DIGOXIN CONCENTRATIONS IN SERUM AND SALIVA: RELATIONSHIP TO ECG CHANGES AND DOSAGE IN HEALTHY VOLUNTEERS

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- 1 After 1 week of baseline observations increasing oral doses of digoxin were administered to four healthy volunteers over a 6-7 week period.
- 2 A dose-response relationship exists with regards to PTQ-changes (a quantitative measure of ECG-changes).
- 3 PTQ-changes were related linearly to both serum and salivary digoxin levels.
- 4 PTQ-changes appear to be useful as a non-invasive measure for studying various aspects of digoxin pharmacodynamics.
- 5 Serial salivary digoxin levels might be a better index of the effect of cardiac glycosides than individual or serial serum levels.

Introduction

In previous studies a statistically significant linear relationship was found between a quantitative index of electrocardiographic (ECG) change, the PTQ-index, and serum digoxin levels in patients with cardiac failure (Joubert, Müller, Pansegrouw & Kleynhans, 1975; Joubert, Kroening & Weintraub, 1975). This relationship also holds for normal volunteers (Joubert, Fleckenstein, Weintraub & Kroening, 1976, unpublished observations).

The PTQ-index is a combination-function of PR-interval duration, corrected QT-time and the amount of T-wave depression based on the notion that the influence of extraneous factors would be minimized by combining various measurements. Extraneous factors would not change *all* these parameters in the same direction as would digitalis, although a marked alteration in one (eg. T-wave depression with progressive myocardial ischaemia) could cause significant changes.

This study involving healthy volunteers was therefore undertaken to obtain confirmation of this relationship, to ascertain whether it is dose-dependent and finally to study mean changes over a time period in an attempt to further minimize the influence of extraneous factors by averaging out day-to-day variation. As salivary digoxin levels correlate significantly with serum digoxin levels (Huffman, 1975), salivary levels were measured and the relationship to the ECG, serum levels and dosage studied.

Methods

After giving informed consent four healthy adult non-smokers entered the trial (details in Table 1). During the trial all subjects had a light breakfast between 7 h 30 min and 8.00 h and thereafter only water was allowed until ECGs had been recorded. ECGs were recorded daily (except weekends) between 10.00 h and 10 h 30 min after a 5 min rest period. Digoxin tablets (Lanoxin®) were taken orally at 10 h 30 min. Saliva was collected daily and venous blood on at least two days per week just prior to taking the digoxin. The trial consisted of three phases: an initial 1-week baseline period, a 2-week post-trial observation period during which no digoxin was taken and a test phase consisting of 1-week periods during which constant daily doses of digoxin following digitalization during the initial 24 h, were administered. All subjects received daily dosages of 0.125, 0.25 and 0.50 mg while two subjects also took a dosage of 0.625 mg.

Table 1 Details of the four subjects

Subject	Sex	Age (years)	Mass (kg)
A	F	21	57
B	F	22	54
C	M	31	74
D	M	27	65

Figure 1 Serial changes in PTQ, salivary and serum digoxin levels in subject A. Broken line in the PTQ-graph represents the mean baseline PTQ-value. (a, b, c and d represent daily digoxin dosages of 0.125, 0.25, 0.50 and 0.625 mg of digoxin/day, whereas e represents time of discontinuation of digoxin.

Figure 3 Linear correlation between PTQ and serum digoxin levels in the four subjects.

As about one-third of the administered dose of digoxin is eliminated in 24 h by subjects with normal renal function (Doherty, 1973), subjects were digitalized with three times the intended maintenance at the beginning of the test phase and three times the increment in daily dosage on the first day of each subsequent 1-week period.

Serum digoxin levels were determined by radio-immunoassay using a standard commercially-available kit. Saliva was handled as if it were serum.

ECGs were recorded at a paper speed of 50 mm/s with a calibration of 10 mm = 1 mV. PR-interval, RR-interval, QT-time and T-wave amplitude were measured cumulatively in ten complexes (in the standard lead with the largest net positive QRS-deflection) and expressed as the

Figure 2 Relationship between PTQ (mean $\pm$ s.e. mean value over 1 week) and digoxin dosage during the same period in the four subjects ($\square$ A; $\blacksquare$ B; $\circ$ C; $\bullet$ D).

Figure 4 Linear correlation between mean PTQ (during 1 week) and mean serum digoxin levels during the same period, in the four subjects.

average of this. PTQ (i.e. $PR \times T/QT_c$) was calculated as reported previously (Joubert *et al.*, 1975), using the PR-interval and rate-corrected QT-time in s, and the T-wave as the T-score (the amount of T-wave depression in mm, when compared to the mean T-wave amplitude during the baseline period plus one).

Results

In Figure 1 the serial changes in PTQ, salivary and serum digoxin are shown in the subject who had

Figure 5 Linear correlation between PTQ and salivary digoxin levels, in the four subjects.

Figure 6 Linear correlation between mean PTQ (during 1 week) and mean salivary digoxin levels during the same period in the four subjects.

the smallest change in PTQ. All subjects showed a considerable degree of day-to-day variation in PTQ-values, but digoxin produced a progressive increase in mean PTQ values with progressive dosage increases to 0.5 mg of digoxin/day. Of the two subjects who also took a dose of 0.625 mg/day, one showed a further increase on the highest dose (Figure 2). Mean PTQ-values had returned to baseline by the second week after discontinuation of digoxin in subjects A and B, but although decreased, they were still significantly elevated in subjects C and D. Both these subjects were lost to follow-up at this stage, but both were back to baseline when followed-up a month later.

The relationship between salivary and serum digoxin levels have already been reported on (Joubert, Aucamp & Müller, 1976). Figure 3 shows the relationship between PTQ-values and mean serum digoxin levels, whereas Figure 4 shows the same relationship but utilizing mean values for each one week period, in an attempt to minimize the effect of day-to-day variation. Figure 5 shows the relationship between salivary digoxin levels and PTQ and in Figure 6 mean salivary values for each 1-week period was plotted against mean PTQ-values for the corresponding period. The mean r -value for the serum digoxin/PTQ correlation using individual values (Figure 3) was 0.82 ± 0.7 whereas it was 0.87 ± 0.08 when mean values were used. For the salivary digoxin/PTQ correlation the corresponding values were 0.53 ± 0.11 (Figure 5) and 0.94 ± 0.06 (Figure 6), respectively.

Discussion

This study has clearly confirmed earlier observations on the relationship between serum digoxin

levels and the ECG. In addition it has shown that there is a definite dose-response relationship for this effect. It appears that correlating mean PTQ-values with mean serum digoxin levels over a period of constant dosage slightly improves the degree of linear correlation.

An interesting and unexpected finding was the fact that although the linear correlation between salivary digoxin and PTQ using individual values was poor, mean PTQ correlated better with mean salivary than with mean serum digoxin levels. As the PTQ represents a non-invasive *in vivo* quantitative pharmacologic effect of digitalis, this might suggest that serial salivary digoxin levels might be a better index of pharmacologic effects of digitalis than with serial or individually determined serum levels, provided that concomitant medication or pathophysiological processes do not affect salivary digoxin levels in therapeutic situations. Individually determined salivary concentrations seem to be of less value because of the marked day-to-day variation (Figure 1).

It is very difficult to quantitate the effects of digitalis in clinical situations. Oedema-resolution is affected by bed-rest and diuretics, pulse rate is influenced by concomitant processes and only bears a crude relationship to serum digoxin levels in atrial fibrillation (Chamberlain, 1970; Redfors, 1972), the electrocardiogram and the PTQ is influenced by factors such as progressive myocardial ischaemia and electrolyte changes. PTQ does however, appear to be dose-dependent in the presence of a stable ECG and controlled circumstances and could be a useful non-invasive tool to assess other possible measures of the effects of digitalis.

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