ENHANCEMENT OF POTASSIUM-INDUCED ATRIOVENTRICULAR BLOCK BY TOXIC DOSES OF DIGITALIS DRUGS *

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(Submitted for publication June 8, 1960; accepted August 3, 1960)

In an attempt to evaluate the concept of K and digitalis antagonism, K was administered to patients with atrial fibrillation with slow ventricular rates due to digitalis. Some of these patients had associated ventricular ectopic rhythms. It was expected that by "unblocking" the effect of digitalis at the atrioventricular (A-V) node, the ventricular rate would increase. Contrary to expectations, the A-V delay was potentiated by the K, parallel with elimination of ventricular ectopic beats when the latter were present (1). This observation suggested that perhaps the concept of K and digitalis "antagonism" can be invoked only in respect to digitalis-induced arrhythmias. The latter observation goes back to 1918 when Dr. Loewi, in order to study the relation of Ca and K to digitalis, induced cardiac arrhythmias with strophanthin and described the effect of K on the arrhythmias in these words: "Schliesslich wurde gezeigt, dass so wie die Ca auch die Strophanthin wirkungen antagonistisch durch Kalium beeinflussbar sind" (Finally it was shown that strophanthin as well as Ca effect can be influenced antagonistically by potassium) (2). The value of potassium salts in abolishing ventricular ectopic beats due to digitalis in man was shown by Sampson, Alberton and Kondo (3) and confirmed by Enselberg, Simmons and Mintz (4). Bettinger and his associates, using intravenous KCl, found that the effect of K in depressing arrhythmias was equally as great whether or not patients received digitalis (5). The beneficial effects of K on atrial arrhythmia was first observed by Enselberg and co-workers (4) and was extensively studied by Lown and Levine (6). The transient nature of the depression of ventricular ectopic beats by K detracts somewhat from its therapeutic value (4,

7, 8). More significant, however, in view of the generally accepted and unqualified concept of K and digitalis "antagonism," has been the observation that while K eliminates ventricular ectopic beats, if given rapidly (about 2.0 mEq per minute for 1 to 2 minutes) it tends to prolong A-V conduction (4, 7, 8). Cardiac arrest has been observed during administration of potassium in patients with A-V block due to digitalis and there is evidence to suggest that the depressing effect of K on A-V conduction in man is more likely to occur after administration of digitalis (8-10).

The uniform but strikingly transient depression of digitalis-induced arrhythmia by K has been recently observed in animal study (11). It has also been shown that in animals poisoned with large doses of digitalis and subsequently infused with K, the average amount of K necessary to kill the animal was less in the digitalis-intoxicated than in comparable control animals (12, 13).

In view of the largely transient nature of the effect of K on ectopic arrhythmias with depression of A-V and intraventricular conduction and lack of evidence that K counteracts any other parameter of digitalis toxicity, the concept of specific K and digitalis "antagonism," as it applies to effects other than arrhythmias, deserves further investigation. The purpose of the present study was to evaluate, in dogs, the effect of K on A-V conduction before and after administration of toxic doses of digitoxin.

MATERIAL AND METHOD

A total of 53 experiments, 42 without digitoxin and 12 with digitoxin, were performed on 9 mongrel dogs weighing 9.8 to 15 kg, over a period of 9 months. The animals were anesthetized with 30 mg of Na pentobarbital per kg of body weight given intraperitoneally. In all but 10 experiments (Table I, Experiments 75, 76, 82, 83, 92, 162, 103, 128, 123 and 156), the administration of K was preceded by intravenous injection of acetyl strophanthidin (Lilly). An ampule containing 0.6 mg of the drug was

* Supported by the Herman C. Krannert Fund of the Indiana Heart Association, the Indiana State Board of Health, Indianapolis, Ind. and the National Heart Institute (H.T.S. 5363).

diluted with 9 cc of saline and 1 cc (0.06 mg) of the solution was injected every 30 seconds. Because the peak action of acetyl strophanthidin may not become manifest for 5 to 10 minutes after the drug is given, the administration was usually discontinued when occasional ectopic

beats appeared, usually A-V nodal or ventricular escape beats or slow escape rhythm. The latter was invariably followed by a tachycardia usually identifiable, because of fusion (combination) beats, as being ventricular in origin. Within 2 to 4 minutes after appearance of the tachy-

TABLE I
Amount of acetyl strophanthidin and potassium required to cause arrhythmia or A-V block in dogs before and after the administration of digitoxin

Dog no.	Exp. no.	A.S.* to arrhythmia	Before digitoxin			After digitoxin				
			Amount of K to A-V block		Plasma K at A-V block	Digitoxin†	A.S. to arrhythmia	Amount of K to A-V block		Plasma K at A-V block
			Total					Total		
		mg	mEq	mEq/kg	mEq/L	mg/kg	mg	mEq	mEq/kg	mEq/L
29	74	0.72	16.5	1.48	7.8					
	75		12.3	1.10	7.5					
	76		15.7	1.42	7.3					
	82		10.5	0.94	7.4					
	86					0.43	0.78	6.4	0.57	7.1
33	79	0.96	16.8	1.09	8.2					
	81	0.78	16.5	1.07	9.4					
	83		20.2	1.31	8.3					
34	84					0.33	0.42	6.0	0.38	6.3
	90	1.02	15.0	1.22	7.3					
	92		23.2	1.90	8.6					
	124	1.08	18.7	1.53	8.6					
	139	1.02	15.7	1.28	8.5					
35	140	1.02	17.3	1.41	9.0					
	146	0.96	22.5	1.84	8.2					
	162		11.5	0.94	6.5					
	93					0.40	0.84	9.8	0.80	6.7
	148					0.45	0.36	10.5	0.86	6.8
36	91	1.14	21.0	2.05	9.0					
	95†	1.02	13.1	1.28	8.2					
	125	1.20	16.8	1.64	8.9					
	137	1.02	12.0	1.17	7.7					
	138	0.96	10.5	1.02	8.6					
38	147	1.14	11.3	1.10	7.4					
	163	0.84	8.2	0.80	7.2					
	96					0.41	0.72	4.8	0.47	6.5
	149					0.49	0.24	4.6	0.45	7.8
	101	1.14	21.0	1.72	8.5					
40	103		18.8	1.54	7.8					
	126	0.90	15.7	1.28	7.4					
	128		17.3	1.41	8.3					
	104					0.33	1.14	5.2	0.42	7.1
	123		19.5	1.57	8.7					
41	127	1.20	19.8	1.59	7.3					
	131	1.20	16.5	1.33	7.5					
	150	0.96	18.7	1.50	9.0					
	164	0.96	17.2	1.38	7.1					
	132					0.40	0.72	5.6	0.45	6.3
42	152					0.42	0.78	12.7	1.02	7.3
	129	1.32	17.2	1.84						
	133	1.38	12.7	1.36	8.6					
	142	1.38	12.8	1.37	8.7					
	144	1.20	9.8	1.05	8.0					
43	136					0.50	0.90	4.5	0.48	7.5
	134	1.56	26.3	1.86	9.9					
	143	1.62	21.0	1.48	9.5					
	145	1.20	19.0	1.34	11.3					
	156		18.0	1.27	9.2					
44	160	0.90	15.7	1.11	8.4					
	135					0.41	1.20	4.5	0.31	6.9
	151	1.32	19.5	1.43	9.3					
	165	1.20	19.9	1.46						
	153					0.35	0.90	12.0	0.88	7.3

* A.S. = acetyl strophanthidin (Lilly).

† Not to exceed 5.0 mg in any animal.

FIG. 1. EFFECT OF POTASSIUM BEFORE AND AFTER DIGITOXIN INTOXICATION IN ANIMALS 36 AND 34. This experiment is characteristic of most of those conducted. Experiment 101, Dog 36, was performed before digitoxin intoxication. The short strip in the upper lefthand corner represents control tracing; the strip marked A.S. indicates the ventricular arrhythmia induced by acetyl strophanthidin. The latter was abolished with 4.6 mEq of K, and after 21 mEq of K was given a higher degree A-V block appeared. Experiment 104, performed after digitoxin intoxication, shows a similar sequence of events with the exception that the acetyl strophanthidin-induced arrhythmia was abolished with 2.3 mEq of K, with intraventricular block and a high degree of A-V block being obvious after only 5.2 mEq of the cation. In Dog 34, before digitoxin intoxication (Experiment 90), the acetyl strophanthidin-induced arrhythmia was abolished with 5 mEq of K and block appeared after 15 mEq of the ion was given. Following digitoxin intoxication (Experiment 93) the acetyl strophanthidin ventricular tachycardia was abolished with 4.3 mEq and block appeared after 9.8 mEq of K was infused.

cardia, isotonic solution (155 mEq per L) of buffered K phosphate in distilled water was injected at a rate of 1.10 to 1.23 mEq per minute until A-V block appeared. A flow meter was used to assure a constant flow. The rate of flow as determined from the flow meter was checked against the rate determined from the volume of solution used and the time required for its infusion. In 12 experiments, following the infusion of K, the animals were given intramuscularly 0.33 to 0.50 (average 0.40) mg of digitoxin per kg of body weight, the total dose not exceeding 5.0 mg. Forty-eight hours later the dogs were returned to the laboratory and reinfused with K in the manner described above.

The entire experiment was monitored with an oscilloscope. All cardiograms were recorded with direct writing equipment using standard lead II connections.

Venous plasma K was determined with a Beckman flame photometer before the start of infusion, during the infusion, and at appearance of A-V block. In a number of experiments, Na, Cl, Ca and O₂ saturation were determined before and after administration of acetyl strophanthidin and K.

Isotonic solutions of KCl and Na phosphate were used as control fluids. KCl was injected to A-V block and Na phosphate was given in amounts twice or three times that of the previously administered K phosphate.

RESULTS

The amount of digitoxin administered (0.33 to 0.50 mg per kg) was considered sufficiently large to cause intoxication. On two occasions the animals failed to eat or drink and had diarrhea. The maximal weight loss during any 48 hour period was 0.4 kg. Ventricular arrhythmia was observed on two occasions only. The P-R interval remained unchanged in seven experiments; in three the duration increased from 0.80 to 0.10, in one from 0.12 to 0.14 and in another from 0.09 to 0.13. Significant degree of ST depression was observed on one occasion only. The preinfusion ventricu-

lar rates in animals not given digitoxin varied from 75 to 200 beats per minute for an average of 126, and after digitoxin the control rate varied from 136 to 206 for an average of 162 beats per minute. The average ventricular rates shortly before the K-induced block appeared were 127 and 119 in the control and digitoxin-intoxicated animals, respectively. Increased sensitivity to acetyl strophanthidin after administration of digitoxin was observed in nine of the experiments, with the reduction of the drug required to produce ventricular tachycardia being from 10 to 25, from 25 to 50, and over 5 per cent in two, five and three experiments, respectively. On three occasions (Table I, Experiments 86, 104 and 135) there was no increase in sensitivity to acetyl strophanthidin, although in two of the experiments (Ex-

periments 86 and 104) the P-R interval increased by 44.0 and 16.0 per cent, respectively.

In all animals acetyl strophanthidin-induced arrhythmia was suppressed promptly by K and, with continued infusion, A-V block followed (Figures 1, 2). In a few experiments, the P waves, although distorted but clearly visible on the oscilloscope, were poorly identifiable on the EKG. The amount of K necessary to produce A-V block was greatly reduced in all animals, following administration of digitoxin. The total amount of K administered before digitoxin was given varied from 8.2 to 26.3 (average 16.6 mEq), while after digitoxin the amount of the cation varied from 4.5 to 12.7 (average 7.2 mEq), for an average reduction of 9.4 mEq of 56.6 per cent in the amount of cation required to induce A-V block. The

FIG. 2. SINO-ATRIAL ARREST AND BLOCK IN TWO DOGS. In Dog 35, Experiment 91 was performed before, and Experiment 96 after digitoxin intoxication. In Experiment 91 the ventricular tachycardia was abolished after 4.9 mEq of K and A-V block appeared with 21.0 mEq; in Experiment 96 these results were accomplished after 1.5 and 3.6 mEq, respectively. In Dog 39, Experiment 133 was performed before, and Experiment 136 after administration of digitoxin. The amount of K necessary to abolish acetyl strophanthidin-induced ventricular tachycardia and to produce A-V block was 7.4 and 12.7 mEq in Experiment 133, and 4.5 in Experiment 136.

FIG. 3. AMOUNT OF K NECESSARY TO PRODUCE A-V BLOCK BEFORE (STIPPLED CIRCLES) AND AFTER (SOLID CIRCLES) DIGITOXIN INTOXICATION IN THE NINE ANIMALS STUDIED. The number of the animal is shown on the abscissa and the amount of K (in millequivalents) necessary to produce A-V block is shown on the ordinate. The average amounts of K (in millequivalents) needed to cause A-V block in the control and in the digitoxin-intoxicated animals are given below the graph. It is obvious from these data that the amount of K necessary to produce A-V block after digitoxin administration was markedly reduced.

FIG. 4. PLASMA LEVEL OF K AT A-V BLOCK (ORDINATE) AND THE AMOUNT OF K (ABSCISSA) NECESSARY TO PRODUCE THE BLOCK, BEFORE (STIPPLED CIRCLES) AND AFTER (SOLID CIRCLES) ADMINISTRATION OF DIGITOXIN.

FIG. 5. COMPARISON OF THE EFFECT OF K PHOSPHATE, NA PHOSPHATE AND KCL ON THE SERUM CA, PLASMA K AND A-V CONDUCTION. The three different solutions are listed on the abscissa. On the ordinate are represented serum Ca, plasma K, and the EKG consisting of a short control strip and tracing at termination of infusion. Sodium phosphate, although administered in large amounts and causing most marked depression of serum calcium, did not affect either the plasma K or A-V conduction. On the other hand, KCl, although not affecting the serum calcium, caused a rise in plasma potassium and produced an A-V block similar to one seen with K phosphate.

amount of K per kg of body weight necessary to produce block before digitoxin administration varied from 0.80 to 2.05 (average 1.37 mEq); after digitoxin intoxication the dose varied from 0.38 to 0.88 (average 0.59 mEq) (Figure 3). The block lasted longer in the digitoxin-intoxicated animals than in the control experiment. In addition sino-atrial (SA) blocks and arrest were seen commonly in the digitoxin-intoxicated animals but were rare in dogs not given digitoxin (Figure 2). The average plasma K level at which A-V block was produced before administration of digitoxin was 8.5 mEq per L; after digitoxin the average plasma K level at block was 6.9 mEq per L (Figure 4). Under the hypothesis of no real difference both the changes in amount as well as in plasma level before and after digitoxin were significant on less than 1 per cent level. The amount of acetyl strophanthidin, K phosphate, digitoxin, and the plasma level of K at A-V block used in

each of the 53 experiments are given in Table I.

The effect of KCl on EKG and plasma K level was the same as that of K phosphate. Na phosphate, although administered in much larger amounts and causing a more pronounced depression of serum Ca than either KCl or K phosphate, failed to alter the P-R interval (Figure 5). Plasma Na, Cl, and O_2 saturation showed no consistent or quantitatively significant change.

Omission of acetyl strophanthidin in nine experiments did not alter the amount of K necessary to produce block. None of the animals in this particular group of nine received digitoxin. The amounts were 16.7 and 16.6 mEq with and without acetyl strophanthidin, respectively.

DISCUSSION

A-V block, as a constant manifestation of experimentally-induced hyperkalemia is rarely referred to in the literature. It was surprising to

us, therefore, to find A-V block with such regularity. We feel that the reproducibility of A-V block was probably due to the rate of infusion, for with slower rates disappearance of P waves and with higher rates cardiac standstill preclude the recognition of A-V block. S-A arrest and S-A block were observed when K was given to digitoxin-intoxicated animals, but were not seen in the control dogs.

The A-V block, S-A arrest and block are doubtless due to K. The results of control studies using isotonic KCl and Na phosphate with frequent determinations of Na, Cl, Ca and O₂ saturation are in keeping with this conclusion. There is also little doubt that the disturbance of impulse formation and conduction due to K was greatly enhanced by previous administration of digitoxin. The depressing effect of both digitoxin and K on spontaneous activity of normal pacemakers, as well as on the refractory period and speed of impulse transmission of the A-V conduction system explains the relative ease with which S-A arrest, S-A and A-V blocks appear when K is administered to a digitoxin-intoxicated dog (14-16). The exact mechanism by which the effect of K is "enhanced" by digitoxin so that the conduction disturbances not only occur with less K but also at a lower plasma level is not clear. In the light of our present knowledge a combination of three possible mechanisms suggests itself: 1) the egress of K from the cells in the presence of a normal extracellular K increases the extra- to intracellular ratio of the cation; 2) the interference with intracellular transfer of K by toxic doses of digitoxin tends to maintain this increased ratio; 3) the consequently more rapid rise of plasma K in the animal given digitoxin produced a critical plasma level with less K. This more rapid rise was observed by Williams, Spirakis and Keyl (17) in strophanthin-poisoned dogs. Although we were unable to detect significant loss of water or change of plasma Na, Cl and O₂ saturation, there is little doubt that disturbance of electrolytes other than K, change in pH, O₂ saturation, and body water that may result from digitalis intoxication, can and possibly may have added to the increased sensitivity to K observed in our animals. It seems reasonable to assume that given a condition in which there exists an abnormally high extra- to intracellular ratio of potassium and in which the

K is prevented from entering the cells, less K is required to produce a critical plasma level. Furthermore, because of intracellular depletion of the cation the critical ratio between extra- and intracellular concentration of K will be reached at lower plasma levels of K than in the nondigitalized animals. A comprehensive review of the cellular basis of digitalis action can be found in a recent paper by Hajdu and Leonard (18).

The doses of digitoxin used varied from 0.33 to 0.50 mg per kg with an average dose of 0.40 mg per kg and did not exceed 5.0 mg in any one animal. Based on observation of the animals, P-R changes, and appearance of ventricular arrhythmias, we felt that in 10 out of 12 episodes of digitalization the animals were under the influence of less than 50 per cent of the lethal dose of digitoxin (15). Why more severe signs of digitoxin intoxication were not evident in our animals is difficult to answer with any degree of certainty. It is possible that the absorption of digitoxin from the site of injection was incomplete or perhaps the excretion in the first 24 to 48 hours was rapid due to large amounts of the initially given drug. It was also noted that the same animals, when repeatedly given the same amount of digitoxin, did not manifest uniform EKG changes. Any estimate of digitoxin intoxication on the basis of EKG changes alone may be misleading.

In our experiments omission of acetyl strophanthidin did not affect the amount of K that was necessary to produce A-V block. The nine experiments, however, in which acetyl strophanthidin was omitted comprise a group too small to make these observations valid. In addition the design of our experiments would not permit a study of transient effects of K flux attending the administration of acetyl strophanthidin. Regan, Talmers and Hellems (19) and more recently Cairns, Love and Burch (20), in experiments specifically designed to study the effect of acetyl strophanthidin on K flux, have shown that the drug causes an efflux of K and blocks re-entry of K into the cell. According to Cairns and his associates the effect lasts about 9 to 12 minutes.

It is possible that potentiation of the vagal effect of digitoxin contributed to S-A arrest and block and A-V conduction delay. However, a major effect is unlikely because of use of pentobarbital as the anesthetic agent. Barbiturates have

been shown to depress reflex activity. Moe and Mendez (15) administered digitoxin to dogs under pentobarbital anesthesia and observed that the effects of the drug were the same both in the denervated and intact animal. Furthermore, administration of 5 mg of atropine intravenously to some of our animals, not in this study, did not prevent the appearance of A-V block during infusion of K. The role of the *in situ* production of acetylcholine that would not be inhibited by atropine is difficult to evaluate.

The control heart rate was consistently higher in the digitoxin-intoxicated animal, but the rate shortly before appearance of A-V block was the same or slightly lower in the intoxicated dogs. It is doubtful, therefore, that the ventricular rate per se contributed significantly to the enhanced depression of A-V conduction observed in the digitoxin-intoxicated animals.

The present day concept of digitalis and K "antagonism" seems to be based only on the rather nonspecific depressing effect of K on ectopic rhythms. There is no doubt, from the studies of Lown and Levine (21), that an elevated plasma K protects against, and lowered plasma K enhances ventricular ectopic beats. On the other hand, experimental evidence, suggesting that depletion of body K without altering plasma K "sensitizes" to digitalis, is less convincing (22, 23). Regardless of the state of body K, there is very little, if any, evidence that K "antagonizes" any features of digitalis activity other than digitalis-induced arrhythmia. There is every reason to believe that in the presence of normal stores of K and perhaps in some K-deficient states, elimination of ectopic rhythms may in many cases be related simply to a rise in extracellular K. This impression is supported by the frequently transient nature of depression of ventricular ectopic beats in man, often paralleled by slowing of A-V conduction (4, 7, 8). Experimentally produced ventricular arrhythmia can be abolished by raising plasma K to 6 mEq per L but recurs when the K level drops below 6 mEq per L (10). We have observed similar behavior of ectopic beats in respect to plasma K level in humans. It is difficult to conceive that 6 to 20 mEq of K would exert a beneficial effect on an arrhythmia through any mechanism than perhaps by a transient elevation of the extracellular levels of the cation (8). Fail-

ure of arrhythmia to reappear after the plasma level of K returns to normal after once being acutely elevated does not necessarily imply, as some have suggested, that the effect of K must be due to intracellular shift of the cation with a change of intra- and extracellular ratio.

The fact that K depresses A-V conduction (4, 7-10) and that this depression is potentiated by digitoxin (10, 12, 13) may be of clinical significance and would imply that, in the presence of impaired A-V conduction, the cation should be given with great caution. This does not mean that K should be withheld in face of digitalis-induced arrhythmia. There is uniform agreement that K is an excellent anti-arrhythmia drug and its use may mean the difference between life and death. Ectopic rhythms are affected by considerably smaller amounts of K than those required to affect A-V conduction. This fact allows for a significant "margin of safety" when the cation is used to control arrhythmias due to digitoxin intoxication.

SUMMARY

1. Buffered isotonic K phosphate was administered 42 times to nine dogs before digitalization. An average of 16.6 mEq of the cation was necessary to produce atrioventricular (A-V) block.
2. The same procedure was carried out 12 times after administration of toxic doses of digitoxin. In this group an average amount of only 7.2 mEq was necessary to produce A-V block, and sinoatrial block and arrest were frequent in this group.
3. Infusion of K into animals intoxicated with digitoxin produced A-V block not only with less K, but also at a lower plasma level. There was also a steeper rise of plasma K level in this group of experiments.
4. These studies suggest that K should be given with caution to digitalis-intoxicated patients in whom the intoxication is manifested by abnormalities of A-V conduction.

ADDENDUM

The experimental data collected in course of infusion of K either before or after administration of acetyl strophanthidin is part of a large series which constitute our laboratory control and is repeatedly used as a standard against which the response to potassium, when other factors (e.g., additional digitoxin) are varied, is meas-

ured. These control data therefore are an integral part of other studies dealing with the subject of potassium and digitalis antagonism.

ACKNOWLEDGMENT

We wish to thank Dr. Kenneth G. Kohlstaedt for his continuous support and encouragement.

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