Effect of a Cardiac Glycoside (Cedilanid) on the Sodium and Potassium Balance of the Human Heart

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Previous studies on the isolated heart have demonstrated that digitalis glycosides can mobilize potassium from the heart muscle. Using catheterization of the coronary sinus of dogs' hearts, it could also be shown that the injection of acetyl strophanthidin results in negative myocardial balances of potassium and in positive balances of sodium. The results described in this report, using Cedilanid in therapeutic dosages, indicate that this glycoside has no effect on the sodium and potassium balance of the human heart. A significant increase in potassium concentration in arterial and coronary sinus blood occurred. The findings suggest that Cedilanid, in therapeutic doses, causes potassium liberation primarily from extracardiac tissues.

In a previous publication, it was shown that the intravenous injection of a cardiac glycoside (Cedilanid) does not alter the myocardial extraction of glucose, pyruvate, lactate, fatty acids, amino acids and ketone bodies in man. The present work is designed to investigate the changes in sodium and potassium balance of the human heart induced by the injection of Cedilanid.

The effect of therapeutic as well as toxic doses of digitalis glycosides on the electrolyte content of the heart muscle has been a controversial subject. Earlier studies suggested that heart failure alone can influence the electrolyte content of heart muscle. The right ventricular muscle of patients dying from acute and extensive pulmonary disease was found to have diminished potassium content while the left ventricular muscle did not. When pulmonary and systemic congestion was present, the potassium content of both ventricles was diminished. Wilkins and Cullen found decreased potassium and phosphorus concentrations in diseased heart muscle and increased sodium concentration in the ventricles of persons who died of congestive failure. However, Scott found no significant difference in potassium and sodium content of the heart muscle of patients who had died in congestive failure as compared to patients who died of various other diseases.

The possibility that the action of digitalis was responsible for the electrolyte changes in failing heart muscle was suggested by Calhoun and Harrison who found that the potassium content of dogs' hearts receiving toxic doses of digitalis was definitely reduced, while digitalis in therapeutic doses did not influence the concentration of potassium in the heart muscle. Since all patients in heart failure in whom the potassium concentration in the myocardium was reduced had received digitalis before death, it was suggested that probably the drug alone had caused the loss of potassium. Hagen found that therapeutic doses of digilanid-C caused a slight increase while toxic doses resulted in marked decrease in the potassium content of the perfused rabbit heart muscle. Wedd's experiments on ventricular strips of turtle heart suspended in digoxin solution indicated that digitalis can exert its therapeutic action without changes in the potassium content of the heart muscle while potassium loss from the muscle represents a toxic effect. Boyer and Poindexter found that digitalis in therapeutic doses increased the intracellular potassium and water content of heart muscle in cats. Chlorides and extracellular water were decreased. They suggested...
that the glycosides maintain potassium in the cell and improve cellular hydration through alterations in the permeability of the cell membrane to electrolytes. On the other hand, using the heart-lung preparation, Wood and Moe\textsuperscript{10} found good correlation between the dosage of the drug administered per gram of heart and the rate of potassium mobilization from the heart muscle. This was true for both toxic and therapeutic doses. There was little correlation between the time of onset of cardiac arrhythmias and the rate of potassium mobilization. These results indicated that potassium mobilization from tissues may be associated with therapeutic as well as toxic doses of digitalis. Friedman and Bine\textsuperscript{11} found that only toxic doses of digitoxin caused a probable loss of potassium from the normal duck heart. They indicated that excess of potassium alone depressed the irritability of the heart and served as a source of potassium to a heart which had lost this ion after exposure to toxic amounts of digitalis.

The preceding data were primarily obtained on the whole heart in vitro or on muscle strips. Recently, catheterization of the coronary sinus in anesthetized dogs has been employed to investigate the effect of cardiac glycosides. Hellem, Regan and Talmers\textsuperscript{12} found that, in anesthetized dogs, acetyl strophanthidin caused the myocardial balance of potassium to become negative, that of sodium positive. After 25 minutes the opposite effect was recorded. Using the same technique, Harris, Firestone and Liptak\textsuperscript{13} found that K-strophanthidin increased arterial concentration of potassium without significant changes in the coronary arteriovenous difference of this electrolyte. In some instances, the potassium concentration in coronary vein blood exceeded that in arterial blood, but this was not an essential finding.

**Methods**

Ten patients were studied (table 1). Their ages ranged from 17 to 49 years. Their weight varied from 100 to 180 pounds. One of them (J.R.) had probable myocarditis of unknown etiology. One (F.M.) had luetic heart disease, one (E.S.) moderate and one (M.L.C.) mild hypertension. Two had rheumatic heart disease (M.R.A. and T.L.D.), one luetic and hypertensive cardiovascular disease (G.H.), two hypertensive cardiovascular disease (D.L.H. and F.W.) and one had a normal heart (M.C.). Only two of the patients (D.L.H. and F.W.) were in moderate heart failure at the time of the study; one (J.R.) had received digitalis previously but had been off the drug for thirteen days at the time of the test.

The coronary sinus of these patients was intubated for sampling of coronary vein blood; simultaneous arterial blood samples were obtained from the femoral arteries by means of an indwelling needle.\textsuperscript{14} Two blood samples from both the coronary sinus and the femoral artery were used as controls. Following this, Cedilanid in doses varying from 0.9 to 1.5 mg. was slowly injected intravenously. Subsequently, blood samples from the coronary sinus and the artery were collected every 3 minutes up to 60 minutes from the time of injection of Cedilanid. The electrocardiogram was usually recorded several times during the test; in most of these, signs indicative of digitalis became apparent after 20 minutes. In one patient (J.R.) slight cupping of the S-T segment occurred 20 minutes after the administration of Cedilanid; one (F.W.) developed supraventricular premature beats and a third (E.S.) showed only slight slowing of the heart rate after the Cedilanid and during the time of observation.

**Table 1.—Average Arterial and Coronary Sinus Difference of Sodium and Potassium (Milliequivalents per liter) Before and After Cedilanid.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before Cedilanid</th>
<th>After Cedilanid</th>
<th>1 minus 3</th>
<th>2 minus 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. R.</td>
<td>Na 0.50 mEq./L</td>
<td>K -0.15 mEq./L</td>
<td>-0.20 mEq./L</td>
<td>-0.33 mEq./L</td>
</tr>
<tr>
<td>F. M.</td>
<td>Na -0.20 mEq./L</td>
<td>K -0.20 mEq./L</td>
<td>0.0 mEq./L</td>
<td>0.0 mEq./L</td>
</tr>
<tr>
<td>D. L. H.</td>
<td>Na -0.75 mEq./L</td>
<td>K -0.02 mEq./L</td>
<td>-0.64 mEq./L</td>
<td>-0.17 mEq./L</td>
</tr>
<tr>
<td>F. W.</td>
<td>Na -0.60 mEq./L</td>
<td>K -0.15 mEq./L</td>
<td>-0.50 mEq./L</td>
<td>0.04 mEq./L</td>
</tr>
<tr>
<td>E. S.</td>
<td>Na -0.60 mEq./L</td>
<td>K -0.05 mEq./L</td>
<td>-0.78 mEq./L</td>
<td>-0.19 mEq./L</td>
</tr>
<tr>
<td>M. L. C.</td>
<td>Na -0.40 mEq./L</td>
<td>K 0.23 mEq./L</td>
<td>-0.67 mEq./L</td>
<td>-0.04 mEq./L</td>
</tr>
<tr>
<td>M. R. A.</td>
<td>Na -0.50 mEq./L</td>
<td>K 0.0 mEq./L</td>
<td>-0.55 mEq./L</td>
<td>-0.16 mEq./L</td>
</tr>
<tr>
<td>T. L. D.</td>
<td>Na -0.10 mEq./L</td>
<td>K 0.05 mEq./L</td>
<td>-0.68 mEq./L</td>
<td>-0.09 mEq./L</td>
</tr>
<tr>
<td>C. H.</td>
<td>Na -2.00 mEq./L</td>
<td>K 0.25 mEq./L</td>
<td>0.01 mEq./L</td>
<td>2.29 mEq./L</td>
</tr>
<tr>
<td>M. C.</td>
<td>Na -2.00 mEq./L</td>
<td>K 0.10 mEq./L</td>
<td>-1.50 mEq./L</td>
<td>0.15 mEq./L</td>
</tr>
</tbody>
</table>

Note—Columns 1 through 4 represent the average coronary arteriovenous differences of sodium and potassium. Columns 5 and 6 show differences between these average values obtained before and after the administration of Cedilanid. The negative values in columns 1 through 4 indicate that the concentrations of sodium and potassium are increased in coronary venous blood above those in arterial blood. The negative values in columns 5 and 6 result if the coronary arteriovenous differences have diminished after Cedilanid.
RESULTS

The results are shown in table 1. Cedilanid appeared to have no effect on the concentration of sodium in arterial blood or on the coronary arteriovenous sodium difference (p of > .9 and > .4). This is in contrast to the findings of Hellem on dogs, using acetyl strophanthidin; these workers found first increased myocardial uptake followed by a loss of sodium from the heart muscle.11

A significant increase in potassium concentration of arterial and coronary sinus blood occurred following injection of Cedilanid (p of < .02 and < .01). The coronary arteriovenous difference of potassium, however, showed no significant change from the control value (p of > .05). These findings suggest that Cedilanid in therapeutic doses causes potassium liberation primarily from extracardiac tissues.

DISCUSSION

The data represented here show no gross interference of Cedilanid with the potassium balance of the human heart. However, a slight action of Cedilanid cannot be completely excluded by these findings. It is likely that there are three main factors which can influence the magnitude of the coronary arteriovenous potassium difference. They are: (1) the coronary flow per unit of time, (2) the speed with which potassium is released from the heart muscle, and (3) the total quantity of potassium lost from the heart. The more rapid and extensive the loss of potassium from heart muscle, the larger will be the coronary arteriovenous difference. On the other hand, an increase in coronary flow reduces the arteriovenous potassium difference. It can be assumed that glycosides do not differ in their action on the coronary flow or the total amount of potassium lost from the heart. Consequently, differences in the action of various glycosides on the potassium balance of the heart must be primarily the result of the speed with which potassium is released from the heart muscle. This, together with species difference, may furnish the explanation for the difference in action of cardiac glycosides on the myocardial potassium and sodium balance.

SUMMARY

The effect of a cardiac glycoside (Cedilanid) on the sodium and potassium balance of the human heart was studied, using intubation of the coronary sinus.

Cedilanid had no effect on the concentration of sodium in arterial blood or on the coronary arteriovenous sodium difference.

The potassium concentration of arterial and coronary sinus blood was significantly elevated following injection of the glycosides. The coronary arteriovenous difference of potassium remained unchanged.

REFERENCES


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Action of Quinidine on Vagal Intracardiac Ganglia

Pharmacologic studies of quinidine on the heart have not given much consideration to its possible effect on intracardiac vagal ganglia. Working with turtles (Glemmys) Henri Fredericq reports that the depressant effect of vagus nerve stimulation on atrial contractions (negative inotropic effect) is abolished or significantly reduced by action of quinidine on preganglionic terminals. A similar, but less effective, synaptolytic effect occurs at postganglionic terminals.

Since quinidine, likewise, abolished the inotropic action of acetylcholine of perfused turtle hearts it is conceivable that the antagonistic action of the two drugs takes place at vagal synapses in the heart.

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