Digoxin Concentration in Saliva and Plasma in Infants, Children, and Adolescents with Heart Disease

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ABSTRACT

Background: Because of its narrow therapeutic index, therapeutic monitoring of digoxin is important in the management of infants and children receiving the drug for cardiac failure or arrhythmias, or following accidental ingestion. Whether saliva can replace plasma in the therapeutic monitoring of digoxin therapy in children is unclear.

Objective: This study assessed the value of determining saliva digoxin concentration in infants, children, and adolescents.

Methods: Infants, children, and adolescents receiving digoxin for various indications, whose digoxin dosage had remained unchanged for ≥ 10 days, and whose compliance was good according to the parents were enrolled. Digoxin concentration was measured in paired specimens of citric acid-stimulated mixed saliva and plasma obtained simultaneously.

Results: Eighteen children (10 boys, 8 girls; mean [SD] age, 42.3 [53.1] months [range, 2 months–14 years]) were included in the study. Digoxin therapy was administered for cardiac failure due to dilated cardiomyopathy in 9 patients (50.0%), ventricular septal defect in 4 (22.2%), supraventricular tachycardia in 3 (16.7%), and after cardiac surgery in 2 (11.1%). Digoxin concentration in the 20 paired specimens obtained varied from 0.0 to 0.92 ng/mL (mean [SD], 0.25 [0.26] ng/mL) in saliva and from 0.27 to 1.54 ng/mL (mean [SD], 0.77 [0.40] ng/mL) in plasma. The mean plasma/saliva digoxin concentration ratio was 2.8.

Conclusions: This study of infants, children, and adolescents receiving digoxin for a variety of indications and whose dose was unchanged for ≥ 10 days showed that marked individual variability in the saliva/plasma concentration ratio precludes the use of saliva in predicting the plasma digoxin concentration. The value of saliva digoxin (as opposed to plasma digoxin) measurements in the assessment of the cardiac effects of the drug in children remains to be

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Key words: digoxin, saliva, plasma, drug monitoring.

INTRODUCTION

Because of its narrow therapeutic index, therapeutic monitoring of digoxin is important in the management of infants and children receiving the drug for cardiac failure or arrhythmias, or following accidental ingestion of digoxin.¹

Determination of plasma digoxin concentration is useful for drug monitoring, assessment of compliance, and evaluation of the effect of renal or hepatic disease or other drugs on digoxin elimination.² The use of saliva instead of blood has been proposed for therapeutic monitoring of theophylline, phenytoin, and other drugs.^{3–6} Sampling saliva instead of blood is particularly valuable in infants and children because it is a painless, noninvasive procedure that averts blood volume loss.⁶ A strong, significant linear correlation between saliva and serum concentrations of digoxin has been demonstrated in adults,^{7–9} and in 1 study in infants.¹⁰ However, another pediatric study¹¹ indicated that saliva digoxin concentration does not satisfactorily reflect plasma concentration.

This study assessed the value of determining saliva digoxin concentration in infants, children, and adolescents.

PATIENTS AND METHODS

Study Design

This study was conducted at the Pediatric Cardiology Unit, Division of Pediatrics, Soroka University Medical Center (Beer-Sheva, Israel). The local ethics committee approved the study, and written parental consent was obtained prior to admission to the study.

Patients

Infants, children, and adolescents attending the Pediatric Cardiology Unit and receiving digoxin for a variety of indications, whose dose was unchanged for ≥ 10 days, who had good compliance according to the parents and who were clinically stable were eligible for the study. Patients receiving other drugs in addition to digoxin, and/or having an illness in addition to cardiovascular disease, were not excluded.

Methods

Saliva and venous heparinized blood samples were obtained simultaneously 10 to 12 hours after a regular oral dose (9–10 $\mu\text{g}/\text{kg}$) of digoxin.

Secretion of mixed saliva was stimulated by placing ~5 mg of citric acid crystals on the patient's tongue.¹² Younger patients (aged ≤ 4 years) rinsed their mouths or drank water prior to saliva sampling to reduce contamination of the saliva with digoxin and with food. Citric acid stimulation resulted in a prompt and rapid saliva flow, and 1 to 2 mL were collected by one of the authors from the oral cavity with a mucus extractor. Older children (aged ≥ 5 years) and adolescents spat citric acid-stimulated saliva into a test tube on request of one of the authors. No difficulties were encountered in obtaining cooperation from the children with regard to the use of citric acid crystals. Parents and (when possible) children were asked which method of sample collection they preferred and why.

Saliva and plasma samples were kept refrigerated at 4°C for up to 24 hours pending analysis. Saliva was centrifuged at 3500 rpm at room temperature for 10 minutes and the supernatant was assayed. Blood was centrifuged and digoxin was measured in saliva and plasma by competitive fluorescence polarization immunoassay (TDx® System, Abbott Laboratories Inc., Abbott Park, Illinois). Sample analyses were performed at the local laboratory.

Statistical Analysis

The coefficient of variation in this test was $<5\%$. Comparison of digoxin concentrations in saliva and plasma was performed using paired Student *t* tests. Correlation between parameters was determined by least squares regression analysis. Statistical significance was set at $P \leq 0.05$.

RESULTS

Eighteen children (10 boys, 8 girls; mean [SD] age, 42.3 [53.1] months [range, 2 months–14 years]) were included in the study (Table). Digoxin was administered for cardiac failure due to dilated cardiomyopathy in 9 patients (50.0%), ventricular septal defect in 4 (22.2%), prophylactic treatment of supraventricular tachycardia in 3 (16.7%), and following cardiac surgery in 2 (11.1%). The mean daily maintenance dosage was 9.3 $\mu\text{g/kg}$ (range, 8–12 $\mu\text{g/kg}$) given every 12 hours, except in a 14-year-old boy, in whom the daily dosage was 250 μg every 24 hours.

Eighteen paired saliva and blood specimens were obtained from the 18 patients. Before sampling, the dosage of digoxin was unchanged for a range of 10 days to 15 months (mean [SD], 17.1 [17.9] months). The mean (SD) saliva digoxin concentration was 0.25 (0.26) ng/mL (range, 0.00–0.92 ng/mL). The mean (SD) plasma digoxin concentration was 0.77 (0.40) ng/mL (range, 0.27–1.54 ng/mL). A significant positive correlation was found between saliva and plasma digoxin concentrations ($r = 0.83$; $P < 0.01$) within a plasma concentration range of 0.1 to 1.1 ng/mL. The mean saliva/plasma digoxin concentration ratio was 2.8.

Table. Characteristics of study patients (N = 18).

Patient No.	Age	Diagnosis	Duration of Therapy	Other Drugs Used	Digoxin Dose, µg/kg
1	4 y	DC	6 mo	Cap/Fur	10.0
2	5 y	DC	6.3 mo	Cap/Ald	10.0
3	4 mo	VSD	4 wk	—	9.0
4	4 mo	TGA (surgery)	8 wk	Cap/Fur	11.2
5	9 mo	VSD	11 wk	—	9.6
6	2 mo	SVT	7 wk	—	10.0
7	8 mo	VSD	7 mo	—	10.0
8	7 y	DC	6.3 mo	Cap/Fur	9.0
9	2 y	VSD	15 mo	—	10.0
10	7 y	TOF (surgery)	11 d	Fur/Cim	9.5
11	4 y	DC	14 mo	Fur	10.0
12	4 mo	DC	3 mo	Cap/Fur	9.0
13	7 mo	DC	7 mo	—	10.0
14	6 mo	DC + COA	2 wk	Cap	11.0
15	6 mo	DC	2 mo	Cap/Fur	10.0
16	4 y	DC	1 mo	Cap/Fur	10.0
17	14 y	SVT	10 d	—	10.0
18	14 y	SVT	1 mo	—	10.0

DC = dilated cardiomyopathy; Cap = captopril; Fur = furosemide; Ald = aldosterone; VSD = ventricular septal defect; TGA = transposition of the great arteries; SVT = supraventricular tachycardia; TOF = tetralogy of Fallot; Cim = cimetidine; COA = coarctation of the aorta.

Variability existed in individual saliva/plasma digoxin concentration ratios (Figure).

Saliva digoxin concentrations were low (0.0–0.16 ng/mL) in 8 samples, with all corresponding plasma concentrations <0.75 ng/mL. Low plasma digoxin concentrations were correlated with negligible or undetectable saliva concentrations. Digoxin concentration in 1 saliva sample was in the toxic range, whereas the corresponding plasma concentration was in the therapeutic range (0.5–2.0 ng/mL). Also, digoxin concentrations were undetectable in 3 saliva samples, whereas corresponding plasma concentrations were in the therapeutic range. No plasma concentrations were in the toxic range (>2.0 ng/mL).

All but 2 of the parents (11.2%) said they preferred saliva sampling because it was easier and painless. One parent (5.6%) had no preference, and 1 (5.6%) preferred blood sampling because it took too long to obtain the saliva specimen. Six children (33.3%) aged >4 years were asked their preference. One child (5.6%), a 14-year-old boy, preferred blood sampling because he found the spitting up required for saliva sampling unpleasant.

Figure. Correlation between digoxin concentrations in plasma and saliva of the 18 paired samples ($N = 18$ patients). $r = 0.83$; $P < 0.01$.

DISCUSSION

The significant correlation between plasma and saliva digoxin concentrations found in this study is similar to previous reports in adults.^{7,8} The differences in the previously reported studies in the ratio of estimated to actual plasma digoxin concentration varied from 0.78 to 1.4 ng/mL.^{7,9} These differences may be related to the method of saliva collection and the analytical methods used. In 1 study,⁹ the correlation was stronger in samples taken following stimulation of saliva secretion than from saliva samples obtained without stimulation.

Although individual plasma digoxin concentrations varied in our study, a previous study in 12 infants¹⁰ showed a positive correlation between saliva and plasma digoxin concentrations. Those authors recommended saliva sampling as the best method for therapeutic digoxin monitoring. On the other hand, Berkovitch et al¹¹ found a weaker correlation between total saliva and plasma digoxin concentrations in 11 infants and children. One of their explanations for this was that residual digoxin in the oral cavity affected the results. Proper sampling is a requisite in the determination of drug secretion in saliva.

Low plasma digoxin concentrations were correlated with negligible or undetectable saliva concentrations because saliva digoxin concentrations were considerably lower than corresponding plasma concentrations. Despite the good correlation between saliva and plasma concentrations, the results of this study do not support the use of saliva digoxin measurements for accurate prediction of the plasma digoxin concentration.

The possibility that endogenous digoxin-like substances (EDLSs) interfered with plasma digoxin determinations was not examined in this study. The existence of EDLSs, especially in infants aged <6 months, may lead to falsely elevated measurements of plasma digoxin concentrations.¹³ However, the potential contribution of EDLSs to digoxin concentrations must have been small because plasma concentrations were <0.98 ng/mL in all of our patients aged <6 months.

CONCLUSIONS

This study of infants, children, and adolescents receiving digoxin for a variety of indications and whose dose was unchanged for ≥ 10 days showed that marked individual variability in the saliva/plasma concentration ratio precludes the use of saliva in predicting the plasma digoxin concentration. The value of saliva digoxin (as opposed to plasma digoxin) measurements in the assessment of the cardiac effects of the drug in children remains to be studied.

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