Br. J. Pharmac. (1970), **38**, 616–619.

The effect of acetyl strophanthidin on the hearts of normal dogs

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Summary

1. The ED50 of acetyl strophanthidin for producing ventricular arrhythmias in normal dogs was 54·5 μg/kg intravenously.

2. Doses up to and including those which caused ventricular tachycardia did not produce either atrial arrhythmias or significant aberration of A–V conduction.

3. Although the classic digitalis-induced rate and e.c.g. waveform changes may appear after administration of acetyl strophanthidin, their presence or absence have no value in predicting the subsequent development of ventricular arrhythmias.

Introduction

Acetyl strophanthidin (AS) has long been known to have a digitalis-like action which can be demonstrated on isolated mammalian papillary muscle as well as on intact hearts (Chen & Elderfield, 1942 ; Greiner & Reilly, 1952). Increased force of contraction, diminished cardiac rate, and various arrhythmias have all been observed after its administration. Of special interest is the fact that AS has a very rapid onset and a brief duration of action, even surpassing ouabain in these respects (Gold, Otto, Modell & Halpern, 1946 ; Gold, Model, Kwit, Shane, Dayrit, Otto, Kramer & Zahm, 1948).

As with all digitalis-like preparations, however, the full therapeutic dose and the toxic dose which will produce cardiac arrhythmias are very close. For example, Root & Chen (1953), using a dog lung preparation, found that the failing heart was restored to near normal function by 100 μg of AS, but 150 μg produced cardiac irregularities in three out of four animals. In general, digitalis effects in man and animals include configurational changes in the e.c.g., atrial and ventricular arrhythmias, and alterations in atrioventricular conduction ; slowing of the failing heart is often an early effect of digitalis, but in the non-failing heart it is seen rarely in man and inconstantly in animals (Goodman & Gilman, 1965). It would therefore be important to define some e.c.g. guide or warning which would herald the approach of the dose which will cause arrhythmias. This would be useful in the laboratory evaluation of cardiac drugs. In this circumstance the rapid development of digitalis action in the normal heart is often necessary and an appropriate e.c.g.

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warning would avert undesired effects. These experiments were planned to seek such a sign.

Methods

Twenty-six adult male mongrel dogs, weighing between 7·25 and 18·0 kg, were used. They were anaesthetized with 30 mg/kg pentobarbitone sodium administered intravenously. Heart rate and electrocardiogram were monitored using a pair of needle-tip electrodes placed in either side of the chest wall and connected to an E & M physiograph. Acetyl strophanthidin (Eli Lilly Co.) was used in alcoholic solution, each ml containing 0·5 mg (equivalent in potency to approximately 3 cat units).

Following a control period of 5–10 min after anaesthesia, the undiluted AS was administered intravenously over approximately 10–15 s. Doses used ranged from 25 to 60 μg/kg and were given to the animals in a random order. Retrospective review of the data revealed no fortuitous correlation between doses/kg and body weights.

A continuous e.c.g. tracing was taken from the control period to at least 20 min after drug administration. The records were evaluated and the following parameters analysed: rate, rhythm, P–R interval, S–T segments, T waves, and Q–T interval. In all cases each dog served as his own control.

Results

Of the twenty-six dogs, eighteen showed a diminution in heart rate ranging from 50% (160 to 80 beats/min) to 7% (150 to 140 beats/min). The remaining eight animals showed either no change or a slight increase in rate. There was no relation between the degree of slowing and the amount of AS given; the largest changes occurred at both the higher and lower doses. The time of onset also did not seem to be dose-dependent.

Eight cases of arrhythmia were noted; all but one were at the higher doses. In every instance the arrhythmia consisted of ventricular contractions, one animal showing only three ventricular premature contractions (VPCs) in a row while the remainder had definite runs of ventricular tachycardia. These beats were unifocal in character. The longest uninterrupted tachycardia lasted for 52 s. No instances of bigeminy, atrial arrhythmias, or alteration in A–V conduction except for slight P–R interval prolongation were seen. No animal developed ventricular fibrillation.

The onset and duration of the ventricular arrhythmias produced varied, but in no case were these dose-related. Further, neither the frequency nor duration of individual runs of ventricular tachycardia was correlated with dose. The ED50 of AS for producing VPCs or ventricular tachycardia as determined by probit analysis was 54·5 μg/kg (95% confidence limits: 48·1–61·7 μg/kg) (Bliss, 1952). Special note should be paid to the fact that in half the animals that subsequently developed a ventricular arrhythmia, there was no antecedent slowing.

Alterations in the e.c.g. configuration were extremely variable, generally slight or moderate and not dose-dependent. There was no consistent relation between such pattern changes and the appearance of arrhythmias. Thirteen dogs exhibited

slight prolongation of P–R interval although the duration never exceeded 200 ms, while five (not necessarily the same animals) showed S–T segment depression. T waves were reduced in amplitude or flattened in six cases and in three they were inverted with upright QRS complexes. Shortening of the Q–T interval was not a prominent feature but did occur in one-quarter of the dogs. The incidence and type of configurational changes seen are listed in Table 1.

All the dogs which developed ventricular arrhythmias returned to a normal sinus rhythm, although in some cases at a rate different from control. None of the dogs died.

Discussion

None of the e.c.g. effects produced by AS in this series of experiments was unexpected (Massie & Walsh, 1960). Although ventricular premature contractions are the most common cardiac rhythm disturbance induced by digitalis (Friedberg, 1966), AS in all but one dog caused runs of VPCs—in effect a ventricular tachycardia. Single VPCs or bigeminy were not otherwise seen alone and did not herald the more serious tachycardia. Further, the ventricular complexes were invariably unifocal, in contrast to the more usual multifocal QRS patterns induced by digitalis.

While it is assumed that these arrhythmias reflect the characteristic digitalis effect on ventricular automaticity, the conspicuous absence of single VPCs or atrial arrhythmias after administration of AS seems anomalous. There are, however, two possible explanations. It may be that AS, compared with other digitalis substances, selectively enhances His–Purkinje automaticity resulting in the early appearance of ventricular tachycardia. Second, and perhaps more likely, the inherent speed of

TABLE 1. *Effects of acetyl strophanthidin in dogs*

Dog Wt. (kg)	Dose μg/kg	Rate control	Rate at Max. change	P-R Prolong.	S-T Segment	T Wave	Q-T Interval	Vent. Arrhyth.	Arrhyth. Onset	Arrhyth. Durat.
9·0	25	160	80	—	—	—	—	—	—	—
9·8	25	220	140	+	—	—	Short	—	—	—
8·5	30	150	140	+	—	—	—	—	—	—
10·8	35	200	180	+	—	Flat	Short	—	—	—
12·3	35	180	120	+	—	—	—	—	—	—
10·0	40	150	120	+	Dep	Dim	Short	—	—	—
12·3	40	180	110	+	—	—	—	+	3′ 8″	6′ 42″
10·5	45	130	80	+	—	—	—	—	—	—
10·0	45	140	90	+	Dep	Invert	—	—	—	—
10·5	50	200	110	—	Dep	—	—	—	—	—
7·25	50	140	100	+	—	—	—	—	—	—
8·5	50	170	170	—	—	Flat	—	—	—	—
10·0	50	180	140	—	—	—	—	—	—	—
10·0	50	180	200	+	—	—	—	—	—	—
10·5	50	150	130	—	—	—	—	—	—	—
10·5	50	180	150	+	—	Dim	Short	—	—	—
11·0	50	120	130	—	Dep	Invert	Short	—	—	—
7·3	55	220	180	—	—	—	—	—	—	—
9·0	55	180	160	—	—	Invert	—	+	2′ 3″	10′ 22″
9·5	55	150	110	—	—	—	Short	+	6′ 3″	4′ 54″
10·0	55	170	120	—	Dep	Dim	—	—	—	—
11·0	55	100	100	—	—	—	—	+	1′ 51″	2′ 52″
8·6	60	190	100	+	—	Dim	—	+	5′ 8″	8′ 21″
9·0	60	120	120	+	—	—	—	+	2′ 7″	8′ 40″
10·0	60	100	110	—	—	—	Short	+	4′ 23″	3′ 49″
18·0	60	140	160	—	—	—	—	+	3′ 54″	8′ 13″

Dep, Depressed. Dim, Diminished. Flat, Flattened. Invert, Inverted. Short, Shortened. +, Present.

development of AS activity may not allow sufficient time for the more familiar effects to become manifest or may mask them with the rapid appearance of a more predominant effect.

The important finding, however, is the absence of any regular or predictable premonitory cardiac event following AS. Neither diminished rate, altered e.c.g. configuration, atrial arrhythmias nor ventricular ectopic beats seem to be reliable signs of impending ventricular tachycardia when this agent is administered. Thus, without prior indication, a given dose of AS may produce severe cardiac disturbance in the normal dog. The same phenomenon has been noted in humans after various digitalis preparations (Rosenberg & Graettinger, 1962), so the possibility of producing unexpected serious ventricular arrhythmias after the rapidly acting AS is ominous. Careful choice of AS doses does not preclude this possibility and even the use of smaller doses, especially in the presence of prior digitalis administration, does not ensure safety.

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(*Received November* 6, 1969)