Saliva Calcium and Potassium Concentrations in the Detection of Digitalis Toxicity

By Margo Swanson, Pharm.B.S., Larry Cacace, Pharm.D., George Chun, M.D., and Masashi Itano, M.D.

SUMMARY
Stimulated whole saliva was collected from 118 subjects: 36 were not receiving digitalis; 40 received digitalis but were nontoxic; 14 were digitalis-toxic; 24 had impaired renal function; and four subjects were followed during the administration of digitalis. Saliva calcium and potassium products in the digitalis-toxic group were significantly higher than in the nontoxic group. Subjects with impaired renal function had a significantly higher saliva calcium and potassium product than those with normal renal function. The subjects followed during the administration of digoxin showed an apparent correlation between electrocardiogram changes and an elevated saliva calcium and potassium product. This study has demonstrated that a whole-saliva calcium and potassium product over 300 in subjects on digoxin with normal renal function correlates with a diagnosis of digitalis toxicity.

Additional Indexing Words:
Saliva electrolytes Cardiac glycosides

Digitalis intoxication

DIGITALIS intoxication is a frequently encountered problem in clinical medical practice. A recent prospective study by Beller et al. demonstrated digitalis toxicity in 23% of hospitalized patients who were receiving the drug prior to admission, and the in-hospital mortality rate for the digitalis-toxic group was more than twice that of the nontoxic group.1

The diagnosis of digitalis toxicity has been based on clinical signs and symptoms, characteristic electrocardiographic abnormalities, and more recently serum levels of the various digitalis preparations. Unfortunately, the clinical signs and electrocardiographic abnormalities are common to other conditions, and serum drug levels do not correlate with the toxic state in a significant number of cases.1, 2 There is need for a simple, rapid, reliable test for the identification of digitalis toxicity.

Bartelstone et al. and Siegel have reported animal studies which demonstrated an elevation of salivary potassium concentration in association with electrocardiographic evidence of digitalis toxicity.3, 4 Wotman et al. demonstrated an elevated product of salivary potassium and calcium concentration associated with digitalis intoxication in human subjects.5

The purpose of this study was to elucidate further the potential value of salivary potassium and calcium concentrations in the identification of digitalis intoxication.

Methods and Materials
Saliva Collection and Analysis
Prior to collection of the saliva sample, subjects were instructed to rinse their mouths thoroughly with water to remove any possible contaminating substances such as food, potassium chloride syrup, and toothpaste. Salivary secretion was stimulated by having subjects chew on a rubber band or a piece of dry filter paper previously soaked in a saturated solution of citric acid. Saliva was expectorated into a convenient container and transferred to a stoppered test tube for transport to the laboratory. A syringe was used to aspirate the saliva if expectoration was impractical. A minimum of 0.5 ml of saliva is required. Saliva samples were collected within 2 to 12 hours of the electrocardiogram and within 8 hours of the collection of serum digoxin levels.

In the laboratory, 50 μl of centrifuged saliva diluted with 4 ml of 1% lanthanum chloride was analyzed for calcium using the Perkin-Elmer 303 atomic absorption spectrophotometer. Potassium levels were determined with the I. L. 113 flame photometer using 40 μl of the specimen diluted with 8 ml of 15 mEq/liter lithium diluent. The standard for both determinations was that recommended by Wotman, containing 25 mEq/liter.

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potassium, 43 mEq/liter sodium, 5 mEq/liter calcium, and 15 mEq/liter phosphate in 1% hydrochloric acid.\textsuperscript{5}

**Serum Digoxin Levels**

In 40 subjects, serum digoxin levels were obtained 8 to 24 hours after the last dose of digoxin. These serum digoxin levels were obtained within 1 to 12 hours of the electrocardiogram and within 8 hours of the collection of saliva samples.

Digoxin levels were determined by radioimmunoassay. Some were determined by the use of the Schwarz/Mann Kit, and others were performed by a reference laboratory.

**Study Population**

Stimulated whole saliva was collected from members of the medical staff, hospital staff, and patients admitted to Memorial Hospital Medical Center over an 11-month period. The subjects in this study were placed in one of five groups. Group A were those subjects not receiving digitalis preparations and included members of the medical staff, hospital staff, and a random selection of hospitalized patients. Group B were hospitalized patients receiving various digitalis preparations with apparently normal renal function who were considered to be nontoxic. Group C were hospitalized patients receiving various digitalis preparations with apparently normal renal function and with a clinical diagnosis of digitalis toxicity.

Groups D and E were hospitalized patients with impaired renal function determined by serum creatinine and creatinine clearances. Group D1 were patients not on digitalis with a 24-hour urine output of 1000 ml or more. Group D2 were patients not on digitalis with a 24-hour urine output of less than 1000 ml. Group E1 were patients on digoxin with a 24-hour urine output of 1000 ml or more. Group E2 included patients on digoxin with a 24-hour urine output of less than 1000 ml. Group E patients did not have arrhythmias or other symptoms related to digoxin therapy. Clinical data for all groups are summarized in table 1.

A cardiologist made the diagnosis of digitalis intoxication based on clinical signs and symptoms and electrocardiographic arrhythmias and the disappearance of these arrhythmias when digitalis was discontinued. All 14 digitalis-toxic patients had one or more of the following arrhythmias: multifocal premature ventricular beats, ventricular bigeminy, paroxysmal ventricular tachycardia, paroxysmal atrial tachycardia with atrioventricular block, complete atrioventricular block, and atrial flutter with a 4:1 block. Thirteen of the toxic patients also had one or more of the following noncardiac signs of digitalis toxicity which also disappeared upon discontinuing the digitalis preparation: nausea, vomiting, anorexia, visual disturbances, confusion, fatigue, and diarrhea.

### Table 1

**Clinical and Laboratory Data for All Groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D1</th>
<th>D2</th>
<th>E1</th>
<th>E2</th>
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<tbody>
<tr>
<td>No. of pt</td>
<td>36</td>
<td>40</td>
<td>14</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Age (yr), mean ± sd</td>
<td>50 = 20</td>
<td>67 ± 13</td>
<td>73 ± 12</td>
<td>56 ± 8</td>
<td>67 ± 11</td>
<td>68 ± 18</td>
<td>67 ± 11</td>
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<tr>
<td>Range</td>
<td>27-88</td>
<td>5-93</td>
<td>44-93</td>
<td>48-66</td>
<td>56-85</td>
<td>38-91</td>
<td>55-78</td>
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<tr>
<td>Digitalis preparation</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>(mg), mean dose = ± sd:</td>
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<td></td>
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</tr>
<tr>
<td>Digoxin</td>
<td>0.25 ± 0</td>
<td>0.25 ± 0</td>
<td>0.19 ± 0.11</td>
<td>0.21 ± 0.07</td>
<td></td>
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<tr>
<td>(N = 37)</td>
<td>(N = 13)</td>
<td>(N = 1)</td>
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<tr>
<td>Digitoxin</td>
<td>0.1 ± 0</td>
<td>0.1 ± 0</td>
<td>0.1 ± 0</td>
<td>0.1 ± 0</td>
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<tr>
<td>(N = 1)</td>
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<td>(N = 1)</td>
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<tr>
<td>Digitalis</td>
<td>0.1 ± 0</td>
<td>0.1 ± 0</td>
<td>0.1 ± 0</td>
<td>0.1 ± 0</td>
<td></td>
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<tr>
<td>(N = 1)</td>
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<tr>
<td>Gitaligin</td>
<td>0.5 ± 0</td>
<td>0.5 ± 0</td>
<td>0.5 ± 0</td>
<td>0.5 ± 0</td>
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<tr>
<td>(N = 1)</td>
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<td>(N = 1)</td>
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<td>Cardiac diagnosis:</td>
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<td>Acute myocardial infarction</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>2</td>
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<td>Old myocardial infarction</td>
<td>2</td>
<td>27</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Coronary heart disease</td>
<td>1</td>
<td>24</td>
<td>8</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Valvular heart disease</td>
<td>0</td>
<td>11</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other disease</td>
<td>8</td>
<td>20</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Mean serum K(^+) (mEq/liter)</td>
<td>4.3 ± 0.05</td>
<td>4.0 ± 0.8</td>
<td>4.3 ± 0.9</td>
<td>4.4 ± 0.6</td>
<td>4.4 ± 0.4</td>
<td>4.3 ± 0.6</td>
<td>5.1 ± 0.8</td>
</tr>
<tr>
<td>(normal 3.5-5.0)</td>
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<tr>
<td>Mean creatinine (mg/100 ml)</td>
<td>1.0 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>6.5 ± 2.4</td>
<td>5.8 ± 4.4</td>
<td>3.7 ± 0.87</td>
<td>8.1 ± 4.0</td>
<td></td>
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<tr>
<td>(normal 0.8-1.7)</td>
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<tr>
<td>Mean BUN (mg/100 ml)</td>
<td>14 ± 3.7</td>
<td></td>
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<td>(normal 8-23)</td>
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<tr>
<td>Creatinine clearance (cc/min)</td>
<td>28-48</td>
<td>1-4</td>
<td>7-51</td>
<td>2-61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(normal 100-130)</td>
<td></td>
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</tr>
</tbody>
</table>
Serial saliva samples and clinical and laboratory data were also collected on four subjects before and during the administration of digoxin (Lanoxin) and deslanoside (Cedilanid D). Three were healthy volunteers and one a patient in atrial fibrillation who was being digitalized. Saliva samples were obtained prior to the administration of each dose and 2 hours after the last dose of digoxin. Electrocardiograms were obtained in

the three volunteers 2 hours after the study began and 2 hours after the last dose of digoxin. Serum potassium levels were obtained 1 hour after the last dose of digoxin.

Results

The whole-saliva calcium and potassium concentrations and the distribution of the individual values

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**Figure 1**

*Stimulated whole-saliva calcium (Ca++) and potassium (K+) and calcium and potassium products (Ca++ × K+) in groups A, B, and C. The line in the middle of the box represents the mean, and the area on either side 1 sd from the mean.*

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Stimulated whole-saliva calcium (Ca\(^+\)) and potassium (K\(^+\)) and calcium and potassium products (Ca\(^+\) × K\(^+\)) in groups D and E. The line in the middle of the box represents the mean, and the area on either side 1 so from the mean.

For each group are shown in figures 1 and 2 and table 2. In 40 subjects in group B the mean saliva calcium concentration was significantly higher (P > 0.05) than in group A. The mean potassium concentration and the mean calcium and potassium product were also significantly higher (P > 0.01) than in group A. Fourteen subjects in group B who were not receiving diuretics had a mean calcium and potassium product of 194.1 ± 54, and 26 subjects who were receiving diuretics had a mean product of 181.4 ± 35. Contrary to Wotman’s results, no significant difference occurred between patients who were receiving diuretics and those who were not.

The saliva calcium and potassium concentrations and the calcium and potassium products of subjects in group C were significantly higher (P > 0.01) than in groups A and B. All 14 subjects in group C were receiving diuretics. Three to 14 days after discontinuing digitalis preparations, saliva tests were repeated in nine of these patients. There was no significant difference between these repeat values and those in group B, indicating that these changes are reversible.

The subjects in group D had impaired renal function and were not receiving any digitalis. The mean saliva calcium and potassium product in group D1 was significantly higher (P > 0.05) than in group A. The mean saliva calcium and potassium concentration and the product in group D2 were significantly higher (P > 0.01) than in group A. The subjects in group E had impaired renal function and were receiving digoxin. There was no significant difference between saliva calcium and potassium concentrations and the products in group E1 and group B. The saliva calcium concentrations and the calcium and potassium products in group E2 were significantly higher (P > 0.01) than in group B. All patients in groups D and E, except one in group D1, were receiving diuretics.

A comparison of the calcium and potassium products for all five groups is shown in figure 3.

Serum Digoxin Levels

The mean ± so and the distribution of the individual values for the serum digoxin levels in groups B, C, and E are shown in figure 4. The mean serum digoxin level for 24 patients in group B was 1.4 ± 1.1 ng/ml; for six patients in group E was 1.5 ± 1.2 ng/ml; and in nine patients in group C was 1.7 ± 1.1 ng/ml. There was no significant difference between the serum digoxin levels in these three groups, and they were of little value in distinguishing toxic from nontoxic patients. This is in agreement with a recent article by Fogelman et al.²

Subjects Studied during the Administration of Digitalis

The serial changes in the saliva calcium and potassium concentration in four subjects during the

![Figure 2](image-url)

![Figure 3](image-url)

Comparison of the calcium and potassium products (Ca\(^+\) × K\(^+\)) in groups A, B, C, D, and E.
administration of digitalis preparations are shown in figure 5. The three volunteer subjects were evaluated for noncardiac symptoms and electrocardiographic manifestations of digitalis intoxication. Subject 1 received digoxin 35 μg/kg of body weight intravenously and had a final saliva calcium and potassium product of 206. No clinical symptoms were reported, but the electrocardiograms showed prolongation of the P-R interval, shortening of the Q-T interval, and flattening of previously upright T waves in leads V_{2} and V_{3}. Subject 2 received digoxin 40 μg/kg and had a final product of 342. Clinical symptoms of nausea, anorexia, marked fatigue, and malaise were reported, and significant changes were observed in the 12-lead electrocardiogram. The P-R interval was prolonged, the Q-T interval shortened, previously upright T waves in leads III and aV_{F} became inverted, and previously upright T waves were flattened throughout the precordial leads. Subject 3 received digoxin in 33 μg/kg and had a final product of 273. No clinical symptoms were reported or observed, and no changes were seen with 12-lead electrocardiograms. Similar changes in salivary electrolytes occurred in subject 4. A summary of these data appears in table 3. Serial saliva calcium and potassium concentrations and products are shown in figures 5 and 6.

Table 2

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Ca++ (mEq/liter)</th>
<th>K+ (mEq/liter)</th>
<th>Ca++ \times K+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (N = 36) No digitalis</td>
<td>5.4 ± 1.9</td>
<td>23.3 ± 4.1</td>
<td>126.2 = 49.5</td>
</tr>
<tr>
<td>Group B (N = 40) Digitalis, nontoxic</td>
<td>6.4 ± 2.0</td>
<td>29.5 ± 6.8</td>
<td>184.1 = 58.6</td>
</tr>
<tr>
<td>Group C (N = 14) Digitalis-toxic</td>
<td>14.6 ± 6.8</td>
<td>36.6 ± 8.6</td>
<td>503.4 = 223</td>
</tr>
<tr>
<td>Repeat (N = 9)</td>
<td>6.7 ± 2.3</td>
<td>27.8 ± 4.9</td>
<td>185 = 63.2</td>
</tr>
<tr>
<td>Group D</td>
<td>1 No digitalis (N = 4)</td>
<td>6.8 ± 0.9</td>
<td>26.3 ± 2.4</td>
</tr>
<tr>
<td>2 No digitalis (N = 6)</td>
<td>27.5 ± 15.3</td>
<td>29.8 ± 5.1</td>
<td>788.2 = 380.8</td>
</tr>
<tr>
<td>Group E</td>
<td>1 Digitalis (N = 10)</td>
<td>6.5 ± 3.2</td>
<td>27.8 ± 7.7</td>
</tr>
<tr>
<td>2 Digitalis (N = 4)</td>
<td>20.5 ± 4.1</td>
<td>30 ± 10.0</td>
<td>626 = 286.5</td>
</tr>
</tbody>
</table>

*Mean = 1 sd.
†With 24-hour urine output less than 1000 ml.

Discussion

The majority of the subjects in this study were receiving digoxin. Therefore, the major conclusions relate primarily to this digitalis glycoside. However, previous animal and human studies indicate that acetylstrophanthidin, ouabain, digitoxin, and digitalis leaf produce similar effects.

The mean saliva calcium and potassium concentrations and the calcium and potassium products in group C were significantly different (P > 0.01) from groups A and B. The distribution of the individual values for each group is shown in figure 1. Some overlap in the saliva calcium and potassium concentrations occurred in all three groups. Therefore, the product was more helpful in distinguishing the toxic from the nontoxic group than either value alone. There was only a small difference between the highest product in the nontoxic group (278) and the lowest product in the toxic group (309). Only those patients who were definitely toxic were placed in group C. Therefore, it is possible that some of the higher values in group B may represent subclinical toxicity. There was no significant difference between the mean age, serum potassium, serum creatinine, cardiac status, or digoxin dose in the toxic and nontoxic groups. The only apparent difference between the two groups was in regard to body weight. Six of the 14 toxic patients (42%)

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Figure 4
Serum digoxin levels in groups B, C, and E. IRF = impaired renal function. The top of the box represents the mean and the area on either side 1 sn from the mean.

weighed 50 kg or less as compared to five of 40 nontoxic patients (12%).

All except two of the patients in groups D and E had a diagnosis of chronic renal disease. Both of these patients were included in group D2. One had acute renal failure postoperatively, and the other developed congestive heart failure and acute renal failure secondary to a pericardial effusion. The increased calcium and potassium products (over 300) found in all patients with impaired renal function on no digitalis (group D2) represents a significant false-positive result, indicating that this test is apparently of no value in patients with impaired renal function. The serum creatinine and creatinine clearances in groups D and E varied markedly between individuals in each group. There was no linear correlation between the serum creatinine or creatinine clearance and the elevation of the salivary calcium and potassium concentrations or products in groups D and E. The salivary calcium concentrations in groups D2 and E2 were significantly higher than those in groups D1 and E1. The reason for the high saliva calcium values found in these patients is not clear and will require further study. The only apparent difference between groups D1 and E1 and groups D2 and E2 was the lower 24-hour urine output in the latter two groups. A study in a larger group is necessary to determine if this is a significant factor.

Several other conditions may also affect saliva electrolytes and thus interfere with the usefulness of this test. Increased submaxillary saliva potassium concentrations may occur in primary hyperaldosteronism. Increased concentrations of submaxillary saliva calcium have been reported in cystic fibrosis, asthma, and following the intravenous administration of 0.5 μg/kg of isoproterenol. These factors must be kept in mind whenever saliva calcium and potassium concentrations are being studied.

The results in the three human volunteers showed that digoxin can significantly increase the whole-saliva potassium concentration. There was a correlation between this increase and the electrocardiogram changes and clinical symptoms as shown in subject 2. The effect of digoxin on the saliva calcium concentration was not clear. There was a
significant increase in the saliva calcium concentration in the toxic group but this was not apparent in the short-term study in the volunteers.

The difference between the mean values for the calcium and potassium products in our study and that of Wotman et al. was primarily due to the higher mean saliva calcium concentrations. This could have been due to a variation in laboratory testing or differences in methodology. Gould et al. have also reported higher calcium values than Wotman in 90 nontoxic patients on digoxin (range 1.6-18.8 mEq/liter).12

The mechanism by which cardiac glycosides induce alterations in salivary potassium and calcium concentrations is unknown, but the magnitude of this effect on the salivary glands seems to parallel their effect on the electrical activity of the heart in the toxic range.2-5 Cardiac glycosides inhibit Na-K ATPase, the enzyme involved in the active transport of sodium out of a variety of body cells against an electrochemical gradient, which results in accumulation of sodium in the cell and loss of potassium into the extracellular fluid. It has been demonstrated that ouabain blocks the uptake of potassium and causes a decrease in the resting potential of unstimulated acinar cells in the salivary gland.18,14

The increased saliva potassium concentration found in digoxis-toxic patients may be related to one or both of these mechanisms.

Cardiac glycosides also influence the metabolism, distribution, and binding of myocardial calcium. Data suggest that tightly bound calcium is transformed by cardiac glycosides into more loosely bound calcium which may be released more easily. It is possible that they alter the characteristics of cellular and intracellular membranes in such a way as to release calcium more easily.1314 These effects may influence calcium concentrations in saliva. Many of the digitalis-toxic patients had a decreased rate of salivary flow compared to the nontoxic group. It has been shown that changes in salivary potassium concentration are slight over a wide range of flow rates.18 The relationship between saliva calcium concentration and flow rate is unknown. If saliva calcium concentration is inversely related to flow rates this may in part account for the higher saliva calcium concentrations in the digitalis-toxic group.

This study has demonstrated that a stimulated whole-saliva calcium and potassium product over 300 in subjects on digoxin correlates with a diagnosis of digitalis toxicity in patients with normal renal function. The studies in subjects followed during the administration of digoxin showed an apparent correlation between electrocardiographic changes and an elevated salivary calcium and potassium product. It is a simple,
rapid, reliable, and objective test and is apparently not dependent on the type of digitalis preparation used. It is hoped that these results will stimulate further studies involving larger subject populations to further elucidate the usefulness of salivary calcium and potassium levels in the identification of digitalis intoxication.

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