

Contributed and Selected

INFLUENCE OF ALCOHOL UPON THE TOXICITY OF DIGITALIS FOR GUINEA PIGS.

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In a recent paper on biological standardization, Eggleston¹ draws attention to the fact that in Hatcher's cat method the presence of alcohol does not influence the results when the digitalis bodies are tested. He suggests that this may not be the case when the guinea pig or frog is used as a test animal. The following experiments were carried out upon guinea pigs and rabbits in the attempt to secure definite information regarding this point. The preparations tested were ordinary U. S. P. tinctures of digitalis, containing originally 48 percent alcohol, in which form they were used in the experiments recorded in Table I. All injections were made subcutaneously with Hitchens' syringe² and the animals were observed for twenty-four hours. It was found convenient to cover the needle hole with collodion to prevent oozing of injected fluid. Doses are given in fractions of a cubic centimeter per gram body weight.

TABLE I.
A. Tests Upon Guinea Pigs.
Tr. No. 1.

Date	Survived	Died	Minimum Lethal Dose
6-11-12004 .004 .004 .0065 .007.		.007+

B. Tests Upon Rabbits.
Tr. No. 2.

9-26-12003 .006		.008+
9-27-12007 .008		

Portions of the two tinctures used in the preceding experiments were evaporated to a semi-fluid consistency on the water bath and this residue suspended in a volume of distilled water one-half that of the amount of tincture taken. When the injections were made an equal amount of distilled water was added, bringing the volume dose up to that of untreated tincture.

TABLE II.
A. Tests Upon Guinea Pigs.
Tr. No. 1 evaporated on water bath; residue suspended in distilled water.

Date	Survived	Died	Minimum Lethal Dose
6-14-12		0.0080 0.0075 0.0060	0.0045
6-15-12		0.005 0.005 0.0045	
6-17-12		0.0040	
10- 4-12	0.004	0.005	

B. Tests Upon Rabbits.
Tr. No. 2 evaporated on water bath; residue suspended in distilled water.

Date	Survived	Died	Minimum Lethal Dose
9-26-12	0.002 0.004		0.006
9-27-12	0.005	0.006	
9-28-12	0.005	0.006 0.006	
9-30-12		0.006 0.006 0.006	
10- 1-12	0.005		

It is evident from these figures that the original tinctures possessed considerably less toxicity for guinea pigs and rabbits than they did after removal of the alcohol. Several factors must be considered, however, before the assumption can be made that this difference is due to the antagonistic action between digitalis and alcohol. It is possible that heating the tinctures upon a water bath might cause a decomposition of the active glucosides into bodies of greater toxicity. The simplest way to decide this is to make the alcoholic strength of the suspension the same as that of the original tincture, and this was done in some instances by taking up the residue with 50 percent alcohol, in others, by using an equal volume of 95 percent alcohol, when the double-strength aqueous suspension was injected, whereby the suspension was brought up approximately to the original volume and alcoholic strength of the tincture.

TABLE III.
A. Tests Upon Guinea Pigs.
Aqueous suspension from Tr. No. 1 with alcohol up to 48% added.

Date	Survived	Died	Minimum Lethal Dose
6-15-12	0.007		0.008
10- 3-12		0.014 0.016	
10- 4-12	0.007	0.008	

B. Tests Upon Rabbits.
Aqueous suspension from Tr. No. 2 with alcohol up to 48% added.

9-28-12	0.008	0.009	0.009
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TABLE IV.
A. Tests Upon Guinea Pigs.
Aqueous suspension from Tr. No. 1. 95% alcohol. Separate injection sites.

Date	Survived	Died	Minimum Lethal Dose
6-17-12		0.007 0.007	0.0045
10- 3-12		0.006 0.008	
10- 4-12	0.0035 0.0040		

B. Tests Upon Rabbits.
Aqueous suspension from Tr. No. 1. 95% alcohol. Separate injection sites.

Date	Survived	Died	Minimum Lethal Dose
9-30-13		0.007 0.007 0.008 0.008 0.006 0.006 0.006	.006

From this, it would seem that when alcohol is injected simultaneously with the treated tincture the toxicity of the latter is no greater than that of the original tincture; or, in other words, the heating and drying did not, in themselves, apparently increase the toxicity of the tincture. As further confirmation, one aqueous suspension was compared with the original tincture by means of Cushny's frog-heart method, and the strength found to be practically the same.

Another point, however, is whether this decreased toxicity of digitalis in the presence of alcohol is due to a true antagonism between the two substances or due to some local action of the alcohol. To decide this, a series of injections was made into guinea pigs and rabbits, the aqueous suspension and 95 percent alcohol being used in equal volumes, but the injection sites being different. The results are given in Table IV.

From these results it would seem that the protective power of alcohol against poisoning by digitalis is due to some local action of the alcohol, because when the digitalis solution and the alcohol are injected into different spots the former appears to have fully as much toxicity for rabbits and guinea pigs as where no alcohol is used. From appearances at the end of 24 hours, the digitalis seemed entirely absorbed whether alcohol was present or not.

It is clearly evident, however, that when digitalis preparations are tested by subcutaneous administration to guinea pigs or rabbits, account must be taken of the alcoholic content of such preparations, because the results will be markedly influenced by the presence of considerable amounts of alcohol.

Experiments, which will soon be published, have been carried out upon frogs, using the one-hour method, and it has been found that alcohol to the amount of 25 percent has no influence upon the results. The dilution of most galenic preparations necessary for testing by Cushny's method reduces the alcoholic contents to this figure when normal saline or water is used as a diluent.

BIBLIOGRAPHY.

1. Eggleston: Am. Jr. Pharmacy, Vol. 85, No. 3, page 99.
2. Hitchens: Journal of Exper. Med., Vol. VIII, page 646.

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