Serum Digitoxin Concentrations in Infants and Children

By Andrea C. V. Giardina, M.D., Kathryn H. Ehlers, M.D., John B. Morrison, M.D., and Mary Allen Engle, M.D.

SUMMARY

Serum digitoxin levels were measured in 18 infants (under two years) and in 23 children (aged 2–13 years) receiving maintenance therapy. Digitalization was carried out because of heart failure in 17 infants and 13 children and for control of dysrhythmia in one infant and 10 children. Mean maintenance dosage for infants was 0.0042 ± 0.0008 (sn) mg/kg/day and for children was 0.0031 ± 0.0012 mg/kg/day. The mean serum digitoxin level was not significantly different in infants (30 ± 10 ng/ml, range 14–58) from that found for children (34 ± 11 ng/ml, range 19–61). Both values were significantly different (P < 0.001) from those determined in this laboratory for adults (mean 24 ± 7 ng/ml, range 5–39). In four infants with electrocardiographic or other evidence of toxicity, the mean serum level was 71 ± 2 ng/ml (range 68–72), and in four children with electrocardiographic or other evidence of toxicity, the mean serum level for digitoxin was 72 ± 14 ng/ml (range 53–84).

The data suggest that infants and children tolerate a higher serum digitoxin concentration without any evidence of toxicity and may require more digitoxin (mg/kg) for therapeutic effect than do adults. Serum digitoxin levels may serve as an important guide in determining the adequacy of digitalization and in the recognition and management of digitalis toxicity.

Additional Indexing Words:

Radioimmunoassay Digitalizing dosage Maintenance dosage
Toxicity

The development of the radioimmunoassay technique for the measurement of serum glycoside concentrations has provided a simple, rapid and safe method which is applicable to the clinical setting. In adults, serum digitoxin and digoxin levels obtained by this method have been found to be a valuable adjunct in the determination of appropriate therapeutic dosage and in the recognition of toxicity.1-5 Data on serum digoxin levels in infants and children have been published and have demonstrated that infants, who generally receive a higher digoxin dosage per body weight than older subjects, tolerate higher serum digoxin concentrations.4-6 To date there have been no available data on serum digitoxin levels for the pediatric age group.

The present study has been undertaken in order to: 1) establish the range of serum concentrations of digitoxin in infants and children being treated for congestive heart failure or dysrhythmia, 2) determine the serum digitoxin levels associated with clinical or electrocardiographic evidence of toxicity, and 3) ascertain if the increased dosage/body weight of digitoxin administered to infants and children is reflected in higher serum levels than those already established for adults.7-10 Such information should serve as an important guide to therapy, since clinically the therapeutic dosage varies within wide limits and the margin in some individuals between the therapeutic and toxic dosage may be narrow. Furthermore, signs and symptoms of toxicity other than electrocardiographic criteria can generally not be appreciated in these small subjects.

Methods

An accurate and specific radioimmunoassay was used to measure serum digitoxin levels in infants and children. The assay could be performed in one hour and only 50 microliters of serum were required, allowing frequent serial determinations on small infants. Sampling was delayed at least six to eight hours after a dose of digitoxin had been given to minimize the effects on serum concentration of absorption and equilibration of the drug within the body.

Serum for radioimmunoassay determination was obtained from blood which was centrifuged immediately after withdrawal at 10,000 rpm for 20 min at 4° C. All samples from a given patient were frozen at −20° C and analyzed in...
the same batch. It had previously been determined in this laboratory that freezing a sample for as long as 12 months does not alter the assay. For the digoxin assay, 50 microliters of serum, 100 microliters of specific antibody (3045/93 at a dilution of 1:12,000) and 1.1 ng of digitoxin-H^+ (New England Nuclear) were utilized. These concentrations of antibody and ligand resulted in an initial binding of approximately 45% and excellent sensitivity in the 5-40 ng/ml range for digitoxin. The specificity of the digitoxin antibody (3045/93) utilized in this study is defined in Table 1.12

Duplicate samples were counted in a liquid scintillation medium composed of p-dioxane, methanol, naphthalene (scintillation grade, Eastman Kodak) and butyl-PBD in toluene (Amersham/Searle). One standard deviation of the digitoxin assay for 200 separate determinations of a sample with a known concentration of 25 ng/ml was ± 2.0 ng/ml. The standard deviation of 60 aliquots of a blood sample containing digitoxin run in the same batch was ± 1.2 ng/ml. Standards were made by the addition of 50 microliters of gravimetrically prepared digitoxin solutions to normal human serum. Determinations were run in duplicate. To serum in test tubes, tritiated digitoxin was added. Anti-digitoxin antibody was then added to this and the mixture incubated. Competition between labeled and unlabeled digitoxin for antibody-binding sites determined the amount of labeled digitoxin antibody complex present at equilibrium. Separation of bound from free labeled digitoxin was then done by the dextran-coated charcoal technique of Herbert et al.12

Patients

Digitalization in all infants and most children was carried out with a digitoxin elixir preparation compounded in The New York Hospital-Cornell University Medical College pharmacy using a formula similar, except for coloring and flavoring, to that used in the preparation of CT-1410. Solution Crystodigin, digitoxin formerly made by E. Lilly and Company.13 Older children received a tablet form of digitoxin (Lilly-Crystodigin). Digitoxin is used for most of the infants and children treated for congestive heart failure at The New York Hospital for several reasons: 1) it can be given in one daily dose, 2) there is no need to increase the dosage when converting from the parenteral to the oral route and 3) it has a longer duration of action than digoxin so that if an occasional dose of medication is inadvertently not given, or the infant regurgitates a dose of medication, the serum level will not be lowered significantly.

The assay was performed on 18 specimens of serum from 18 infants under two years of age (2.4-7.8 kg) receiving maintenance digitoxin. Digitalization was carried out because of heart failure in 17 infants and for control of dysrhythmia in one infant. These infants were all digitalized by parenteral administration of 0.035 to 0.06 mg of digitoxin per kilogram of body weight in divided doses over 12 to 24 hours. Maintenance dosage was calculated at 1/10 of the total digitalizing dosage. Maintenance dosage, given in one daily dose by an experienced nurse, had been administered for a minimum of eight days at the time the blood sample was drawn. Mean maintenance dosage for infants was 0.0042 ± 0.0008 mg/kg/day. Mean maintenance dosage for babies with congestive heart failure was 0.0043 ± 0.0008 mg/kg/day; for the one infant with a dysthymia, it was 0.0035 mg/kg/day. All infants in the study had normal serum potassium and sodium concentrations. None had abnormal renal nor hepatic function and none were hypoproteinemic. There were no patients with clinically apparent gastrointestinal problems. Some patients received a diuretic in the form of furosemide. None received spironolactone. Electrocardiograms in this group demonstrated no evidence of digitalis excess and none of the infants demonstrated any symptoms such as vomiting, diarrhea, or anorexia suggesting digitalis toxicity.

Twenty-three specimens of serum were assayed in 23 children, two to thirteen years of age (12-47 kg). Digitalization was carried out for congestive heart failure in 13 of these children and for control of dysrhythmia in ten others. The children in both the congestive heart failure group and the dysrhythmic group were digitalized at a dosage of 0.02 to 0.06 mg/kg of body weight given in divided doses over a period of 24 hours. Maintenance dosage was calculated at 1/10 of the total digitalizing dose. Specimens were drawn after patients had received maintenance therapy for a minimum of eight days. Mean maintenance dosage for the

Table 1

<table>
<thead>
<tr>
<th>Compound added</th>
<th>Digitoxin antiserum*</th>
<th>Amount (ng/ml)</th>
<th>3045/93</th>
<th>1:12,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td></td>
<td>2</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Deslanoside</td>
<td></td>
<td>2</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Digoxigenin</td>
<td></td>
<td>20</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Digoxigenin bis-digitoxoside</td>
<td></td>
<td>20</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Gitalin</td>
<td></td>
<td>20</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Compound F</td>
<td>1000</td>
<td>500</td>
<td>51</td>
<td></td>
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<tr>
<td>Progesterone</td>
<td>1000</td>
<td>10000</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Preguanetriol</td>
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<td>10000</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
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<td>5000</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>1000</td>
<td>25000</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>1000</td>
<td></td>
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</tr>
</tbody>
</table>

*Figures represent the % of 1.1 × 10^-6 moles of tritiated digitoxin bound by specific antiserum in the presence of the stated concentration of a particular compound.
congestive heart failure group was 0.0031 ± 0.0012 mg/kg/day and that for the dysrhythmia group was 0.0032 ± 0.0013 mg/kg/day. Again, there was no electrocardiographic or clinical evidence to suggest digitalis excess. Renal and hepatic function was normal in all these children.

Serum digitoxin levels were also obtained in four infants and four children with electrocardiographic and/or other evidence of toxicity. The range of total digitalizing dosage was 0.04-0.12 mg/kg for the infants and 0.04-0.07 mg/kg for the children. All four infants were being treated for intractable congestive heart failure and all four children were receiving digitoxin for control of a refractory dysrhythmia. Electrocardiographic or other evidence deemed consistent with toxicity consisted of: ventricular fibrillation (1), multiple ventricular premature contractions (1), atrioventricular dissociation (1), atrial tachycardia with 3:1 and 2:1 block (1), marked ST elevation or depression (> 4 mm) (1), prolongation of P-R interval and anorexia (1), anorexia, nausea, vomiting in a child (1), and refusal to feed in an infant (1).

Results

Infant Studies

Table 2 summarizes the results of these studies. All but one infant in this group received digitoxin for the treatment of heart failure. The mean serum digitoxin level in these infants, 30 ± 10 ng/ml (range 14-58), was significantly different (P < 0.05) from that determined at The New York Hospital for 175 adults, mean 24 ± 7 ng/ml (range 5-39 ng/ml).11 The adult patients had received 0.1 ng digitoxin orally daily for one month to five years at the time samples were drawn. Mean maintenance dosage/body weight was calculated for this group at 0.0014 mg/kg/day, assuming the average patient weight to be 70 kg. This adult group did not manifest any electrocardiographic or clinical evidence of digitalis excess and had normal hepatic function. In spite of the higher serum digitoxin concentrations which ranged up to 58 ng/ml, none of the infants had electrocardiographic or clinical evidence of digitalis intoxication. Figure 1 shows the rather wide range of concentrations associated with clinical improvement. In general, there appeared to be some correlation of the serum level to dosage. The mean serum concentration for the 14 infants receiving a maintenance dosage of digitoxin in the range of 0.0035-0.0045 mg/kg/day was 29 ng/ml whereas in the four subjects receiving 0.005-0.006 mg/kg/day it was 34 ng/ml.

Table 2

<table>
<thead>
<tr>
<th>Serum Digitoxin Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
</tr>
<tr>
<td>Infants</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>0-2 years</td>
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<tr>
<td>2.4-7.8 kg</td>
</tr>
<tr>
<td>Toxic</td>
</tr>
<tr>
<td>Children</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>2-13 years</td>
</tr>
<tr>
<td>12-47 kg</td>
</tr>
<tr>
<td>Toxic</td>
</tr>
</tbody>
</table>

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Studies in Children

The mean concentration of digitoxin in serum drawn from 23 children (2–13 years) was not significantly different from the mean serum concentration of digitoxin in our infant population (table 2). The mean serum digitoxin level for children was 34 ± 11 ng/ml (range 19–61) which again was significantly different (P < 0.001) from that determined in this laboratory for the 175 adult patients treated with digitoxin. The mean serum digitoxin level for the 13 children treated for congestive heart failure was 31 ± 8 ng/ml (range 19–51) and the mean serum digitoxin level for the ten children treated for dysrhythmia was 37 ± 13 ng/ml (range 22–61). There was a significant difference in the mean values for each group (P < 0.05). None of these children demonstrated electrocardiographic evidence or other signs of digitalis excess. Figure 1 again demonstrates a rather wide range of concentrations which were associated with a satisfactory clinical response. As in the infant group there appeared to be some correlation of the serum level to the dosage. Mean serum digitoxin concentration for 11 children receiving 0.002–0.0025 mg/kg/day of digitoxin was 27 ng/ml. In four children receiving 0.003–0.0035 mg/kg/day of digitoxin, mean serum digitoxin concentration was 53 ng/ml and in five children receiving 0.004–0.0045 mg/kg/day of digitoxin it was 47 ng/ml. However, in three subjects receiving 0.005–0.006 mg/kg/day of digitoxin, the mean serum digitoxin level was 35 ng/ml.

Toxic Studies

In four infants with electrocardiographic or other evidence of toxicity, the mean serum level for digitoxin was 71 ± 2 ng/ml (range 68–72), a figure significantly different from the mean values obtained for the infant group (P < 0.001). In four children with electrocardiographic or other evidence of toxicity, the mean serum level for digitoxin was 72 ± 14 ng/ml (range 53–84). This was significantly different from the mean values obtained for the children’s group (P < 0.001).

Discussion

The results of this study indicate that infants and children tolerate somewhat higher serum concentrations of digitoxin without any evidence of toxicity and require more digitoxin on a mg/kg basis for therapeutic effect than adults. The serum digitoxin levels in those infants and children were significantly different from the levels of adults performed in the same laboratory at The New York Hospital. Our values for infants and children are higher than the mean serum digitoxin level for adults reported by Smith (17 ng/ml) by radioimmunoassay and by Lukas and Peterson (17 ng/ml) using the double isotope dilution method. Digitalizing dosage for infants in our study was approximately three times that commonly used for adults, whereas the children received about two times the usual adult dosage. The maintenance and digitalizing dosages used in our infant group were those in general use by pediatricians and pediatric cardiologists. The dosages used for some of the children (2–13 years) were somewhat higher than those ordinarily recommended for this age group since higher than usual dosages were required for control of intractable heart failure or for control of dysrhythmias that were difficult to manage. This group included four children who had undergone extensive atrial surgery, e.g. for transposition of the great arteries or for cor triatriatum.

Although no other reports of serum digitoxin levels in the pediatric age range have appeared in the literature, studies by Mirkin and Larese, Rogers et al., using digoxin have also documented higher serum concentrations in infants than in adults. It is interesting to note that the serum levels obtained for infants (< 2 years) and for children (2–13 years) in our study were not significantly different, whereas the results of Hayes et al. using digoxin demonstrated that in children over two years of age, serum digoxin concentrations more closely resembled adult values. This finding may be a reflection of age-related differences in digitoxin vs digoxin metabolism and/or excretion, or in myocardial sensitivity, or may merely reflect the appreciably higher dosage of digitoxin required for control of heart failure or dysrhythmia in the children studied in comparison to adult dosages. In a study using tritiated digoxin in neonates and infants, Hernandez et al. reported no substantial differences in absorption, excretion, or tissue concentration of this drug between these infants and adults. Tritiated digoxin turnover studies reported by Dungan et al. in infants and children confirm that serum turnover times and percentage digoxin excretion are similar in these subjects to those in adults. The range of individual serum half times was large, but the mean value (32.5 hr) was nearly identical to that observed in adults. These workers concluded that the increased dosages of digoxin in these young subjects are accompanied by higher serum levels and presumably by increased myocardial levels. Thus the percentage of digoxin excreted in a three day collection of urine and stool was 55% of administered dose in both the infant and adult subjects. The similarity of these values reflects an increased amount of excretion of the drug because of the larger dosage administered per unit of body weight.
Our experience with digitoxin in infants and children has shown that this drug when given in a single daily maintenance dosage results in steady serum concentrations from day to day. Since digitoxin excretion depends primarily on metabolism by the liver and to a lesser extent on the kidney, it is especially useful in subjects with immature, impaired and/or varying renal function. The pharmacodynamics of digitoxin in infants and children have not as yet been studied. Such studies are essential for the interpretation of the higher dosages and serum levels of this drug in the small subject than in the adult.

References
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