Importance of Pharmacokinetics and Dosage in Digoxin Maintenance Therapy

A RETROSPECTIVE ANALYSIS OF SERUM DIGOXIN LEVELS

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SUMMARY

A retrospective analysis of serum digoxin levels in 105 patients above 16 years of age revealed that a daily maintenance dose of 0,25 mg digoxin appears to be preferable to higher doses. The incidence of therapeutic levels (8,0 - 1,8 ng/ml) did not differ significantly from that obtained with higher doses—whereas the incidence of 'toxic' levels was significantly lower with this dosage.

Patients diagnosed as being digitalis-toxic or as exhibiting refractory cardiac failure on clinical grounds, had digoxin serum levels significantly higher than those found in patients with satisfactorily controlled cardiac failure but without signs of digitalis toxicity.

Serum digoxin levels were significantly raised in patients with raised blood-urea.

It is concluded that pharmacokinetic considerations are important in the clinical application of digoxin and that determination of serum levels is an important adjuvant in determining correct dosage in select cases.

Estimation of serum digoxin levels has become a practical proposition since the introduction of techniques such as radio-immunoassay[1] and [56]Rb-uptake[2] for the quantitative detection of cardiac glycosides.

Our department has been carrying out serum digoxin estimations as a routine and emergency laboratory service since 1972. This report deals with a retrospective analysis of the information obtained during the first 18 months with regard to the relationship between serum digoxin levels and the following factors: dosage, clinical status and renal function.

PATIENTS AND METHODS

Blood specimens were received from patients on digoxin treatment for the management of congestive cardiac failure or supraventricular arrhythmias. The patients com-

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prised members of various racial groups and both sexes. No differentiation was made on these grounds.

The following criteria were used to select 105 patients: (i) oral treatment with digoxin (Lanoxin) tablets; (ii) known dosage; (iii) time interval since last dose of digoxin and collection of blood samples had to exceed 3 hours, but not 24 hours; (iv) duration of digoxin therapy longer than 7 days; (v) age above 16 years.

Serum digoxin estimations were done with the Schwarz/Mann digoxin radio-immunoassay kit with ^{125}I as a marker.

RESULTS

Of the 105 patients studied 25 received 0,25 mg, 70 received 0,50 mg and 10 received 0,75 mg of digoxin daily. Fig. 1 shows the serum digoxin levels associated with these doses, the mean values ($\pm$ SEM) being $1,1 \pm 0,1$ ng/ml, $1,7 \pm 0,2$ ng/ml and $3,3 \pm 1,0$ ng/ml respectively.
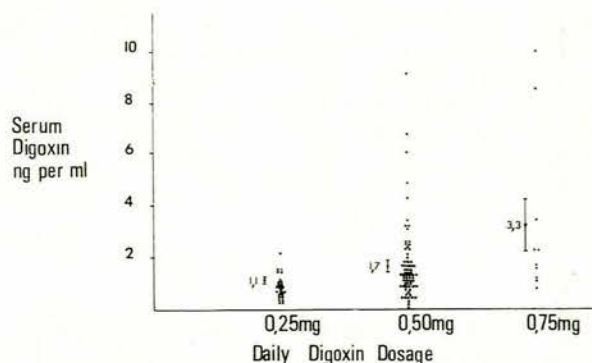

Fig. 1. Serum digoxin levels in 105 patients on different dosages.

The distribution of serum digoxin levels with respect to the locally accepted therapeutic range of 0,8—1,8 ng/ml is shown in Table I.

Analysis of the results using the chi-squared test showed no statistically significant difference in the incidence of 'therapeutic' serum digoxin levels. The incidence of levels in excess of 1,8 ng/ml was, however, significantly higher in the group receiving 0,50 mg of digoxin daily ($P<0,05$), and those receiving 0,75 mg of digoxin daily ($P<0,01$), when compared with patients receiving 0,25 mg of digoxin per day.
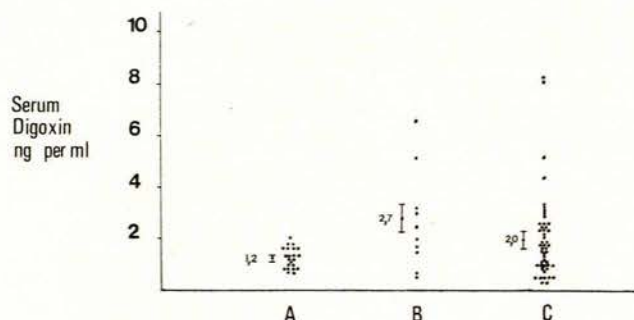
TABLE I. SERUM DIGOXIN LEVELS FALLING BELOW, WITHIN AND ABOVE THE LOCAL THERAPEUTIC RANGE (0,8 - 1,8 ng/ml) AFTER 3 DIFFERENT DOSAGE REGIMENS

Digoxin dose (daily)	Number of patients		
	Serum digoxin <0,8 ng/ml	Serum digoxin 0,8 - 1,8 ng/ml	Serum digoxin >1,8 ng/ml
0,25 mg	8 (32%)	16 (64%)	1 (4%)
0,50 mg	12 (17%)	40 (57%)	18 (26%)
0,75 mg	0 (0%)	5 (50%)	5 (50%)

Fig. 2. Serum digoxin levels in patients with good control of cardiac failure and no signs or symptoms of digitalis toxicity (A), refractory cardiac failure (B) and clinical digitalis toxicity (C).

The relationship between serum digoxin levels and clinical status in 81 patients is shown in Fig. 2. The mean values (± SEM) were 1,2 ± 0,1 ng/ml, 2,7 ± 0,6 ng/ml and 2,0 ± 0,3 ng/ml respectively for patients with good control of cardiac failure, patients with refractory cardiac failure and those with clinical digitalis toxicity.

In 36 patients receiving 0,50 mg of digoxin daily we were able to trace blood-urea levels. The relationship between serum digoxin level and blood-urea is shown in Fig. 3, the linear correlation coefficient being 0,726 ($P<0,001$).

Blood Urea mg per 100ml
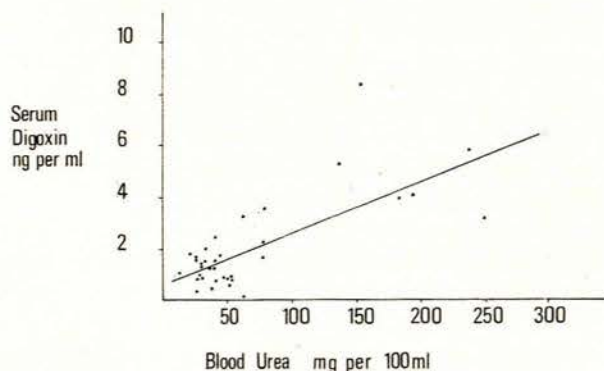
Fig. 3. Relationship between serum digoxin and blood-urea in patients receiving 0,50 mg digoxin daily.

Separation of these patients into those with a normal blood-urea (<40 mg/100 ml) and those with a raised blood-urea (>40 mg/100 ml) showed a significant difference

($P<0,01$) in the serum digoxin levels, the mean values (± SEM) being 1,2 ± 0,1 ng/ml and 2,5 ± 0,4 ng/ml respectively. These results are shown in Fig. 4.
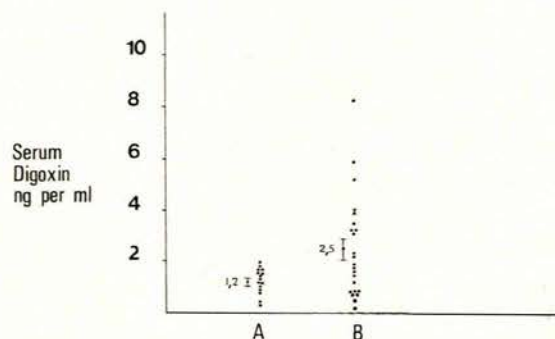
Fig. 4. Serum digoxin levels in patients with blood urea values of <40 mg/100 ml (A), and levels >40 mg/100 ml (B). Daily digoxin dose = 0,50 mg.

DISCUSSION

According to the classic manuscript by William Withering,[3] digitalis administration was often guided by the development of toxic signs and symptoms. At present the incidence of digitalis toxicity is still alarmingly high. In the patients we studied 23% had serum levels of digoxin in excess of the therapeutic range. This is in accordance with figures from other centres.[4,5] In the light of present techniques and wealth of information on pharmacokinetics, it should be possible to reduce this figure considerably.

Clinicians can come close to this ideal by selecting the correct dosage for a particular patient. In the patients we studied it seemed that, irrespective of other factors, a daily maintenance dose of 0,25 mg of digoxin in preference to a higher dosage will significantly reduce the incidence of digitalis toxicity in the average patient, while therapeutic serum digoxin levels are attained.

A further reduction in the incidence of digitalis toxicity can be achieved by consideration of renal function. Although a linear relationship exists between renal clearance of creatinine and of digoxin,[6] a simple investigation such as a blood-urea estimation may indicate patients at risk of developing digitalis toxicity with conventional dosage regimens. This is clearly illustrated in our series by the marked difference in serum digoxin levels in patients with normal blood urea values receiving 0,50 mg of digoxin daily, compared with those with raised values receiving the same dose. Obviously, additional factors such as serum potassium, serum calcium, the nature of myocardial disease and thyroid status, should also be kept in mind.

Although patients can be refractory to conventional digitalis therapy due to a specific clinical situation (e.g. hyperthyroidism) or inadequate dosage, the incidence of high serum digoxin levels in patients with refractory cardiac failure in our series is striking. This may reflect dose increases due to lack of response, but may also include patients with cardiac failure aggravated by digoxin therapy.

Wide variations in digoxin concentrations in various parts of the myocardium appear to exist and several reports failed to indicate a simple relationship between myocardial and serum digoxin levels.[7,8] It is, however, clear from our study and the work of others[6,9,10] that serum digoxin levels do correlate with clinical efficacy. Blood samples are easily obtained and lack of correlation between myocardial and serum digoxin levels does not negate the clinical value of the latter.

A time lapse of more than 3 hours between ingestion of last dose and obtaining of blood samples is imperative if results are to be meaningfully interpreted. Peak serum levels are attained within 45 - 60 minutes after oral intake, with steady state levels only being reached 2 - 3 hours later.[11]

Our findings underline the importance of pharmaco-kinetic considerations when digoxin is administered to man and the value of determining digoxin serum levels as a therapeutic guide in selected patients.

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