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STUDIES ON THE PHARMACOLOGY AND TOXICOLOGY OF ACOVENOSIDE A.

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INTRODUCTION.

The tree *Acokanthera venenata* (gifboom, poison tree) has long been known to cause deaths from cardiac arrest in animals. Veldsman (1949) isolated a glycoside which he originally named "venenatin" from the plant. The name now given to the principle is Acovenoside A. Sapeika (1949) reported that it had a digitalis-like action. The object of this paper is to report further investigations into the pharmacological and toxicological actions of the glycoside.

EXPERIMENTAL RESULTS.

1. *Perfused Rabbit's Heart.*

Perfusion of the excised rabbit heart with fluid containing 1/500,000 acovenoside A. confirmed the digitalis-like action as shown in Figure 1.

2. *Arterial Blood Pressure of the Narcotised Dog.*

Dogs were anaesthetised with nembutal and the femoral blood pressure recorded by direct canulisation to a mercury manometer. As shown in Figure 2. the subcutaneous injection of ·05 mg. per kilo body weight caused a marked augmentation of pulse pressure and a rise in mean arterial pressure within 15 minutes. The dose was repeated after 20 minutes and a further rise in blood pressure resulted. A total dosage of ·2 mg. per kilo body weight raised the blood pressure from the original ± 100 mm. Hg to ±130. The further injection of ·1 mg. per kilo caused excessive hypertension (± 145 mm. Hg) and cardiac arrest.

From three such experiments performed it appeared that the minimal dose to cause an immediate and demonstrable alteration in blood and pulse pressures was of the order of ·05 mg. per kilo body weight while the rapidly lethal dose was between ·3 and ·5 mg. per kilo. This applies to healthy dogs anaesthetised with nembutal.

The Isolated Coronary Artery.

W. H. Andrews of this section investigated the action of acovenoside A on rings of ox coronary artery in the Dale Bath. As shown in Figure 3 the glycoside proved some four times more active in causing coronary constriction than acetylcholine.

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FIGURE 1.

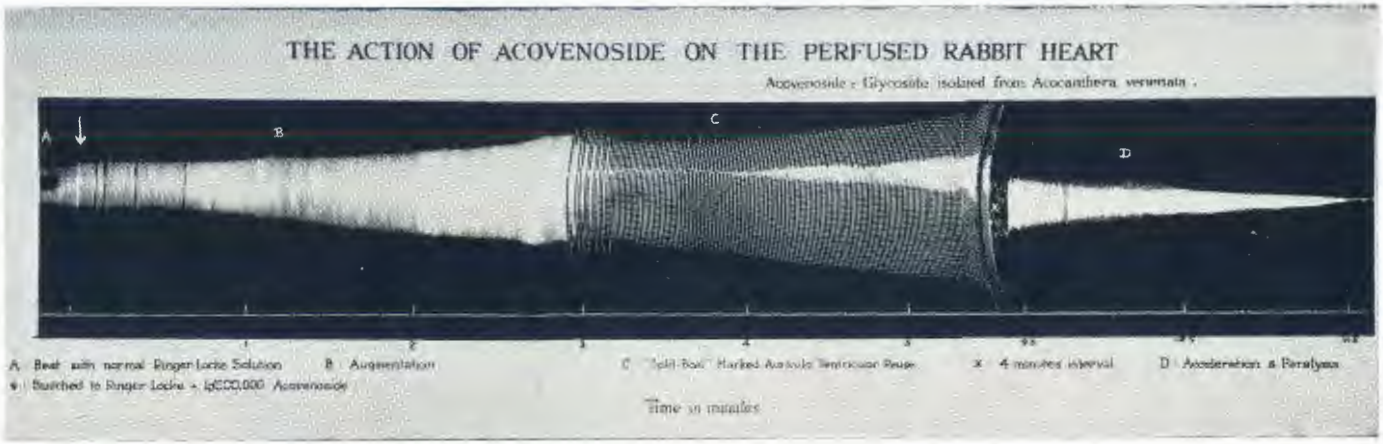


FIGURE 2.

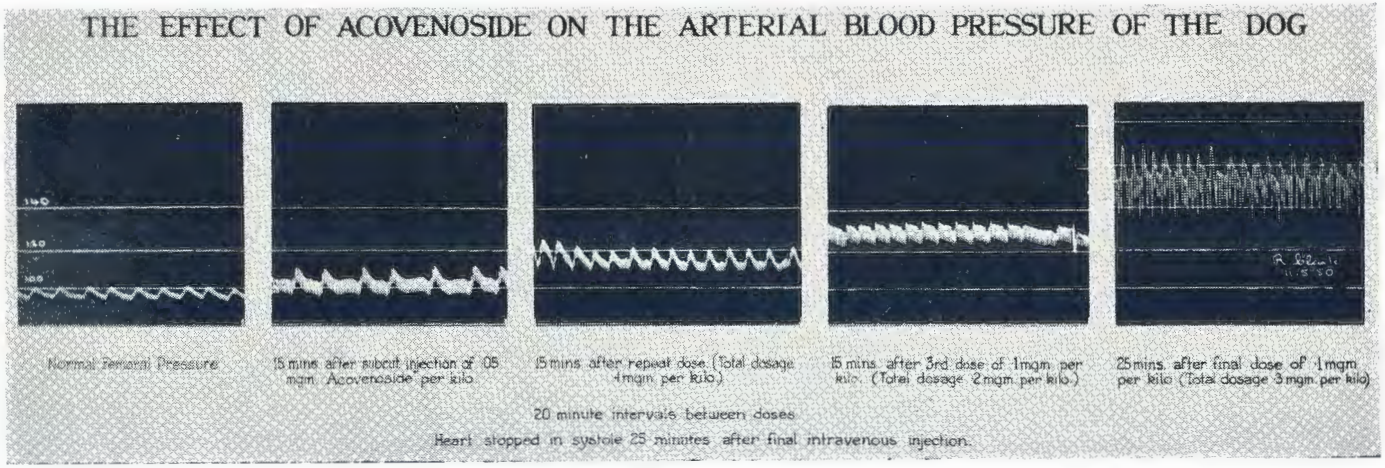
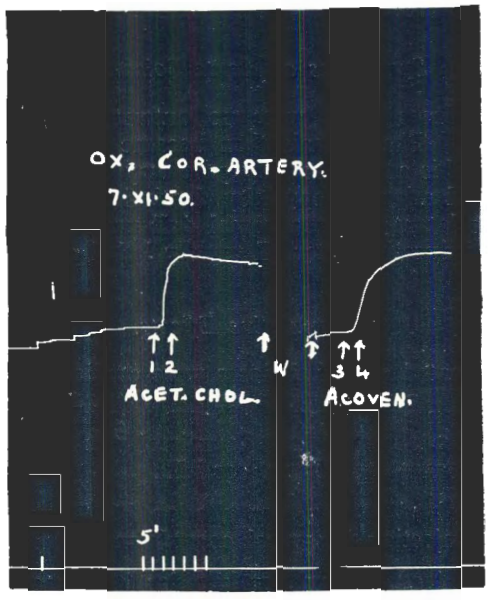


FIGURE 3.

The Action of Acovenoside A. on the Coronary Artery of the Ox.



OX-CORONARY ARTERY.

Chain of 4 rings, in Locke's fluid at 38° C. Lever magnification 6:1. Botha 90 c.c.

1. Added acetylcholine—0·5 c.c. solution, containing 5 mgm.
2. Added acetylcholine—0·5 c.c. solution, containing 5 mgm.

W Washed.

3. Added acovenoside—0·2 c.c. alcoholic solution, containing 1·0 mg.
4. Added acovenoside—0·3 c.c. alcoholic solution, containing 1·5 mg.

Up equals contraction.

Time tracing 5 minute intervals.

Toxicity for Goats.

As ruminants are usually affected with acokanthera poisoning the toxicity of the glycoside for goats was investigated. The following table summarises the initial experiments.

TABLE 1.

Goat No.	Dose mg./Kilo.	Result.
1	2·0	Died in ½ hour.
2	1·5	Died in 1¾ hour.
3	1·0	Died in 1 hour.
4	5·0	Died in 2 hours.
5	0·5	Survived.
6	0·1	Survived.

The drug was in all cases injected subcutaneously. As will be seen the Ld 50 of a single dose would appear to be in the vicinity of ·5 mg. per kilo body weight or approximately the same as for dogs. The survival time was roughly proportional to the dose.

Symptoms of Acute Poisoning.

Even with large doses there were no outward visible signs for some 30 minutes after injection. The animals then became dull and listless and showed increased salivation. This apathy rapidly gave way to intense excitement, restlessness and continuous bleating followed by death in convulsions. Smaller doses merely lengthened the latent and prodromal dull periods, the acute attacks being similar in severity and duration after all rapidly lethal doses.

Cumulative Effects.

The effects of repeated sublethal doses were studied in dogs and goats.

Dogs.—One dog was injected with ·05 mg. per kilo body weight daily. No gross clinical effects were observed but the animal was found dead on the twelfth day, i.e. after a total dosage of ·55 mg. per kilo.

Goat No. 1.—Received ·1 mg. per kilo on 26, 27 and 30/11/50 and died 3 hours after the last injection in typical convulsions.

Goat No. 2.—Received ·5 mg. per kilo for 7 consecutive days and died 2 hours after the last injection.

Goat No. 3.—Received ·05 mg. per kilo on 14 occasions over a period of 35 days without showing any ill-effects. It was finally destroyed with a view to the histopathological examination of the internal organs.

Post Mortem Findings.

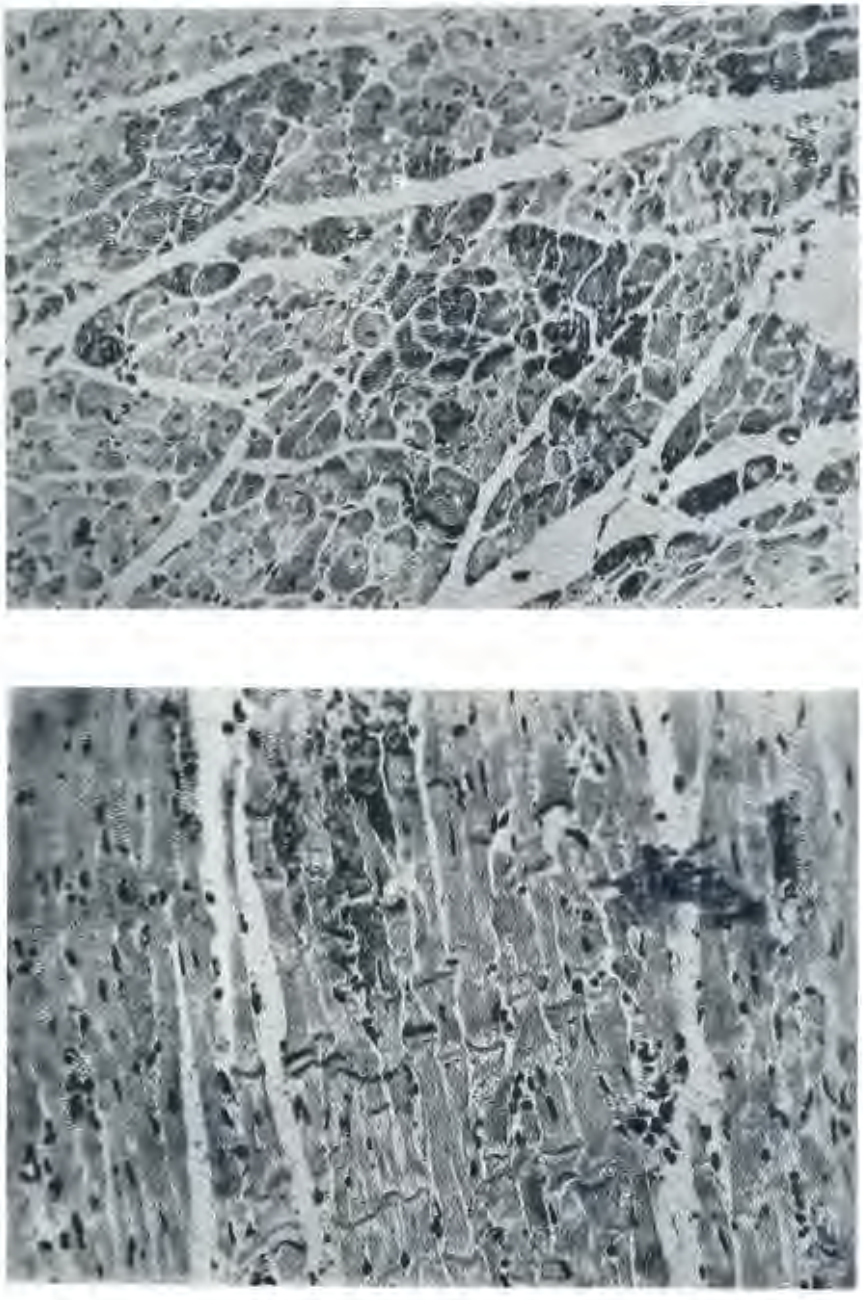
The post-mortem findings were identical in all deaths from acovenoside poisoning whether these were caused by single doses or by cumulative small doses. The ventricles of the heart were found in rigid systole while the auricles were distended with blood clots. There was also a marked generalised venous stasis and oedema of the lungs.

The dogs all showed an acute haemorrhagic diathesis throughout the intestine and patches of acute reddening of the mucosa of the large intestine were found in the goats that died from repeated doses. This finding may account for the haemorrhagic diarrhoea described by Steyn (1934) as a symptom of acokanthera poisoning.

No macro- or microscopic morphological changes were found in the myocard of animals which died from single large doses. The myocard of animals which received repeated injections, however, all showed morphological changes to a greater or lesser extent. This consisted of a very diffuse fine fibrosis associated with focal collections of fibroblasts and round cells. There was also a disseminated focal myocardial degeneration in which the fibrillae disappeared and the fibre became either homogeneous or granular with pyknosis of the nuclei. Fibrillar rupture was frequently seen. These changes are very similar to those described by Rothlin (1947) in a case of prolonged administration of digitoxin to a cat.

FIGURE 4.

Myocardial Degeneration.



One of the goats (No. 2) which died after receiving ·5 mg. acovenoside per kilo body weight for seven consecutive days showed a very peculiar lesion of the myocard. This consisted of a degeneration in which the interlopated discs appeared to have swollen both laterally and longitudinally, giving the fibre the appearance of a bamboo cane. On either side the fibrillae were degenerated and frayed. These changes are shown in Figure 4.

DISCUSSION.

It has been shown that Acovenoside A. is a typical cardio-active glycoside in both its pharmacological and toxicological actions. It is highly cumulative. either materially or functionally, and by prolonged action can cause disseminated interstitial fibrosis and focal degeneration of the myocard.

The macroscopical post-mortem lesions are very similar to those of heart-water (*Rickettsia ruminantium* infection) but the characteristic rigid systole of the ventricles in acovenoside poisoning should differentiate the two conditions.

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