The Influence of Hemodialysis on Concentration of Serum Digoxin-Like Substance

*ZIJAD DURAKOVIC**
*ASAF DURAKOVIC***
*SENADIN DURAKOVIC****

SUMMARY

Digoxin concentrations in serum samples measured before and after hemodialysis of 31 uremic patients who either never took digoxin or who had not taken digoxin for at least one year. False positive digoxin was found in 22 of 31 patients (71%) before hemodialysis and in 14 of 31 patients (45%) after hemodialysis. The concentration ranged from 0.1 to 0.5 nmol/L, mean value was 0.20±0.16 before hemodialysis and after hemodialysis ranged 0.1 to 0.4 nmol/L, mean value was 0.11±0.14 nmol/L. The difference before and after hemodialysis is statistically significant. Some of the patients had a constant value before and after hemodialysis, none had a higher value after hemodialysis than they did before. Eight patients, who had positive serum digoxin before hemodialysis with concentrations up to 0.5 nmol/L, became negative after hemodialysis. Our results indicate that a digoxin-like substance in uremic serum could be at least partly dialyzable.

INTRODUCTION

The radioimmunoassay for measuring serum digoxin concentration have given clinicians a chance to study the pharmacokinetics of digoxin, its interactions with other drugs, the determination of the therapeutic range, and the documentation of high concentrations in the serum of patients with clinical signs of digoxin toxicity. It was believed that the radioimmunoassay method for digoxin measurement would be very useful in the treatment of patients with decreased excretion of digoxin due to renal failure. However, a number of reports have recently appeared which analyze the false positive concentrations of digoxin in experiments on animals (1,2), in newborn infants (3,4), and in salt-loaded healthy subjects as well as in mild hypertonic volunteers (5,6). Of particular importance in clinical work is the appearance of false positive concentrations of digoxin in patients with renal failure. An unusual increase in the concentration of digoxin has been reported in a patient with acute renal failure after termination of drug treatment (7). Thereafter, false positive digoxin concentrations, in the serum of more than 60% of uremic patients, were reported as well as great differences in the concentration of digoxin measured by different immunoassays in the single serum specimen (8). In this work, we were interested in finding out whether hemodialysis has an influence on the false positive concentrations of digoxin in the serum of uremic patients. This fact has been reported in literature in a very small group of patients (9,10).

* Department of Internal Medicine, Rebro University Hospital Zagreb, Yugoslavia.
** Medical Division, Oak Ridge Associated Universities. Washington, DC, USA.
*** Faculty of Biotechnology, University of Zagreb, Yugoslavia.

PATIENTS AND METHODS

The investigation included all patients with acute and chronic renal failure who were treated with extracorporeal hemodialysis in our Hemodialysis Centre during January and February 1984, and who had never received digoxin, or who had not received digoxin during at least the last year. Samples of 2 ml of blood were taken from all patients in supine position before and after hemodialysis. The concentration of digoxin was measured immediately, or the serum was separated by centrifugation for 10 minutes at 3000 to 3500 RPM and held at a temperature of +4°C until analysis was complete, total elapsed time did not exceed 16 hours. The method used was a radioimmunoassay kit of "Pharmacia" Sweden. The limit of sensitivity was 0.05 nmol/L. For the low concentrations, the intraassay variability was 5.2% and the interassay variability was 9.2%. All patients were treated with extracorporeal hemodialysis 12 to 15 hours weekly (2 to 3 hemodialyses), and the patients with acute renal failure up to 20 hours weekly (4 hemodialyses). Some patients (most of them were never treated with digoxin) had several hemodialyses before the serum specimen for digoxin measurement was taken, and the majority of patients were on a program for chronic maintenance hemodialysis over several years, at most for seven years. In all patients, hemodialysis was carried out with the capillary hemodialyser "Plivadial", Zagreb (surface 1.4 to 1.8 m^2). In all patients serum creatinine concentration was more than 600 nmol/L. Some patients were hypertensive, but their blood pressure was not changed significantly during hemodialysis. None of the patients had taken drugs which are known to interfere with radioimmunoassay determination of serum digoxin (spironolactone, corticosteroids, furosemide), nor drugs which increase serum digoxin concentration by various mechanisms (amiodarone, verapamil, nifedipine, quinidine, spironolactone). According to the foregoing criteria, the investigation included data on 31 patients. The serum digoxin concentration was also determined in a control group of five healthy volunteer physicians (one female and four males) who had never received digoxin nor the aforementioned drugs.

Statistical analysis of the obtained results was expressed as the difference of the arythmetic means of the small dependent samples (11).

RESULTS

In the control group of five healthy subjects, concentrations of digoxin were at or near zero. The age range of the group was 36 to 41 years, with an average of 38 years. In the group of 31 patients with renal failure, there were 10 females and 21 males, (18 to 63 years) with an average age of 43 years. Twenty-eight patients in this group were on the program of chronic maintenance hemodialysis for chronic renal failure, and three male patients had acute renal failure which had to be treated with hemodialysis. The false positive digoxin was found in 22 of 31 patients (two of them in acute renal failure) prior to hemodialysis (71%), and values ranged from 0.1 to 0.5 nmol/L (in acute renal failure 0.0 to 0.4 nmol/L). The mean value for the group with false positive concentrations was 0.28 nmol/L, while the mean value for the entire group was 0.20 nmol/L (the mean values of two patients in acute renal failure were 0.20± 0.20 nmol/L).

The patients whose concentration levels were at zero before hemodialysis, had the same results after. Of the group of 22 patients with false positive digoxin before hemodialysis, 14 patients (45% of 31 patients) remained false positive after the procedure (one in acute renal failure), having the same or decreased concentrations, and no one had increased concentration following hemodialysis. Eight patients, who were false positive before hemodialysis, became negative after hemodialysis. One of them was patient in acute renal failure, with the false positive serum digoxin concentration of 0.2 nmol/L before hemodialysis. The mean concentration after hemodialysis, for the group of 22 patients who were false positive before hemodialysis, was 0.15 nmol/L and ranged from 0.1 to 0.4 nmol/L; for the whole group (31 patients) the mean value was 0.11 nmol/L. The difference in the digoxin concentration before (0.20±0.16) and after hemodialysis (0.11±0.14) is statistically significant ($p < 0.001$). The results are shown in Fig. 1.

The average weight loss during hemodialysis was as follows: the whole group (31 patients) 1.8 kg (0.5 - 2.6 kg), the group with false positive

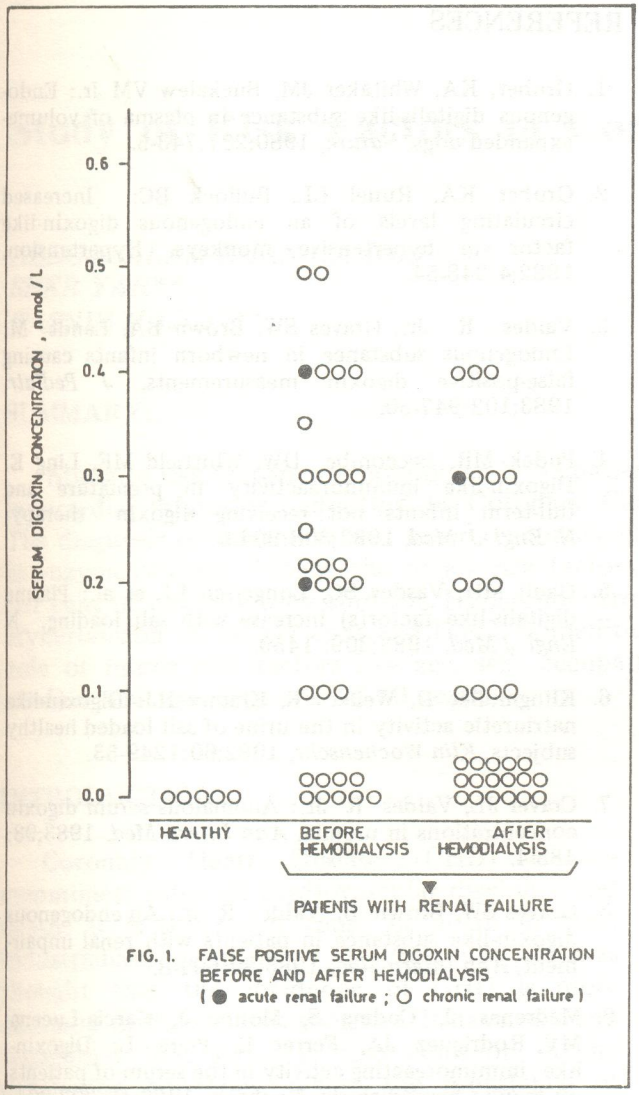

FIG. 1. FALSE POSITIVE SERUM DIGOXIN CONCENTRATION BEFORE AND AFTER HEMODIALYSIS
(● acute renal failure ; ○ chronic renal failure)

serum digoxin concentration before hemodialysis (22 patients) 1.75 kg (0.55 - 2.60 kg), the group with false positive serum digoxin concentration before and negative after hemodialysis (8 patients) 1.9 kg (0.6 - 2.5 kg), and patients who were negative before and after hemodialysis 1.75 kg (0.5 - 2.4 kg). The serum sodium concentration before hemodialysis was 122 - 142 nmol/L (average 136±4.2 nmol/L) and potassium between 3.5 - 5.2 nmol/L (average 5.2±0.8 nmol/L).

DISCUSSION

Circulatory endogenous plasma substance, which reacts with antibodies against digoxin, has been of scientific interest from the first observation in experiments on dogs (1) and monkeys (2). It was assumed that it could be a natriburetic hormone-like substance. The natriburetic hormone characteristics of that digoxin-like substance were later determined in the urine of salt-loaded healthy volunteers (6), and significant increase in the activity of a digoxin-like substance has been recorded in the serum of mild hypertonic patients after salt loading (5). The digoxin-like substance has also been found in the serum of newborn infants (3,4), and in the serum of the patient with monoclonal gammopathy (12). The false positive concentrations of digoxin in serum have also been found in uremic patients who had not received digoxin (8), and great differences in the concentrations of digoxin have been found, when digoxin was measured with different immunoassay kits in the single uremic serum specimen, including patients who were and those who were not taking digoxin (8). This prompted us to study the concentrations of digoxin-like substances in our uremic patients with special interest to its possible dialyzability. The frequency of the false positive digoxin concentrations in our uremic patients before hemodialysis was 71% (22 of 31 patients), which is similar to the results reported by Graves et al. (8). In the study by Wide (10), only five out of 25 patients on maintenance hemodialysis had a digoxin-like immunoreacting activity in their serum. It is interesting to note in our study that after hemodialysis, the frequency of the false positive results was reduced to 45% (14 of 31 patients). Some patients had normal and some had high blood pressure, but the number of hypertensive patients in the group with false positive was equal to the number in the group with negative serum digoxin-like substance, both before and after hemodialysis. Our results indicate that hemodialysis can significantly decrease endogenous digoxin-like substance. Some of the patients had constant concentrations, although no one had a higher value after hemodialysis than before hemodialysis. None of the patients, who were negative before hemodialysis, became positive afterwards, but eight patients who were false positive before hemodialysis became negative after hemodialysis. These results indicate the possibility of at least the partial dialyzability of the endogenous digoxin-like substance, although the molecular nature and the role of the substance in the human organism is an open question. With regard to our results it is difficult to accept the possibility that this is a protein substance (13), as it is at least

partly dialyzable, which indicates a small molecular weight.

In Wide's stuy (10), a very small number of uremic patients on hemodialysis had digoxin-like immunoreacting activity concentrations before hemodialysis, with 0.091 and 0.079 mg/ml after hemodialysis, suggesting that they can not relate to the theoretical removal of an uremic toxin and/or endogenous inhibition of the Na, K pump. The other reason for decreased digoxin-like activity after hemodialysis have to be considered (e.g. changes in the circulatory volume, osmolality, electrolytes, acid — base balance etc.).

Although the question is still of important scientific interest, it should be remembered that clinicians frequently have to treat uremic patients with digoxin, and that laboratory findings of serum digoxin concentration will not be of great benefit, but rather the clinical status and electrocardiogram should be dependent on the evaluation of the therapeutic as well as toxic effects of digoxin. However, if uremic patients on a chronic hemodialysis program are to be treated with digoxin, a basal digoxin-like activity should be measured before the treatment. During the treatment with digoxin, more valuable results will be obtained after hemodialysis.

In conclusion: In serum samples of 31 uremic patients who either never took digoxin or not taken for at least 12 months, we detected false positive serum digoxin concentration, in 71% before and in 45% after hemodialysis. The concentration of that substance reached up to 0.5 nmol/L before and up to 0.4 nmol/L after that treatment. The results suggest that this substance is partly dialyzable. These facts have to be calculated in a clinical practice in an analysis of serum digxon level in patients treated with digoxin: the serum digoxin concentration has to be determined after hemodialysis than before that treatment.

To the Memory of Our Beloved Mother Remza Durakovic

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