Interrelation between Potassium Metabolism and Digitalis Toxicity in Heart Failure.* (18636)

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A relationship between potassium metabolism and the cardiac effects of digitalis has long been recognized. In isolated heart muscle preparations, digitalis action can either be enhanced or inhibited by appropriate changes of potassium concentration(1). A number of investigators have reported that orally administered potassium temporarily abolishes electrocardiographic manifestations of digitalis intoxication in patients(2,3). Whether these represent transient pharmacologic effects or physiologic restitution of intracellular potassium depletion has not been established. Reevaluation of certain clinical observations in terms of present understanding of electrolyte distribution suggests that diminution of myocardial potassium concentration alters the response of the heart to digitalis. Increased sensitivity to digitalis to the point of toxicity is encountered after mercurial diuresis, acute myocardial infarction, pulmonary embolism, acute infections, etc. In each of these circumstances, negative potassium balance has been observed either as a result of a mercurial induced loss(4) or as a part of the bodily response to acute stress(5). Similarly, the normal, in contrast to the failing, heart is resistant to the development of signs of digitalis intoxication. Recent work(6) confirms the older observation(7) that the failing heart is depleted of potassium to an extent which is dependent upon the degree of myocardial insufficiency.

The present study is an attempt to determine whether alterations in digitalis sensitivity can be demonstrated following changes in potassium metabolism encountered clinically.

Material and methods. The subjects were 10 patients in various stages of congestive heart failure who were maintained on a low sodium (20-25 milliequivalents) diet. During the control period, in 6 of the patients, the threshold of mild toxicity to a rapidly acting digitalis preparation, ouabain or acetyl strophanthidin§ was determined. The electrocardiographic criteria of digitalis toxicity were ventricular extrasystoles, impairment of auriculo-ventricular conduction, or alterations in the pacemaker. The short acting glycosides facilitate early electrocardiographic recognition of digitalis toxicity and permit repetition of studies at more frequent intervals. When acetyl strophanthidin was used, a test dose of 0.6 mg was first given. Then, after lapses of at least 48 hours, a second dose of 1.2 mg was injected, and if no toxic signs appeared, a final dose of 1.8 mg was given. Electrocardiograms were taken continuously

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§ Acetyl strophanthidin is a synthetic ester of the aglycone strophanthidine. Its cardiac effect in man is evident within 1-5 minutes, reaches a peak at about 16 minutes and generally is dissipated in 60 minutes. The usual intravenous digitalizing dose is 1.2 to 1.8 mg.(8)

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TABLE I. Summary of Results.

Patient		Agency inducing K change	Serum K, m.eq./l	Gross K balance	Digitalis dosage, mg	Digitalis toxicity
H.D.	a.	0	5.2	Unchanged	1.2A*	0
	b.	0	5.7	"	1.2	0
	c.	Amm. chloride and thiomerin	5.0	—83 m.eq.	1.2	Vomiting. Multifocal VPBs. Runs of ventricular tachycardia
H.S.	a.	0	5.6	Unchanged	1.8A	0
	b.	0	4.8	"	1.8	0
	c.	Amm. chloride and thiomerin	4.7	"	1.8	0
S.S.	a.	0	4.8	"	1.8A	0
	b.	0		"	1.8	0
	c.	Amm. chloride and thiomerin	4.9	"	1.8	0
A.R.	a.	Amm. chloride and thiomerin	5.1	—100 m.eq.	0.7O†	Vomiting. Changing pacemaker. Complete A-V block. Rare VPB
	b.	Amm. chloride and thiomerin	3.6	— 70 "	0.7	"
	c.	KCL 100 m.eq./day for 7 days	5.2	+210 "	1.3	"
A.S.	a.	Thiomerin (5 observations)	4.8	—	0.25-0.5D‡	Vomiting. Bigeminy
	b.	KCL 67 m.eq./day at time of diuretic (3 observations)	4.4	—	0.25-0.5	0
G.R.	a.	0	5.75	Unchanged	1.2A	Nausea and tingling
	b.	DCA—20 mg/day for 5 days	5.35	—85 m.eq.	1.2	Nausea, tingling and bigeminy
L.C.	a.	0	4.9	Unchanged	1.8A	0
	b.	0	—	"	1.8	0
	c.	DCA—25 mg/day for 10 days	4.3	"	1.8	Nausea, tingling; incomplete A-V block. Occasional VPB
	d.	DCA and thiomerin	—	"	1.8	"
W.E.	a.	Malnutrition and gastrointestinal loss	5.1	Probable depletion	1.2A	Ventricular flutter - fibrillation
	b.	"		"	0.6	Frequent VPBs in pairs and triplets
A.F.	a.	Malnutrition, dehydration & gastrointestinal loss	2.3	"	0.6A	Bigeminy, A-V block, ventricular tachycardia and fibrillation (fatal outcome)
M.F.	a.	Glucose and insulin§	4.1 3.0	—	0	Nausea, dizziness, faintness, angina pectoris, multifocal VPBs with pairs and triplets
	b.	Glucose and insulin	5.0	—	0	
			3.9			0

* A = Acetyl strophanthidin.
† O = Ouabain.
‡ D = Digoxin.
§ Glucose and insulin given 2 days after loss of digitalis toxicity, 9 days without digitalis.
No digitalis for 6 wk.

for fifteen minutes after the injection, and thereafter at 5 minute intervals for 90 minutes or until disappearance of digitalis effect. Ouabain was administered as follows: after two 0.25 mg doses, given at a 30 minute interval, 0.1 mg was injected every 30 minutes

until signs of mild toxicity were noted. Before, and 5 minutes after each injection of ouabain, 2 minute electrocardiographic records were obtained. After the final dose, which produced evidence of toxicity, similar frequent electrocardiographic records were taken for at least 2 hours. A similar technic with the same glycoside was used to test digitalis sensitivity after the induction of alterations in body potassium by either of the following procedures: in four patients (H.D., A.R., H.S., S.S.) by the administration of the mercurial diuretic Thiomerin, after 3 days of pretreatment with ammonium chloride, which is known to promote increased urinary potassium excretion(9), and in 2 (G.R. and L.C.) by the administration of desoxycorticosterone acetate (DCA).¶ In 2 other patients (W.E. and A.F.) who had been depleted of potassium by vomiting, diarrhea and malnutrition, digitalis sensitivity was tested with subtoxic doses of acetyl strophanthidin. Other experimental details are discussed below.

Blood electrolyte levels and 24 hour urine excretions of creatinine, sodium, chloride and potassium were determined. Chemical analyses were performed by the following methods: chlorides by Van Slyke's modification of Sendroy's iodometric technic(10), sodium and potassium on a lithium internal standard flame photometer; and creatinine by Peter's modification of the Folin-Wu procedure(11).

Results. In each case with significant shifts of potassium changes in digitalis sensitivity were observed (Table I). The gross K balance indicated in Table I refers to changes in urinary potassium excretion, which was relatively constant before the experimental procedures employed to remove or replace body potassium.

In patient H.D. an 83 milliequivalent loss of potassium after ammonium chloride and Thiomerin, without any significant changes in the serum potassium concentration, was associated with markedly increased sensitivity to acetyl strophanthidin. In contrast, the 2 patients (H.S. and S.S.) in whom these diuretics induced no increase in urinary potassium excretion, failed to develop any signs of digitalis overdosage.

In patient A.R. after diuretics, 0.7 mg of ouabain produced toxicity. However, after daily oral administration of 100 milliequivalents of potassium citrate for a week, 1.3 mg of ouabain were required to achieve the same effect. Moreover, there was not only an increase in the threshold for digitalis toxicity, but also a marked reduction in the duration of toxic manifestation. Over a 2 month period patient A.S., while on a constant maintenance dose of digoxin, consistently developed severe toxicity the day following diuretic therapy. Oral administration of 67 m.eq. of potassium citrate on days when mercurials were given, prevented all signs of her usual toxicity 24 hours later.

Increased sensitivity to digitalis was observed in patients G.R. and L.C. after the daily administration of 20-25 mg of DCA for four and ten days, respectively. In patient G.R., who was on a complete metabolic balance study, an 85 m.eq. potassium loss was sustained during the period of DCA administration. In patient L.C. there were no demonstrable changes in potassium excretion.

There was no consistent lowering of serum K levels in any of these patients in whom potassium loss was induced and digitalis sensitivity was enhanced. One (A.F.) of the 2 patients with malnutrition and gastrointestinal potassium loss was hypokalemic, whereas the other (W.E.) had a normal serum potassium concentration. Nevertheless, both exhibited profound digitalis sensitivity. In patient M.F., bigeminy due to an overdosage of digitalis could be abolished by oral potassium and reinduced by mercurial diuresis. Nine days after discontinuing digitalis, when diuretics no longer produced ventricular extrasystoles, 50 g of glucose and 25 units of insulin were injected intravenously over a 15 minute period. The resulting decrease in serum potassium from 4.1 m.eq./l to 3.0

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¶ Supplied by Schering Corp.

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m.eq./l was associated with the development of severe digitalis toxicity, which was abolished by a single oral dose of 130 m.eq. of potassium citrate. She received no more digitalis and 6 weeks later was fibrillating with a ventricular rate of 150. At this time, repeating the same intravenous dose of glucose and insulin induced no signs of toxicity.

Discussion. This study suggests that depletion of potassium increases the sensitivity of the heart to digitalis. The absence of signs of digitalis overdosage when mercurials did not produce an increase in potassium excretion demonstrates that the mercurial itself is not the responsible agent in those instances in which toxicity does ensue. Ordinarily, the reduction of ventricular extrasystoles after oral potassium begins within 30 minutes, is maximal at 2 hours, and subsides within 4 to 8 hours(3). This transient effect of K in the usual case with more persistent signs of digitalis overdosage may represent the continuing operation of the factors which initially produced the underlying intracellular potassium depletion. If potassium intake is maintained at a high level, there may be no recurrence of ventricular extrasystoles. In patient A.S., however, signs of digitalis intoxication occurred only after mercurial induced potassium loss. It is noteworthy that when the latter was corrected by orally administering potassium on the day of diuresis the digitalis induced premature beats usually occurring 24 hours later, did not develop.

From the present data, it would appear that the increased myocardial sensitivity to digitalis observed after potassium losses probably results from alterations in intracellular potassium distribution. Changes in extracellular potassium concentration probably are not of primary importance, since there were no significant changes in serum K levels in all but two of the patients. The decreased tolerance to digitalis observed after DCA was not accompanied by a demonstrable increase in potassium excretion in one of two patients. Unless there is a synergism between this steroid and digitalis(12), the altered digitalis sensitivity in this case may be a reflection of a shift in myocardial potassium(13). In relation to total intracellular potassium, such shifts of cardiac electrolyte, leading to the altered response to digitalis, may be too small to be measured by available technics.

A similar shift in myocardial potassium distribution may be involved in the electrocardiographic signs of digitalis intoxication observed after glucose and insulin when patient M.F. was still digitalized. The marked drop in serum potassium may have promoted a decrease in that fraction of myocardial potassium which is involved in the production of extrasystoles. In patients who had never received any digitalis, analogous electrocardiographic changes have been observed without any previous digitalis therapy, after shifts of potassium induced by glucose injection in patients with hypokalemia(14) or familial periodic paralysis(15), or by prolonged DCA administration(16).

In all previous studies, including our own, the influence of possible simultaneous changes in distribution of water and electrolytes other than potassium cannot be ruled out. However, in preliminary experiments performed by one of us (B.L.) with Merrill in Boston it has been possible to control these variables. With the artificial kidney, by the selective removal of potassium, digitalis toxicity has been induced in digitalized patients, and then abolished by the restoration of the removed potassium. Further studies are in progress.

Summary and conclusion. 1. In a series of patients in congestive failure, potassium depletion, either occurring spontaneously with malnutrition and gastrointestinal disorders or induced by mercurial diuresis after pre-treatment with ammonium chloride, was found to be associated with increased sensitivity to digitalis. 2. In 2 patients a similar decreased threshold of digitalis toxicity was observed after daily doses of 20 mg of desoxycorticos-

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terone acetate for 4 to 10 days. 3. In one digitalized patient, digitalis toxicity was precipitated by intravenous injection of insulin and glucose, which was followed by the development of hypokalemia. 4. It is suggested that this increased myocardial sensitivity to digitalis probably results from alterations in intracellular potassium distribution since no significant changes in serum (or extracellular) potassium were observed in 8 of 10 patients.

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Hair Loss from Squalene.* (18637)

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In previous reports the reversible local depilatory action of the intermediary polymers (cyclic dimers) of chloroprene was described (1,2). These compounds, when applied to the skin of laboratory animals, caused localized temporary cessation of hair growth with marked thickening of the epidermis and anomalous keratinization(3). *In vitro* the dimers inactivated the free sulfhydryl groups of glutathione and of tissue homogenates in amounts which corresponded well with the *in vivo* depilatory concentrations. We have attributed the sulfhydryl inactivating action of the dimers to the unsaturated bonds in the molecule which alkylate the –SH group according to the equation: $-CH=CH- + RSH \longrightarrow RS-\underset{|}{CH}-CH_2-$. The theory was advanced that naturally occurring unsaturated compounds may owe their effect upon keratinization to a similar chemical reaction(4). Such a compound is vit. A, a polymer of isoprene; isoprene differs from chloroprene in having a CH_3 group in place of the Cl atom of chloroprene. We have confirmed previous findings that vit. A, in addition to causing generalized hair loss in animals(5-7) and human beings(8-10), has a distinct local depilatory effect(4,11). However, vit. A had no demonstrable effect on free sulfhydryl compounds *in vitro* and it is possible that its depilatory action is due to a metabolic breakdown product.

The present paper deals with the localized reversible depilatory effect of another naturally occurring isoprene polymer, squalene. Squalene, an unsaturated hydrocarbon, is a normal component of human sebum(12) and therefore it may have a direct effect on normal, as well as pathologic, hair formation in man.

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