Suicidal and Accidental Digoxin Ingestion

Report of Five Cases with Serum Digoxin Level Correlations

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SUMMARY
Clinical and serum digoxin concentration data are presented for five cases of accidental or suicidal ingestion of large amounts of digoxin. Three patients, 20 years of age or less, were without previous evidence of heart disease and responded with the development of atrioventricular block or sino-atrial exit block, which was reversed in two instances by atropine. The third died with refractory hyperkalemia, suggesting generalized inhibition of the cellular sodium-potassium transport system. Ventricular ectopic beats did not occur in any of these three. In contrast, two patients with pre-existing advanced coronary artery disease developed multifocal ventricular premature beats, ventricular tachycardia, and ventricular fibrillation as initial manifestations of toxicity.

Serum digoxin levels 4 or more hours after each ingestion were markedly in excess of those ordinarily encountered in patients receiving usual therapeutic doses, reaching levels as high as 42 ng/ml. Apparent serum half-times between 5 and 48 hours after each ingestion were shorter than those usually observed with normal therapeutic doses of digoxin.

Additional Indexing Words:
Digoxin intoxication Suicide Serum digoxin concentration Radioimmunoassay

INGESTION of large amounts of digitalis glycosides accidentally or with suicidal intent constitutes at once a clinical emergency, a therapeutic challenge, and an unusual opportunity for observation of severe digoxin intoxication. Such cases have been reported previously but have included very few instances of digoxin ingestion. No reported cases have, to our knowledge, been studied with measurements of serum digitalis glycoside concentration. It is the purpose of this report to describe five patients who accidentally or suicidally ingested large amounts of digoxin, and in whom serial measurements of serum digoxin concentration are available for correlation with the clinical course.

Methods
Detailed serial clinical observations and serial electrocardiograms were available for each of the five patients included in this series.

Blood was obtained for serum digoxin assay by routine venipuncture at the times indicated in table 1. Following separation of formed elements by centrifugation, serum was assayed in duplicate for digoxin concentration by a sensitive and precise radioimmunoassay method previously described.5 The serum was diluted when very high concentrations were encountered, in order that the level measured might fall on an optimally sensitive portion of the standard curve.
### Table 1

**Summary of Serum Digoxin Concentration Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Estimated digoxin dose (mg)</th>
<th>Time after ingestion (hr)</th>
<th>Serum digoxin concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (J.F.)</td>
<td>5.75</td>
<td>1</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41</td>
<td>2.2</td>
</tr>
<tr>
<td>2 (M.B.)</td>
<td>Uncertain</td>
<td>5</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>5.2</td>
</tr>
<tr>
<td>3 (N.M.)</td>
<td>23</td>
<td>4</td>
<td>42.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>39.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>25.5</td>
</tr>
<tr>
<td>4 (J.R.)</td>
<td>7.5</td>
<td>4</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96</td>
<td>0.7</td>
</tr>
<tr>
<td>5 (N.M.)</td>
<td>5</td>
<td>4</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>4.8</td>
</tr>
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<tr>
<td></td>
<td></td>
<td>96</td>
<td>0.7</td>
</tr>
</tbody>
</table>

### Case Studies

**Case 1**

J. F., a 2½-year-old boy weighing 37 lb., accidentally ingested 5.75 mg digoxin in the form of 0.25-mg tablets. He was given ipecac within approximately 30 min of the ingestion, and brought to the hospital. There was no previous history of cardiac disease. On initial physical examination he had a blood pressure of 90/60, a regular pulse rate of 85 beats/min, and normal respirations and temperature. The results of the remainder of the physical examination were within normal limits. An ECG taken on admission showed slight sinus arrhythmia. Four hours after admission, intermittent sino-atrial (SA) pauses or, more likely, SA exit block was observed, with probable atrioventricular (A-V) junctional escape beats. Atropine in small doses immediately restored normal sinus rhythm (fig. 1). Electrocardiograms taken 2 hr subsequently demonstrated first degree A-V block followed by 2:1 second degree A-V block. Atropine was not given at this time. Twenty-eight hours after admission stable first degree block was present, soon followed by normal sinus rhythm.

**Case 2**

M. B., a healthy 20-year-old woman weighing 110 lb., was admitted to the hospital 4 hr after ingesting an uncertain number of digoxin tablets with suicidal intent. Blood pressure on admission was 140/80, and heart rate was regular at 80 beats/min. The results of cardiovascular and chest examinations were unremarkable. She remained conscious throughout her hospital stay. An electrocardiogram taken 6 hr after admission demonstrated sinus rhythm with first degree A-V block. Soon thereafter high grade A-V block appeared (fig. 2), with ventricular rates as slow as 25 beats/min. Small amounts of intravenous atropine (0.4 mg) given at this time completely eliminated the high grade A-V block with reversion to a sinus tachycardia with normal P-R interval. On the second day, sinus rhythm with only first degree
Twelve-lead electrocardiogram from case 2, taken approximately 8 hr after ingestion of digoxin with suicidal intent. High grade A-V block is present, which could be completely reversed by atropine with reversion to a sinus tachycardia with normal P-R interval.

block was present. On the third hospital day, all ECG evidence of digoxin excess had disappeared.

Case 3*

N. M., a 17-year-old female previously in good health (weight approximately 115 lb.), entered the hospital 3 hr after ingesting 23 mg digoxin and 1300 mg propoxyphene hydrochloride (Darvon) with the intention of committing suicide. She vomited an uncertain amount of the ingested material later.

On admission to the hospital she appeared lethargic, but responded to questions. Her blood pressure was 100/60, and her pulse was 55 beats/min. Her initial electrocardiogram demonstrated A-V dissociation with QRS widening, which progressed from 0.09 sec to 0.40 sec during the first few hours after hospital admission. Her initial serum potassium level was 7.8 mEq/liter (range on serial determinations, 7.7 to 9.8 mEq/liter); the arterial pH was 7.40. Despite intensive efforts to control the hyperkalemia with sodium bicarbonate, glucose and insulin, and sodium polystyrene sulfonate (Kayexalate) therapy, she expired 3½ hr after admission with an asystolic arrest. Resuscitative efforts were unsuccessful. During the resuscitation, attempted pervenous

*This case is to be separately reported in detail by Drs. P. LaRaia, C. Blum, and B. Lown.
right ventricular pacing failed to elicit any electrical response from the heart.

Case 4

J. R. was a 208 lb., 65-year-old man with known coronary artery disease and two previous myocardial infarctions. He was admitted to the hospital 2 hr after taking 7.5 mg digoxin and 18 g chlorothiazide with suicidal intent. He had been on a chronic oral maintenance dose of digoxin of 0.25 mg/day up to the time of the ingestion. On physical examination he had a blood pressure of 100/60, pulse rate of 60 beats/min (atrial fibrillation), and a grade 2/6 apical systolic murmur. His initial ECG demonstrated atrial fibrillation with a relatively slow ventricular response and evidence of old inferior and anteroseptal myocardial infarctions. Approximately 3 hr after admission, recurrent runs of ventricular tachycardia and three episodes of ventricular fibrillation developed, which were managed with intravenous lidocaine and DC defibrillation. Ventricular tachycardia, with rates varying from less than 100 beats/min ("slow ventricular tachycardia") to 150 beats/min, occurred intermittently during the first 6 to 20 hr following admission. Twenty-four hours after his arrival at the hospital, A-V junctional rhythm at a rate of 66 beats/min appeared. At this time the ventricular ectopic beats had almost entirely disappeared. Subsequently type I second degree A-V block (Wenckebach block) developed, followed 1 day later by sinus rhythm with first degree A-V block. Three days after admission all ECG evidence of digoxin excess had disappeared, and antiarrhythmic agents were uneventfully discontinued.

Case 5

N. M. was a 155 lb., 51-year-old white male with a past history of severe coronary insufficiency. He was admitted to the hospital after suicidally ingesting 5 mg digoxin in the form of 0.25-mg digoxin tablets. He had been hospitalized several times previously for coronary insufficiency. He had been maintained since 1968 on digoxin (0.25 mg/day) for chronic congestive heart failure. In April, 1969, coronary arteriography demonstrated three-vessel coronary artery disease with severe proximal narrowing of all three vessels. He subsequently had anterior and posterior internal mammary artery implants without marked influence on the frequency or severity of his chest pain. On physical examination at the time of admission he had a blood pressure of 170/110, a regular pulse rate of 80 beats/min, and normal respirations and temperature. A grade 2/6 systolic ejection murmur was heard along the left sternal border; at the apex, prominent third and fourth heart sounds were noted.

Figure 3

Rhythm strips from case 5, showing multifocal ventricular premature beats following ingestion of 20 0.25-mg digoxin tablets superimposed on a chronic oral maintenance dose of 0.25 mg/day.

Figure 4

Semilogarithmic plot of serum digoxin concentration vs. time for case 5. Values are shown over a time span from 4 to 96 hr after the ingestion. Only after 48 hr, when the serum level has fallen to almost the usual therapeutic range, does the half-time reach the expected value of 32 hr.
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Within 1% hr after admission, multifocal ventricular ectopic beats appeared (fig. 3) with brief runs of ventricular tachycardia responding to intravenous lidocaine and diphenylhydantoin. A temporary pervenous pacemaker catheter was inserted, and the demand rate was set above his own intrinsic rate so that both "overdrive" and drug suppression of his ventricular ectopic beats could be used. This proved to be effective in controlling the ventricular extrasystoles, and 24 hr later only first degree A-V block was present. Three days after admission he was in sinus rhythm with a normal P-R interval.

Serum Digoxin Concentrations

Results of measurements of serum digoxin concentration in each of the five patients are summarized in table 1. Duplicate determinations agreed within 5% in each instance. Semilogarithmic plots of serum concentrations against time for samples drawn 5 hr or later after the ingestion yielded apparent half-times for clearance from the serum of 12, 14, 6, and 22 hr for cases 1, 2, 3, and 4, respectively. It should be noted that the limited numbers of serum samples available for study in cases 2, 3, and 4 allow only approximations of average half-times over the indicated time spans. For case 5, in which serum levels were measured over a wider range of times and concentrations, a progressive lengthening of the apparent serum half-time from 10 to 31 hr was observed, as plotted in figure 4.

Discussion

Although uncommon, accidental or deliberate ingestion of very large quantities of digoxin occurs with sufficient frequency that we have studied five cases in a period of slightly over 1 year. This has provided the opportunity to observe the effect of severe excess of digoxin on previously normal as well as diseased hearts, and to correlate the clinical state with serum digoxin concentrations. Our general experience has yielded a mean serum digoxin concentration of 1.4 ± 0.7 (SD) ng/ml in a series of 131 adult patients on oral maintenance digoxin without evidence of toxicity.7 Ninety percent of these nontoxic patients had serum levels less than 2.0 ng/ml. Among 48 hospitalized patients with cardiac disease who showed definite evidence of digoxin intoxication, 87% had serum levels greater than 2.0 ng/ml, with a mean of 3.7 ± 1.0 (SD). Hence the levels observed in the patients in this study (table 1) document the exposure to extraordinary amounts of digoxin.

Of the five patients reported here, all had blood urea nitrogen or serum creatinine values in the normal range. Three were 20 years of age or less and were without previous evidence of heart disease. In all three, the cardiac response to ingestion of very large doses of digoxin was the development of heart block: high grade A-V block in two instances and first and second degree A-V block in the third. Ventricular premature beats did not occur in any of the three. Two of the three patients survived despite very high serum, and presumably myocardial, levels of digoxin. In one of these patients, atropine reversed significant A-V block to a normal conduction pattern, and sino-atrial exit block was reversed in the other. Thus, despite the well-known extragadal effects of digitalis glycosides on the conducting system,8-10 the therapeutic success of atropine in these obviously toxic patients underscores its potential role in the management of digitalis-induced SA or A-V block. A case similar to our case 1 has been described by Surawicz and Mortelmans, in which atropine abolished depression of SA node activity (or exit block) in a healthy 17-year-old woman following suicidal ingestion of digitoxin.11 It may be that the generally unfavorable experience with atropine in digitalis-induced A-V block reported by some authors12 is relevant chiefly to situations in which digitalis has been administered chronically to patients with diseased hearts; the cases reported here differ both in the absence of preexisting heart disease and in the acute nature of the toxic insult. The efficacy of atropine in reversing digitalis-induced A-V block has also been noted by Miller.13

The third patient with no prior history of cardiac disease succumbed with refractory hyperkalemia and high grade A-V block despite the most vigorous and sophisticated supportive efforts. This patient had a serum

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digoxin level of 42 ng/ml 4 hr after the ingestion, which is the highest level we have observed in over 6000 determinations covering a broad spectrum of clinical circumstances. The occurrence of refractory hyperkalemia in this case is of interest, and suggests that generalized inhibition of the sodium-potassium activated adenosine triphosphatase (ATPase) of the cell membrane may have occurred with this massive dose of cardiac glycoside, resulting in impairment of the ability of cells to maintain the normally high ratio of intracellular to extracellular potassium concentration.\textsuperscript{14,15} Consistent with this hypothesis are the observations of Gaultier et al.,\textsuperscript{5} who found an elevated mean serum potassium level following acute ingestion of large amounts of cardiac glycosides compared with nondigitalized control subjects; cases with a fatal outcome, in turn, had a higher mean level than that of those patients who survived. Thus, despite its usefulness in many cases of digitalis intoxication characterized by ectopic impulse formation, supplemental potassium may increase A-V block and should not be used as a matter of routine without due consideration of the type of rhythm disturbance, serum potassium concentration, and renal function.\textsuperscript{10}

The possibility that propoxyphene intoxication played a role in this patient's demise cannot be excluded. Transient QRS widening has been observed in association with seizures, apnea, and cyanosis in a reported case of severe propoxyphene intoxication, but there was no evidence of A-V block or electrolyte disturbance.\textsuperscript{16} It seems reasonable to presume that the primary clinical problems in this case were directly related to digoxin intoxication.

The remaining two patients exhibited frequent ventricular premature beats with episodic ventricular tachycardia or ventricular fibrillation during the initial 24 hr after ingesting the digoxin. In both instances A-V block appeared after the ventricular excitability had diminished under the influence of antiarrhythmic drugs. Both of the latter two patients had coronary artery disease with previous myocardial infarctions. This experience is consistent with previous observations that the response of the normal human heart to digitalis excess tends to be development of A-V conduction disturbances, while the diseased heart frequently responds with ectopic impulse formation, particularly from ventricular foci.\textsuperscript{1,2,17,18}

An interesting analogy to these observations in normal hearts may be found in pediatric clinical experience, where P-R interval prolongation constitutes a frequent sign of impending digitalis excess and the sudden emergence of ectopic ventricular arrhythmias as a manifestation of digitalis intoxication is uncommon.\textsuperscript{19,20} One may speculate that the absence of coronary artery disease with attendant areas of focal ischemia may be an important factor. The converse of this situation may be reflected in the increased incidence of coronary artery disease among adult patients who exhibit digitalis intoxication at relatively low serum concentrations of digoxin or digitoxin.\textsuperscript{21,22}

The apparent serum half-times for digoxin clearance exhibited by these patients are of interest. The mean serum half-time for orally administered tritiated digoxin following tissue uptake and distribution in subjects with normal renal function is about 31 hr.\textsuperscript{23} This plateau is reached within about 6 hr after oral doses of digoxin.\textsuperscript{23,24} Although the data from cases 1, 2, 3, and 4 allow only approximations of serum half-times, the range of values from about 6 to 22 hr for samples drawn 5 or more hr after the ingestion represents a departure from the expected mean. The more detailed data from case 5 (see fig. 4) indicate that only after 48 hr, when the serum level has fallen to the usual range encountered in patients on therapeutic doses of digoxin, does the serum half-time reach the expected value of 32 hr. One explanation of these results lies in the possibility that gastrointestinal absorption of these larger doses was slowed, and that tissue uptake and distribution was occurring later than usual. The relatively high level at 13 hr compared with that at 1 hr in case 1 is compatible with a prolonged phase of gastrointestinal absorption. Hence a relatively late
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The peak serum peak with continuing tissue uptake may have combined with renal clearance to shorten the serum half-times in some cases. However, since gut absorption of digoxin appears to be a passive process without evidence of saturation kinetics,\textsuperscript{25} this mechanism must remain conjectural. Alternatively, it may be that the half-time for tissue uptake and distribution is prolonged with massive doses, independent of the rate of gastrointestinal absorption. Here again, the combined effects of tissue uptake and renal excretion would be operative during the period when renal excretion alone dominates the clearance from the serum of usual doses. Finally, it may be that the relationship between tissue and serum levels is altered with massive ingestions in favor of higher serum:tissue ratios, resulting in a relatively greater proportion of the total body burden of drug being presented to the glomerulus per unit time for filtration and excretion.

The clinical experience reported here indicates that accidental or suicidal digoxin intoxication can be successfully managed in most cases by appropriate use of antiarrhythmic and vagolytic drugs combined, when necessary, with temporary percutaneous pacing techniques. The death of a previously healthy young woman following massive digoxin ingestion, however, underscores the need for more effective therapeutic modalities in such instances.

Acknowledgment

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References


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Correction

Baron MG: Circulation 43: 768, 1971. Figures 7A and 7B were incorrectly labeled.

What is now figure 7A should be figure 7B, and what is now figure 7B should be figure 7A.
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