The Action of Several Cardiac Glycosides on Conduction Velocity and Ventricular Excitability in the Dog Heart

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The effects of digitoxin, ouabain, lanatoside C and K-strophantoside on ventricular excitability and conduction velocity were studied. All agents caused an initial slight increase followed by a decrease of ventricular excitability, and depression of A-V and intraventricular conduction. Conduction, while depressed in the specialized tissue, was well maintained in the muscle itself until death of the heart. No significant qualitative differences between the glycosides were observed.

Among the cardinal differences between the various cardiac glycosides are the speed of onset of action, the degree of absorption from the intestine, and the rate of elimination. The importance of such differences in the clinical use of digitalis and strophanthus preparations is too well recognized to need further emphasis. Other differences have been proposed without, as yet, gaining widespread confirmation. Moe and Visscher studied the actions of the pure glycosides of digitalis lanata in the heart lung preparation, observed wide differences in the ratio of toxic dose (dose causing ectopic rhythms) to "therapeutic" dose (smallest dose causing a measurable increase of mechanical efficiency in the failing heart) for the three substances. Their conclusions were not confirmed by Cattell and Gold, who carried out somewhat similar assays on the isolated papillary muscle, or by Farah and Maresh, who used the heart-lung preparation but administered the glycosides by continuous infusion. If one assumes that the toxic activity represents an "extension" of the therapeutic action, one would not expect significant differences in the "therapeutic ratio". However, it does not seem necessary to make such an assumption. For example, both quinidine and digitalis are capable of producing ectopic rhythms and fibrillation, yet the former has a negative, and the latter a positive inotropic action on the muscle.

Occasional reports in the clinical literature suggest that various preparations are not identical in their cardiac actions. Chavez, on the basis of wide experience with ouabain and digitoxin (Digitaline Nativelle), believes that the former agent is particularly useful for its positive inotropic action in acute congestive failure with regular rhythm, whereas the digitalis glycoside is more active in reducing the ventricular rate in patients with auricular fibrillation. Similar observations have been made by Codina. Since ouabain is used only rarely in most clinics in the United States, little support for this concept may be found in the North American journals. Chavez' observations would suggest that depression of A-V conduction is a characteristic more prominently displayed by Digitaline than by ouabain.

In an attempt to determine whether important differences exist between the effects of various glycosides on excitability and conduction velocity, a comparative study of digitoxin, lanatoside C, ouabain, and K-strophantoside was carried out.

Methods

Dogs of both sexes weighing from 6 to 12.5 Kg. were prepared under intravenous chloralose anesthesia. The chest was opened in the midline and the pericardium was opened widely and fixed to the edges of the sternum. Artificial respiration was maintained at a volume which just failed to abolish activity of the respiratory muscles, and was adjusted frequently in order to ensure a reasonably constant
level of arterial oxygen and carbon dioxide. Electrical stimuli from a Grass stimulator were introduced to the right auricle through a pair of electrodes attached to the margin of the appendage, or to the right ventricle through electrodes attached to the pulmonary cone. Recording electrodes were attached to the right auricle, to two points on the surface of the right ventricle in line with the stimulating electrodes, and to a point near the apex of the left ventricle. (See fig. 4.) Records were taken by means of a Grass six-channel ink-writing electroencephalograph. One channel was used to record the stimulus, one to record the auricular response, one (connected to A and V₃) to record A-V conduction time, and the others to record responses at the three ventricular electrodes.

Excitability of the ventricle was determined, as described previously,⁶ by estimating the threshold voltage necessary to drive the heart at a shock duration of 0.05 millisecond. Conduction time was estimated by measuring the delay between the stimulus artefact and the electrical response at the various points. It was recognized, of course, that conduction velocity cannot be accurately measured by this means, since the actual path traveled by the wave front cannot be determined.

In an effort to eliminate differences between the glycosides due to variations in their speed of action, the drugs were administered at 30 minute intervals in doses estimated to be 12 to 16 per cent of the "acute" lethal dose. The experiments therefore lasted from three to six hours. Observations of excitability, conduction time, and spontaneous activity were made after each fractional dose. This technic of administration necessitates the use of relatively larger doses of a slowly acting agent such as digitoxin, and the quantitative differences observed therefore are of little significance.

**Results**

1. **Ventricular Excitability.** The course of changes in ventricular excitability is illustrated in figure 1. The curves are plotted as averages of three experiments for each drug. To enable plotting on a common scale, the time of cardiac death in each experiment was taken to represent 100 per cent of the lethal dose. Since fractional doses were administered at regular intervals, 20 per cent of the time intervening between the first dose and cardiac death was taken to represent 20 per cent of the lethal dose. On the ordinate scale, the initial value of electrical excitability (inverse of the threshold voltage) was assigned a value of 100, and changes are plotted as per cent of the normal initial value. Similar conventions were used in the construction of figures 2 and 3.

In every case an initial slight increase of excitability occurred, and excitability was maintained until well over half the lethal dose...
had been administered. After 60 to 80 per cent of the lethal dose had been administered, excitability declined progressively to reach values of 40 to 80 per cent of normal shortly before death. In every experiment it was still possible to drive the ventricle up to the time when ventricular fibrillation terminated the experiment.

In all experiments ectopic beats of ventricular origin appeared after the injection of 40 to 60 per cent of the lethal dose, at a time when ventricular excitability was slightly enhanced.

Fig. 3. Intraventricular conduction plotted as percentage of normal "rate" (rate = inverse of time interval between responses at point V1 and V2, figure 4).

Idioventricular beats occurred with increasing frequency as the experiments progressed, until shortly before or at the time of auricular arrest, at which point an irregular ventricular rhythm occurred, usually at a frequency exceeding the normal sinus rate. There were no significant qualitative differences between the glycosides.

2. Atrioventricular Interval. As expected, all agents prolonged the A-V interval (as measured between the right auricle and the apex of the left ventricle). The response is charted as conduction "rate" (inverse of time) in figure 2. Complete block, indicated by failure of the ventricle to respond to stimuli applied to the right auricle, occurred at from 65 to 75 per cent of the lethal dose. Block always developed before the auricle itself became unresponsive to stimuli. Digitoxin and lanatoside C uniformly caused A-V block earlier than the strophanthys glycosides, but the difference is of questionable significance with the small number of experiments.

3. Ventricular Conduction. Ventricular conduction rate was estimated by driving the ventricle with shocks of twice-threshold strength and measuring the time interval between the shock artefact and the appearance of electrical activity at each of the ventricular electrodes.

Since this measure includes latency at the stimulated point as well as actual conduction time, the values plotted in figure 3 represent the inverse of the time between excitation at point V1 and V2. (See figure 4.) This value reflects the average rate over a path which includes both Purkinje and muscular tissue.

With Digitaline and ouabain a slight acceleration of conduction velocity occurred early in the course of the experiments, but the difference between these agents and Cedilanid is probably insignificant. As was true of ventricular excitability, conduction within the ventricle was well maintained, and was slowed much later than A-V conduction.

In most experiments, the point of electrode...
V₁ (fig. 4) was within 12 mm. of the stimulating electrode “S.” In every case, the stimulus-response interval at this near point failed to increase. A typical experiment is illustrated in figure 4. While the stimulus-response interval for the more distant points V₂ and V₃ began to increase rapidly after 160 minutes (about two-thirds of the lethal dose), conduction to the nearer point was maintained at a normal level until death occurred.

4. Idioventricular Activity. All agents caused ventricular extrasystoles increasing in frequency until a multifocal tachycardia developed. With ouabain occasional extrasystoles appeared on the average earlier than with the other agents at about 40 per cent of the lethal dose, while with digitoxin this manifestation of increased automaticity was delayed until a little more than 60 per cent of the lethal dose (fig. 1). A similar difference between ouabain and digitoxin was described by Krueger and Unna in the cat.⁹

**Discussion**

No major qualitative differences between the four glycosides, representing four different plant sources, were apparent in the limited number of experiments carried out in this study. However, the agents were compared in terms of fractions of the ultimate lethal dose of each, a method of comparison which might be expected to minimize qualitative differences since in each case the functional changes measured represent actions which may be considered to be toxic manifestations contributing eventually to death of the heart. If depression of conduction, depression of excitability, and the initiation of ectopic foci of activity in the ventricles may be assumed to be responsible for the disorganization of ventricular rhythm leading to death, one would expect that these functions would be similarly altered by all the glycosides. These results should not be interpreted to mean that no important differences in the myocardial actions exist. It is probably true that doses of the cardiac glycosides used in the careful treatment of heart failure are well below 35 per cent of the lethal dose, a dose range at which no important alteration of conduction rate or excitability occurred in these experiments. The possibility remains that the positive inotropic action, which is of major importance in the therapeutic use of these agents, may not correlate well with the toxic actions studied here. The clinical differences between ouabain and digitoxin observed and emphasized by Chavez may be due to differences in speed and duration of action, and to differences in the degree of improvement of myocardial contractile strength effected by these two agents. However, Mendez and Pisanty, using technics similar to those of the present study, have observed a significantly greater depression of A-V conduction with digitoxin than with ouabain.⁸

The data presented above serve to emphasize a characteristic of digitalis action which is all too frequently misinterpreted. The statement is commonly made (as in various textbooks*) that extrasystoles, bigeminal rhythm, and ventricular tachycardia occurring as a result of digitalis intoxication represent an expression of increased “excitability” or “irritability” of the myocardium; the implication is made that such idioventricular activity develops because the ventricle is more irritable. That this conclusion is invalid can easily be demonstrated. Reference to figure 1 will indicate that the first idioventricular beats occurred at a time when the electrical excitability of the ventricle was indeed slightly increased (threshold voltage slightly diminished), but in our experiments, while ectopic beats began to appear at a time

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* From Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 1941, p. 520: “The cause of the ectopic beats is the increased irritability of the myocardium...” From Sollmann, *A Manual of Pharmacology*, ed. 6, 1944, p. 531: “...the muscular excitability becomes greater and greater; so that the final effects are mainly muscular (increased tone, heightened irritability, spontaneous ventricular rhythm, extrasystoles).” From Krantz and Carr, *Pharmacologic Principles of Medical Practice*, 1949, p. 713: “The cardiac manifestations that may occur are extra ventricular systoles resulting from a hyper-irritability of the heart.”

A more accurate statement can be found in Moott’s monograph, *Digitalis and other Cardiotonic Drugs*, 1949, p. 40. Discussing the initiation of ectopic rhythms by digitalis, he says, “All depressors of cardiac excitability, including quinidine, may cause ectopic rhythms when given in large doses.”
Museums and to assume stimulus. 

do excitability at normal values, and terminating in ventricular fibrillation at a time when ventricular excitability was, on the average, less than 70 per cent of normal. The error is probably one of terminology. The physiologist quantitates excitability essentially as the inverse of the stimulus strength necessary to cause a response. The property of automaticity, or the ability to initiate activity, should not be confused with electrical excitability or irritability. The ability to fire spontaneously is undoubtedly distinct from the capacity to respond to a stimulus. This distinction was well recognized by Sir Thomas Lewis as follows: "It is reasonable to assume that extrasystoles are due to effective impulses let loose in the muscle; [but] to assume raised excitability is not only gratuitous but is opposed by observation. The strength of the threshold stimulus may be found to be above normal in hearts which at the time exhibit spontaneous extrasystoles."

While it has long been known that delay of A-V conduction occurs following doses which do not greatly affect intraventricular conduction as judged by the duration of the QRS complex, the observation illustrated in figure 4 was quite unexpected. Due to the close proximity of the recording electrode V1 to the stimulated point S, it would be expected that the response appearing at the point V1 should be propagated by a path through the muscle itself. The time lapse from point S to points V2 and V3 must represent conduction through muscle, plus propagation through the more rapidly conducting subendocardial network, plus conduction outward from the endocardium to the surface at the respective points. The cardiac glycosides caused in every experiment an increase of conduction time to the distant points, which must include conduction through the Purkinje network, but never altered the interval between stimulus and response at the proximal ventricular electrode, which was probably attached to the same muscle unit as the stimulating electrode and therefore was reached directly through muscle tissue. The conclusion seems inescapable that conduction over muscle tissue is not impaired by digitalis, while conduction through the fibers differentiated for rapid propagation of impulses is greatly depressed.

The action of the glycosides on conduction must play an important role in the development of ventricular fibrillation occurring as the terminal event in digitalis intoxication. It was proposed by Moe, Harris, and Wiggers that electrically induced fibrillation results when a discharging ectopic focus fires at an accelerating rate into a myocardium through which conduction becomes progressively slower, with the result that the first or second of a series of beats may just have reached the remotest area of the ventricle at the moment when the second or third discharge is leaving the focus. A ventricle responding, in different areas, to two impulses at the same time is already disorganized, and can hardly escape the further complex disorganization which is fibrillation. Thus in terminal digitalis poisoning of the heart, Purkinje conduction, which is normally so rapid as to ensure activation of the whole myocardium within a short time and therefore prevent the development of alternate bands of refractory and excitable tissue, becomes depressed to the point where multiple responses are possible. This would be particularly true when the impulse-generating capacity of the myocardium is simultaneously increased.

Summary

The effects of ouabain, K-strophanthoside, lanatoside C, and digitoxin on ventricular excitability and conduction velocity were compared in dogs under chloralose anesthesia. All agents caused a slight increase of ventricular excitability at dose levels of from 20 to 60 per cent of the lethal dose, followed by a decline to subnormal levels toward the end of the experiments. No significant differences between the various glycosides were observed.

All the agents caused depression of A-V conduction, terminating in complete block at about 65 per cent of the lethal dose for lanatoside C and digitoxin, and about 75 per cent of the

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lethal dose for ouabain and K-strophanthoside. The slight difference was not regarded as significant.

Conduction rate within the ventricle was well maintained up to 50 to 60 per cent of the lethal dose for all the glycosides, after which progressive slowing occurred. Depression of intraventricular conduction was most marked where the conduction pathway must have included Purkinje tissue, and slight or absent between the stimulating electrodes and a close recording electrode, where the path must have been chiefly muscular.

The independence of the properties of excitability and automaticity is emphasized, and an attempt is made to interpret the induction of ventricular fibrillation by the glycosides in terms of their effects on conduction velocity and automaticity.

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