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Effect of Sympathicolytic and Other Agents on Toxicity of Digitalis in Cats.

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Wegria *et al.*[1] note that ventricular fibrillation caused by toxic doses of digitalis in the dog is of a different type than that evoked by electric stimuli or coronary occlusion and that ventricular fibrillation accordingly may be induced by more than one mechanism. The present study offers proof that the type elicited by digitalis differs also from that caused by epinephrine, chloroform or other adrenergic agents.

A number of substances have been found effective against fibrillation provoked by treatments other than digitalization.[2-9] Of these, the 2 sympathicolytics, piperidinomethylbenzodioxane (933F) and diethylaminomethylbenzodioxane (883F), and procaine are most certain. Their mode of action is not satisfactorily explained; but slitting the pericardium produces the same result,[10] which suggests that a sudden rise in intracardiac pressure may be the precipitating factor for fibrillation. While the cardiac dilatation which occurs terminally in digitalis intoxication is considered a result rather than a cause of arrhythmia and fibrillation, a test of these agents was thought warranted. Recent introduction of potent digitalis derivatives[11] and revival of interest in rapid digitalization[12] have increased therapeutic hazards, for the absence of more frequent clinical accidents is a measure of skill in administering digitalis rather than of the margin of safety of the agent.

Tr. digitalis was administered as in a cat assay method.[13] One cc/kg of a 1:15 dilution was rapidly injected intravenously every 5 min in 33 cats lightly anesthetized with ether, until the heart stopped. Phases of the digitalis effect were followed by frequent auscultation. The test agents were dissolved in the diluted tincture and their administration was usually begun after the heart showed definite digitalis effects. In some instances, as noted in Table I, these agents were given from the first digitalis injection, and in 2 cats saline solutions of 933F or quinidine sulfate were given at 5 min intervals prior to digitalization.

Haag[14] has shown that kittens are similar to cats in their resistance to lethal effects of digitalis, and 6 kittens were distributed proportionately in the 5 groups. Cats were also divided approximately equally as to sex, in each group. Neither weight nor sex was related to toxicity of digitalis, although the endpoint was less sharp in kittens because fibrillation apparently took a longer course than in cats. Hearts were removed after death, opened, trimmed, washed, blotted dry and weighed. In g/kg, the heart weight/body weight ratios and their standard errors were:

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14 Haag, H. B., and Corbell, R. L., Jr., *J. Pharmacol.*, 1940, **68**, 45.

TABLE I.
Effect of Various Agents on Toxicity of *Tr. digitalis* in Cats.

Agent	Single doses, mg/kg	Time of injection single doses (digitalis inj. No.)	Total dose, mg/kg	Lethal dose of *Tr. digitalis* in cc/kg	
				Individual cats	Mean ± Std. Error
None	—	—	—	.60, .60, .67, .73 .73, .80, .80, .80 .87, .87, .93, .93	.78 ± .03
Procaine	1	9-14	6	.93, .93	
	2	9-11	6	.73	
	3	9-11	9	.73	.77 ± .07
	3	9-12	12	.80	
	10	6-7	20	.47	
933F	1	4-11	8	.73	
	1	4-12	9	.80	
	1	1-11	11	.73	.78 ± .01
	2	8-12	10	.80	
	2	1-12	24	.80	
	—	2x5 mg + 5x2 mg prior inj.	20	.80	
883F	1	4-11	8	.73	
	1	1-12	12	.80	.79 ± .06
	1	1-14	14	.93	
	2	8-10	6	.67	
Quinidine	2.5	1	2.5	.07	
	2.5	6-8	7.5	.53	
	2.5	6-10	12.5	.67	.40 ± .14
	2.5	1-10	25	.67	
	—	4x2.5 mg prior inj.	10	.07	

4.61 ± 0.12, 4.67 ± 0.41, 4.62 ± 0.17, 4.36 ± 0.24 and 4.61 ± 0.32 for groups treated with digitalis alone, and digitalis + procaine, 933F, 883F, and quinidine, respectively.

Results are noted in Table I. None of the drugs except quinidine produces a difference in the lethal dose of digitalis. Results with quinidine are most variable: 1 cat, not included in Table I, died after administration of 2.5 mg/kg alone; another from 2.5 mg/kg in 0.067 cc/kg of Tr. digitalis; and another following 10 mg/kg before 0.067 cc/kg of tincture. The lethal dose of quinidine alone is stated[15] to be 80-100 mg/kg when given intravenously in cats but idiosyncrasy is common. With 933F and 883F, the higher doses given approach the lethal range; the former particularly causes light narcosis, so that ether anesthesia is not required during the period of digitalization when it is given. A cat treated with a single injection of 10 mg/kg of 933F alone died of respiratory failure when ether anesthesia was continued, while another received 20 mg/kg and survived when ether anesthesia was promptly discontinued; consequently the depth of anesthesia was closely controlled in digitalized cats receiving 933F or 883F.

Cardiac failure was the cause of death in all cats receiving digitalis, with the exception of 1 cat treated with 20 mg/kg of procaine during digitalization which died of respiratory failure. The lethal dose of procaine is 55-60 mg/kg in cats on intravenous administration.[15] In the remaining 32 cats, the symptoms were entirely those of digitalis: bradycardia followed by increasing tachycardia, arrhythmia and fibrillation. Despite the failure of procaine, together with the other agents, to increase the lethal dose of digitalis, small doses elicited a definitely beneficial effect on the arrhythmia preceding fibrillation in the later extravagal phases of the digitalis action. This beneficial effect of procaine was of short duration, never exceeding 2 min after each

[15] Sollmann, T., and Hanzlik, P. J., *Fundamentals of Experimental Pharmacology*, J. W. Stacey, San Francisco, 1939.

injection, and was evoked as well by single doses of 1 mg/kg as by 3 mg/kg. While procaine had an inappreciable effect on toxicity of digitalis under the conditions of the experiment, it might be of at least transient beneficial effect under other conditions.

Summary. 933F, 883F, procaine and quinidine do not increase tolerance of cats to lethal effects of digitalis. Ventricular fibrillation induced by digitalis overdosage is of a different type than that elicited by epinephrine or related agents.

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Fatal Loss of Plasma Volume After Lymph Heart Destruction in Toads.

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In certain cases of shock and after severe burns there is a tendency toward blood concentration. Determinations of total red cell volume or count per cubic millimeter when compared with determinations of plasma proteins and other plasma constituents suggest that the hemoconcentration is due to loss of whole plasma from the blood vessels into the tissue spaces, where it remains manifest as an edema. Normally, the lymphatic system returns any excess intercellular fluid to the blood circulation.

In batrachians, lymph flow is aided by 4 lymph hearts. In both toads (*Bufo arenarum* Hensel) and frogs (*Leptodactyllus ocellatus*) the 2 anterior and 2 posterior lymph hearts can be easily destroyed by thermocautery. Foglia and his collaborators[1,2,3,4] found that if the operation was complete, death ensued in 4 days. Marked changes were found to occur in the water and electrolyte concentrations of blood, lymph and tissues, beginning at operation and continuing until death. There was an enormous increase in body weight due to water retention (60%). These animals were kept in sinks moistened by dripping water and the water absorbed through the skin was retained in the tissue spaces. Since the interstitial fluid failed to reach the blood stream it could not be eliminated by kidney excretion. A complete bibliography of the problem will be found in the paper by Braun-Menendez and Foglia.[3]

During the course of the experiments by Foglia and Gerschman,[2] some animals without lymph hearts were kept in a chamber with high humidity but no liquid water. These toads died with no gain or loss in body weight.

We thought it worth while to investigate the fluid distribution and concentration in this type of experiment since with diminished urine excretion, most of the changes would involve an internal redistribution of water.

Material and Methods. The toads (*Bufo arenarum* Hensel) were operated in one stage under ether anesthesia. All 4 lymph hearts were destroyed by electrocautery using the technic described in previous papers.[1,3] In operated controls an equal connective tissue and muscle area was burned in a nearby region.

Red cell volume was determined in a 10 cm capillary tube with freshly drawn blood, by centrifugation at 3500 r.p.m. for 20 minutes. Coagulation was prevented by a few grains of dry heparin (Connaught Labs.).

Specific gravity of plasma and lymph were determined by the falling drop technic of Barbour and Hamilton.[5] This was converted

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3 Braun-Menendez, E., and Foglia, V. G., *Arch. Inter. de Pharm. et Therap.*, 1940, **64**, 273.

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5 Barbour, H. G., and Hamilton, W. F., *J. Biol. Chem.*, 1926, **69**, 625.