Serum, Atrial, and Urinary Digoxin Levels During Cardiopulmonary Bypass in Children

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SUMMARY

Serum, urine, and tissue samples were collected from 42 children undergoing open-heart surgery and analyzed for digoxin by radioimmunoassay. Of these, 24 had been digitalized prophylactically (RECENT) and 18 had been receiving maintenance therapy (MAIN) for one month or longer. Twenty-five percent of the RECENT patients exhibited arrhythmias during the postoperative period as compared to none in the MAIN group. Serum digoxin levels were equivalent in the two groups throughout the study. Although no change in tissue digoxin concentrations occurred during bypass, right atrial appendage concentrations were significantly higher in the RECENT group (109 vs 62 ng/g; P < 0.001). This high atrial digoxin concentration presumably resulted from the large doses used for initial digitalization, and concomitant with postoperative hypokalemia and myocardial metabolic changes secondary to perfusion, may have been responsible for the high incidence of arrhythmias in the RECENT group. Both digoxin and creatinine excretion were depressed following bypass. The amount of biotransformation of digoxin was 2-59.

Additional Indexing Words:

Digoxin toxicity  Open-heart surgery  Pharmacokinetics
Postoperative care  Digitalization

THE OPTIMUM USE OF DIGOXIN in patients undergoing complete cardiopulmonary bypass remains unsolved. In the patient with congestive heart failure who has been chronically digitalized, questions arise as to whether digoxin should be continued prior to surgery, discontinued for a day or two, reinstituted immediately after surgery, or withheld for several days. In the nondigitalized patient, it is debatable whether digoxin should be instituted. Because of its known effect of increasing contractility, even in the nonfailing heart, several centers routinely administer digoxin before major cardiac surgery. Such therapy may not be without possible adverse effects. Intra- and postoperative arrhythmias, particularly with procedures involving or adjacent to areas of the conduction system, are not uncommon, and the presence of digitalis may increase the difficulty in differentiating operatively-induced arrhythmias from those caused by digitalis toxicity.

Previous studies in dogs have demonstrated both an increased and decreased tolerance to cardiac glycosides following bypass. Postoperative cardiac failure accompanied by conduction disturbances can lead to a situation wherein it is unclear whether to give more digoxin or to discontinue its administration. The decision to delay or not to administer digoxin is supported by observations of potassium and magnesium depletion following cardiopulmonary bypass which tend to sensitize the myocardium to digitalis toxicity.

Our goals were to 1) determine changes in serum concentrations of digoxin occurring during and after bypass, 2) relate these changes to urinary excretion, the major route of digoxin elimination, and 3) to study changes in digoxin levels in the right atrial appendage, skeletal muscle, and adipose tissue.

Methods

Patients and Dosage

Forty-two pediatric patients with congenital heart disease were hospitalized for corrective surgery. They were divided into two groups depending upon the duration of digoxin therapy (table 1). The mean values for age and weight differed significantly, since the patients in the maintenance group had developed cardiac failure at an earlier age, necessitating operative intervention. Although the recently digitalized patients were somewhat older and heavier, there
was much overlap and the types of congenital defects were similar in both groups. Mean and range of bypass time were similar.

Twenty-four patients exhibited no evidence of heart failure but were prophylactically digitalized two to five days before surgery (RECENT). The mean digitalizing dose in this group was 0.046 ± 0.003 (mean ± SEM, range 0.031-0.068) mg/kg over 18 hrs. Most then received one-fourth of the digitalizing dose per day in two divided doses for one or two days prior to surgery. The remaining 18 patients (MAINT) had been on daily maintenance therapy for one month to six years. They received a mean daily dose of 0.013 ± 0.001 (0.010-0.022) mg/kg. Digoxin was discontinued in both groups 24 hours prior to surgery, and none was given during the study. Only patients without clinical or electrocardiographic evidence of toxicity prior to surgery were included in the study.

Surgical Procedure

A median sternotomy incision and complete cardiopulmonary bypass were employed in all cases. The pump was primed with equal volumes of 5% dextrose in Ringer’s lactate and 6% low-molecular-weight dextran in saline (20 ml/kg). In the usual course of the operation a portion of the atrial appendage was sacrificed during cannulation of the vena cava and used for the prebypass myocardial digoxin specimen. At the termination of the procedure, a portion of the atrial appendage (20 to 40 mg) proximal to, but not within the purse string suture around the cannula was used for the postbypass specimen. The cannula was then removed and the atriotomy secured by an additional suture. Specimens were obtained from the adjacent subcutaneous adipose tissue and rectus abdominus muscle exposed at the lower end of the sternotomy wound.

Following surgery patients were transferred to the cardiovascular surgery intensive care unit where electrocardiograms and blood pressure were continuously monitored for at least 48 hours.

Sample Collection and Preparation

Blood samples were collected before, at 15 min intervals during, and at various intervals after bypass from 39 of the 42 patients (22 RECENT and 17 MAINT). Urine was collected from the final 23 patients (14 RECENT and 9 MAINT) starting several hours before bypass until 18 hours after perfusion. Prebypass myocardial samples were collected from the last 28 patients to undergo surgery; in addition, postbypass samples were obtained from the last 11. Skeletal muscle and subcutaneous adipose tissue were obtained from the final 12 patients. These various subgroups all formed in a random fashion and did not differ with respect to serum digoxin levels or electrolytes.

Digoxin was measured by a radioimmunoassay (RIA) procedure developed in our laboratory, the antibody having an affinity of 3.6 x 10⁹ M⁻¹ and Sips index of heterogeneity equal to 0.94. One-tenth ml aliquots of serum were assayed directly, while urine samples were diluted with distilled water to a concentration within the range of the assay (0.2 to 8 ng/ml). Tissue samples were homogenized in absolute ethanol for 30 sec with an Omnimixer (Ivan Sorvall, Inc., Norwalk, Conn.). The homogenates were centrifuged at 1000 g for 10 min and the supernatants removed. The precipitates were twice resuspended and centrifuged in additional ethanol. The combined supernatants were evaporated to dryness, and resuspended in phosphate-BSA buffer. After chronic administration of H-digoxin to guinea pigs, it was determined that 95% of digoxin was extracted from the myocardium, the extract reacting in the RIA with an affinity identical to that of nonextracted digoxin. Serum electrolytes, blood urea nitrogen (BUN), and creatinine were determined by standard clinical laboratory techniques.

Separation of Metabolites

Urinary digoxin and metabolites were extracted in a manner similar to that previously described by Doherty et al. An 0.5 ml aliquot of urine was saturated with sodium chloride, extracted three times with 4 ml of chloroform, and the volume of extract reduced to 1.0 ml. Recovery of digoxin and metabolites was greater than 90%. The extracts were then separated by thin-layer chromatography. Aliquots of each extract (approx. 100–200 ng) were applied to 20 x 20 cm silica gel-coated plates (Brinkmann Instruments, Des Plaines, Ill.) and allowed to dry. The middle lane of each plate contained a mixture of standards (digoxin, digoxigenin, and digoxigenin mono- and bisdigitoxosides). They were developed four times with isopropyl ether-methanol (9:1) and once with methyl ethyl ketone-chloroform (3:1), allowing time to air dry between developments. The lane containing the standards was isolated, sprayed with anisaldehyde reagent (0.5 ml anisaldehyde, 1.0 ml sulfuric acid, and 50 ml acetic acid), and placed in a 100° oven for 5 min. The lanes containing the extracts were divided into areas corresponding to the migration of the standards. Each area was scraped from the plate, and the gel eluted with 5

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td><strong>Age, Weight, and Duration of Cardiopulmonary Bypass of Patients Recently (RECENT) or Chronically (MAINT.) Treated with Digoxin.</strong></td>
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<tr>
<td><strong>Patient groups</strong></td>
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<tr>
<td>---</td>
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<tr>
<td>RECENT</td>
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<tr>
<td>MAINT</td>
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</tbody>
</table>

Each value reported as mean ± SEM, with range in parenthesis.

*P < 0.05.
ml of ethanol. The eluant was evaporated to dryness, redissolved in phosphate-BSA buffer, and the amount of digoxin (or metabolite) determined by RIA. On a molar basis the binding of each metabolite to the antisera was identical to that of digoxin.10

Results

Serum Digoxin

The serum digoxin level in each patient fell immediately after the onset of bypass and remained low but constant throughout the procedure. Shortly after bypass was discontinued, the serum level rose and reached the prebypass level within two hours.

Mean serum digoxin levels were equal in the groups prior to bypass (1.2 ± 0.1 ng/ml*). During bypass the levels in both groups fell significantly (P < 0.01) to 0.7 ± 0.1. By seven hours postbypass the levels in both groups returned to the prebypass value, but again fell significantly after ten hours (P < 0.02). At no time did the mean serum levels in the two groups differ.

Tissue Digoxin

No change in digoxin levels in the atrial appendage occurred during surgery in either group (fig. 2). The pre- and postbypass-atrial concentrations in the RECENT group, 109 ± 9 (88-174) and 104 ± 5 (94-124) ng/g, were 60% higher than in the MAINT group, 62 ± 6 (30-113, P < 0.001) and 67 ± 15 (44-111, P < 0.05) ng/g, respectively.

Skeletal muscle and subcutaneous adipose tissue digoxin levels, which were considerably lower than atrial digoxin, also remained unchanged after bypass (fig. 2). Unlike atrial tissue, however, the digoxin levels in the MAINT skeletal muscle, 24 ± 7 (6-32) and 14 ± 3 (10-21) ng/g, were significantly higher than those found in the RECENT group, 8 ± 1 (5-10, P < 0.01) and 8 ± 1 (5-11, P < 0.02) ng/g, respectively. Subcutaneous tissue digoxin concentrations were equal.

Urine Digoxin

Urine was collected from 14 RECENT and nine MAINT patients. Although there was no difference between the two groups, the rate of digoxin excretion was significantly lower (P < 0.01) during and 15 hours after bypass. Creatinine excretion was similarly lower during these periods.

Since serum digoxin and creatinine levels changed during the study period, clearance values were calculated whenever possible. Following bypass the clearance values in both groups were significantly lower than before surgery (fig. 3). Digoxin and creatinine clearances fell to 50% of their prebypass levels.

Nineteen prebypass urine samples (10 RECENT and 9 MAINT) were extracted, chromatographed, and assayed (table 2). Although there was no difference between the two groups, each group exhibited a lower percentage of unaltered digoxin (P < 0.05) than did a typical preparation of Lanoxin (Burroughs Wellcome Co.), which had been extracted and chromatographed in the same manner. A more adequate control would have been attained by first adding Lanoxin to urine and then extracting and chromatographing it; however, it seems unlikely that the relative recoveries

*All values are expressed as the mean ± SEM.

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of metabolites would be significantly altered. Since no difference in urinary metabolites was found between the two patient groups, this additional control was not performed. Our findings indicate that only a small amount of digoxin underwent biotransformation.

Blood Chemistries

Serum electrolytes, pH, and hematocrits were comparable in the two groups both before and at four hours after bypass. Serum Na+, Cl, and BUN exhibited no significant changes throughout the study. After bypass the K+ levels were significantly lower in both groups \((P < 0.001)\) but decreased the same extent in each, i.e., 4.7 ± 0.1 to 3.5 ± 0.1 mEq/L in the RECENT group and 4.6 ± 0.1 to 3.6 ± 0.2 mEq/L in the MAINT group. In the RECENT group serum creatinine was significantly higher following bypass, 0.93 ± 0.08 vs 0.70 ± 0.05 mg/100 ml, \(P < 0.05\). Although it also tended to be higher postbypass in the MAINT group, it was not significantly so, perhaps due to the relatively small number of samples.

During bypass the hematocrits fell to 55% of the initial value \((P < 0.001)\), and returned to 80% \((P < 0.001)\) within four hours after termination of the procedure. This increase was secondary to either transfusion and/or diuresis.

Postoperative Course

During the postoperative period six of the 24 patients in the RECENT group exhibited arrhythmias. Four of these (bigeminy, trigeminy, atrioventricular (A-V) nodal tachycardia, and A-V nodal rhythm) were consistent with but not necessarily diagnostic of digitalis toxicity, while the remaining two (left atrial rhythm and A-V nodal escape beats) may or may not have been related to the drug. Although some of these arrhythmias may appear in nondigitalized patients following open heart surgery, it should be emphasized that none of the ECGs of the 18 MAINT patients exhibited arrhythmias during the recovery period.

Discussion

Twenty-five percent of the ECGs of children prophylactically digitalized before open-heart surgery exhibited arrhythmias during the postoperative period, while all of those on maintenance therapy were in normal sinus rhythm postoperatively. These findings did not correlate with serum digoxin, electrolyte levels, or creatinine clearance, for levels were the same in both groups throughout the study. Whereas bypass itself had no effect on digoxin concentrations in the atrium, skeletal muscle, or subcutaneous adipose tissue, the mean atrial digoxin concentration in the RECENT group was significantly higher than that in the MAINT group. This relatively high concentration probably resulted from the large doses used for digitalization. It seems likely that hypokalemia and myocardial metabolic changes secondary to perfusion may have been sufficient to lower digoxin tolerance to a degree that the relatively high myocardial digoxin levels in the RECENT group precipitated arrhythmias.

Table 2

Urinary Digoxin, Digoxigenin-Bis-Digitoxoside (Bis), Digoxigenin-Mono-Digitoxoside (Mono), and Digoxigenin (Genin), as Compared to a Typical Lanoxin Preparation (Lanoxin).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Origin (%)</th>
<th>Digoxin (%)</th>
<th>Bis (%)</th>
<th>Mono (%)</th>
<th>Genin (%)</th>
<th>Front (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent</td>
<td>10</td>
<td>0.5 ± 0.1</td>
<td>95.9 ± 0.8*</td>
<td>1.9 ± 0.4</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.2</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>MAINT</td>
<td>9</td>
<td>1.2 ± 0.4</td>
<td>92.6 ± 1.9*</td>
<td>2.1 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>1.1 ± 0.4</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>LANOXIN</td>
<td>6</td>
<td>0.3 ± 0.1</td>
<td>98.3 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
</tbody>
</table>

Origin refers to amount of material not migrating on TLC plate. Front, to amount migrating with solvent front. *Differs from Lanoxin \((P < 0.05)\).
DIGOXIN DURING BYPASS

Both increased\textsuperscript{4-15} and decreased\textsuperscript{16, 17} serum digoxin levels following bypass have been reported. Morrison and Kilip\textsuperscript{18} found a higher serum digoxin level in eight adults exhibiting arrhythmias during the post-bypass period than in 12 with normal sinus rhythm. This was not true with our patients, even when the six patients exhibiting arrhythmias were considered as a separate group.

The rapid decrease in serum levels we observed has been reported by others\textsuperscript{16, 18, 19} and seemed due to dilution by perfusate. Although determination of the volume changes in the vascular compartment is difficult because of redistribution, if one assumes an initial plasma volume of 51 ml/kg,\textsuperscript{20} the total priming volume of 20 ml/kg would dilute the plasma by 30%. Additional dilution occurs due to the intraoperative administration of large volumes of fluid. Our data show that serum digoxin fell 40% and the hematocrit 45%, values which are compatible with the fall predicted from hemodilution alone.

Studies of myocardial digoxin have, in general, agreed with our results. Using a similar RIA, Colart et al.\textsuperscript{21} found the digoxin concentration in the left ventricular papillary muscles to be 78 ng/g in eight adults on long-term maintenance therapy, equivalent to the 62 ng/g in our MAINT group. They also found a skeletal muscle concentration of 11 ng/g, similar to our results. In ten patients given a digitalizing dose of tritiated digoxin before surgery, Beall et al.\textsuperscript{19} found right atrial appendage digoxin to be 140 ng/g, only slightly higher than the 109 ng/g in our RECENT group. Binnion et al.\textsuperscript{22} however, reported an atrial digoxin level of 219 ng/g in 16 surgical patients on maintenance therapy. Digoxin was measured by inhibition of Rb\textsuperscript{58} uptake by red blood cells, and the range of their values was enormous (34-648 ng/g).

Hernandez et al.\textsuperscript{23} reported atrial digoxin\textsuperscript{3H} concentrations of 6 to 31 ng/g in nine children digitalized two days prior to surgery. Their digitalizing and maintenance doses were considerably lower (30% and 50%, respectively) than those we employed.

The reasons for the higher myocardium : serum digoxin ratio in the RECENT group than in the MAINT group, as indicated by higher atrial digoxin concentrations in the presence of identical prebypass serum levels, and the apparent redistribution resulting in higher skeletal muscle concentrations in the MAINT group are not known at present. When taken into consideration with previous data showing that serum digoxin levels in recently digitalized infants do not correlate with toxicity,\textsuperscript{24} it can be concluded that tissue and serum relationships during this period may be different from those following chronic digitalization.

The constancy of myocardial digoxin during bypass has also been demonstrated previously in both dogs\textsuperscript{19} and man.\textsuperscript{17, 22} One group, however, has reported a 15-24% decrease in myocardial digoxin concomitant with a fivefold increase in serum digoxin in both species.\textsuperscript{4, 15} No apparent explanation could be found for these discrepancies.

The decrease in glomerular filtration during the postoperative period as shown by lowered digoxin and creatinine clearances has been reported in adults by Colart et al.,\textsuperscript{16} and suggested in dogs by a lengthened serum half-life.\textsuperscript{25} Considering that 75-90% of an i.v. dose of digoxin is excreted in the urine,\textsuperscript{26, 27} extreme caution is necessary in readministering digoxin during the early postoperative period.

The amount of chloroform-extractable urinary metabolites of digoxin was extremely low (2 to 5%) and agrees with values for infants and children\textsuperscript{12, 28} and studies in adults which have found less than 10% metabolites in urine,\textsuperscript{26, 29} Only one study has reported the presence of water-soluble metabolites following oral digoxin.\textsuperscript{30}

The following procedures are recommended for children undergoing open-heart surgery: 1) when prophylactic digitalization is planned, it probably should be initiated four weeks or longer before surgery, 2) serum digoxin levels should be determined preoperatively to assure that they are within normal limits (1-2 ng/ml), 3) additional digoxin should generally not be given for at least ten hours following bypass, 4) postoperative dosage should be modified in relation to the patient's creatinine clearance\textsuperscript{31} and his or her serum digoxin level as periodically monitored, and 5) serum levels of K\textsuperscript{+} and Mg\textsuperscript{2+} should be monitored and their losses replaced within 12 hours after surgery.

References

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RICHARD W. KRASULA, ALOIS R. HASTREITER, SIDNEY LEVITSKY, RUTH YANAGI and LESTER F. SOYKA

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