Number	Name of Compound	Reaction with Ephedrine Base
1	Allyl bromide	+
2	Allyl iodide	+
3	Allyl chloride	+
4	*i*-Amyl bromide	+
5	*i*-Amyl chloride	+
6	Benzotrichloride	+
7	Benzyl chloride	+
8	Bromal	+
9	Bromoform	+
10	Carbon tetrachloride	+
11	Chloral	+
12	*o*-Chlorobenzaldehyde	+
13	β-β′-Dichlorethyl ether	+
14	Ethyl chloride	+
15	Ethylene chlorhydrin	+
16	Ethylene bromohydrin	+
17	Ethylene dichloride	+
18	Glycerol α-monochlorohydrin	+
19	*n*-Propyl chloride	+
20	Propylene dichloride	+
21	Tribromoethanol (avertin)	+
22	Tribromoethylene	+
23	Trichloroethylene	+
24	*i*-Amyl iodide	+
25	Bromobenzene	−
26	Chlorobenzene	−
27	*o*-Chlorophenol	−
28	Iodobenzene	−
29	*tert*-Butyl chloride	−
30	*o*-Chlorophenetole	−
31	Trichlorobenzene	−

* From the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.