SERUM DIGOXIN CONCENTRATIONS DURING CHRONIC COR PULMONALE TREATMENT

H. Tzekov, B. Kanazirev, T. Ruseva

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At present, there still exists certain reservation concerning digitalis glycosides treatment of decompensated cor pulmonale. This reservation is based mainly on the known unwanted hemodynamic effect of glycosides related to the increase of pulmonary arterial pressure and to a less extent — of pulmonary vascular resistance (1—5).

Some authors contrast the risk of rapid advancing digitalis intoxication induced by progressed respiratory insufficiency with the increased myocardial contractility by digitalis giycosides (6—8).

The determination of the serum levels of cardiac glycosides with small cumulative effect such as of digoxin enables a more profound evaluation of the side effects and risk from overdosage.

The purpose of the present work consists in:

1. Estimation of serum digoxin levels in case of moderately rapid and slow saturation during advanced respiratory and right-side heart insufficiency.
2. Ascertaining of the maximal levels of serum digoxin and of clinical symptoms of toxic doses.
3. Follow-up of the risk factors of the digitalis intoxication.

Material and methods

A total of 35 patients (32 males and 3 females) at an average age of 59±8 years with chronic obstructive lung disease (COLD) and chronic cor pulmonale at the stage of decompensation were studied. At lying position, serum levels of digoxin, potassium, sodium, calcium and chlorides were estimated prior to digoxin therapy as well as on the 1st, 5th and 10th day after beginning of treatment. Serum levels were assessed on the 5th and on the 10th day 8 hours after the last taking of the drug. All the patients were administered the rest adequate therapy including chemotherapeutics, bronchodilatators, and mucolytics. Diuretics were commonly administered intermittently observing the rule to exclude aldosterone antagonists. Clinical characteristics was based on the physical, functional, roentgenological, and electrocardiographical examination as well as on the follow-up of both objective and subjective symptomatics of digitalis preparation overdosage. Patients were divided into 3 groups in the course of treatment and investigation: 1st group of 19 patients treated with digoxin (Richter, GDR) at dosis of 1 tablet thrice daily for 5 days up to total dosis of 3.75 mg followed by maintenance dosage of one tablet (a dosis of 0.25 mg) daily. 2nd group consisted in 8 patients in which a maintenance dosage was started. Blood gases were examined at the onset as well as on the 10th day after beginning of treatment. In the 3rd group consisting in 8 patients with chronic respiratory failure and cor pulmonale maintenance dosage of one digoxin tablet daily was of 3 month duration prior to investigation.

Table 1

Serum digoxin levels (SDL)

Indexes	Patients'groups							
	first			second				third
	before treatment	5th day	10th day	before treatment	5th hour	5th day	10th day	3rd month
SDL nmol/l	0.99± 0.56	3.02± 1.35	2.51± 1.46	0.19± 0.07	0.68± 0.09	1.1± 0.21	2.14± 0.25	1.56± 0.39
Sodium mmol/l	146±11	146±9	143±13	136±8	—	—	133±5	—
Potassium mmol/l	4.76± 0.23	4.99± 0.19	4.44± 0.36	4.86± 0.68	—	—	4.78± 0.74	—
Creatinin mkmol/l	106±18	119±24	114±21	101±11	—	—	105±13	—
Calcium mmol/l	2.44± 0.31	2.62± 0.56	2.39± 0.33	—	—	—	—	—
Chlorides mmol/l	104±8	102±11	103±9	—	—	—	—	—
pO_2 kPa	—	—	—	7.42±0.1	—	—	8.21±0.21	—
mm Hg	—	—	—	56±0,8	—	—	62±1,2	—
pCO_2 kPa	—	—	—	8.64± 1.57	—	—	7.01± 0.96	—
mm Hg	—	—	—	67±12			53±7.2	

We considered reference values of therapeutic digoxin concentrations for adults these given by the firm between 1.5 and 1.8 nmol/l but toxic ones — over 2,6 nmol/l.

Results and discussion

Digoxin levels were studied after a 5-day interrution in order to achieve disappearance of its effect in the patients of the first group. The serum concentrations (presented on table 1) — 0.99±0.56 nmol/l — showed that excretion was delayed despite the absence of renal failure. Digoxin administration at a dosis of 0.75 mg daily for 5 days elevated the concentrations up to 3.02±1.35 nmol/l. In two patients with chronic pulmonary failure, 1st stage, the levels reached up to 5 nmol/l without any electrolyte changes. Electrocardiographically, 6 patients demonstrated diffuse ST-T changes due to digitalis but one patient — due to sinusoidal bradycardia. Maintenance dosage administration during the next 5 days resulted in serum digoxin level reduction down to 2.51±1.46 nmol/l. Heart frequency decreased statistically significantly ($p<0.001$) on the 5th day as compared with that of the initial rate and then increased insignificantly on the 10th day after beginning of the study (fig. 1).

Patients of the 2nd group had not received digoxin 3 months long before treatment and investigation. It was confirmed by the levels established prior to investigation — namely 0.19±0.07 nmol/l. Five hours after the first taking of the drug a considerable change of serum digoxin level occurred — 0.68±0.09 nmol/l reaching up to 1.1±0.21 nmol/l, i. e. nearly to the therapeutic one on the 5th day but then insignificantly prevailing over it on the 10th day (2.14±0.25 nmol/l) (fig. 2). The rates of partial pressure of CO_2 — pCO_2 and of oxygen — pO_2 were prior to treatment 8.64±1.57 kPa (67±12 mm Hg) and 7.42±0.1 kPa (56±0.8 mm Hg), respectively. Therefore, we considered the respiratory failure an ad-

vanced one. After a 10-day treatment both hypoxemia and hypercapny persisted but they were considerably reduced down to the following rates: pO_2—8.21±0.21 kPa (62±1.6 mm Hg) and pCO_2 — 7.01±0.96 kPa (53±7.2 mm Hg). Concerning the patients of the 3rd group who were on maintenance therapy for more than 3

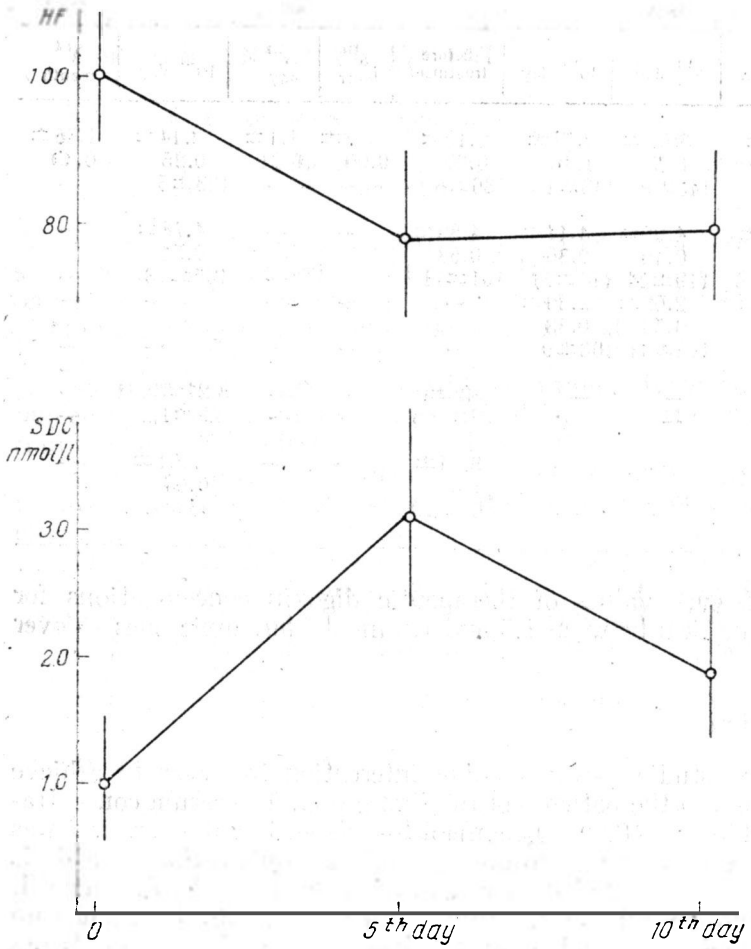

Fig. 1.

months prior to study it could be noted that stabile therapeutic concentrations (1.56±0.39 nmol/l) were warranted (fig. 3).

We established high residual levels inspite of 5-day long digoxin therapy interruption. When we related this fact to the early therapeutic levels during maintenance treatment of the patients of the 2nd group we could realize that digoxin resorption was much higher than the presumed one but excretion quota was lower, on the contrary. The absence of severe phenomena of digitalis intoxication made rather doubtful the known fact that myocardium was more sensible in hypoxemic patients. P. Souich and J. P. Clozel (9) proved that hypoxemia prolonged plasma half-life of digoxin from 25 up to 33 hours but digoxin concentrations increased in the brain and diaphragm musculature and did not in the heart muscle despite high serum levels. A. Nanjii and D. Greenway (10) rendered

account of the presence of digoxin-like immuno-reactive substances in hepatic and renal lesions as well as in premature newborns.

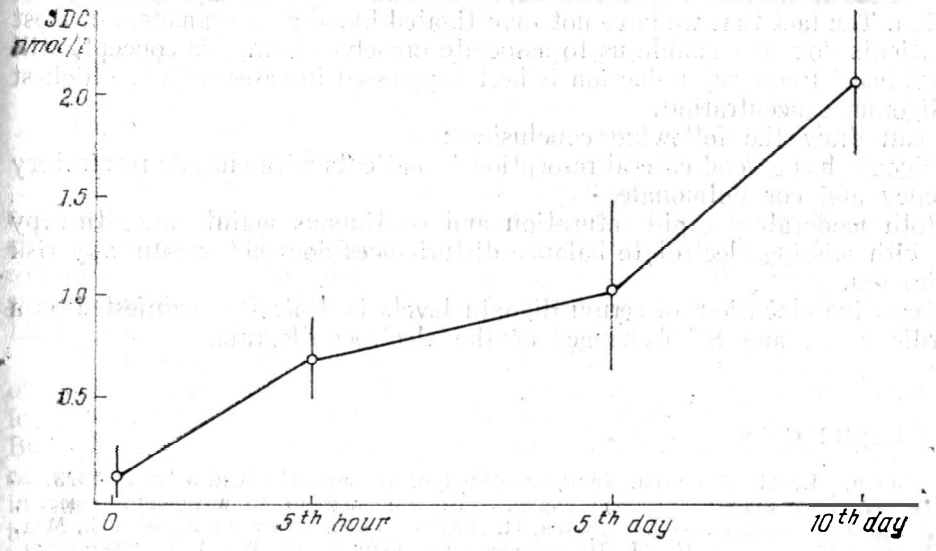

Fig. 2.

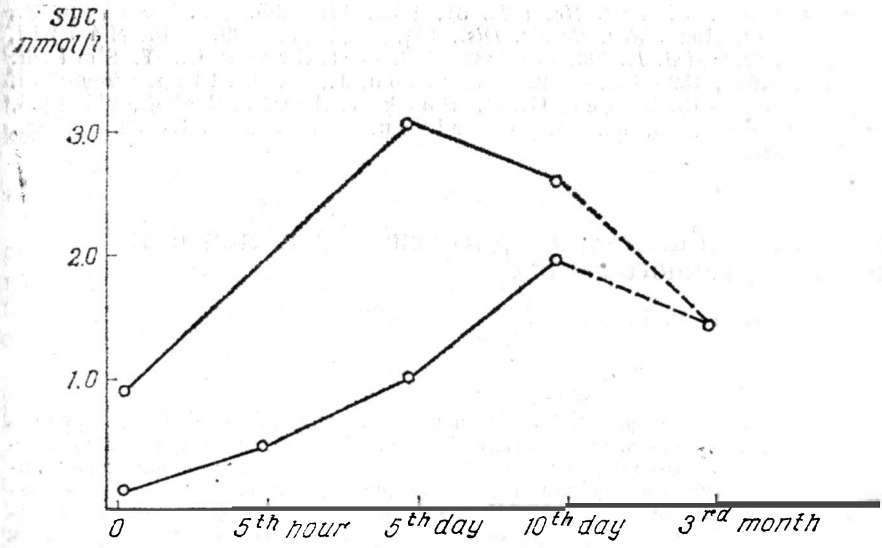

Fig. 3.

The lack of any digitalis intoxication inspite of the high digoxin levels should be explained by the absence of electrolyte disturbances in our patients. L. Green and T. Smith (11) point out that hypokaliemia and renal lesions cause digitalis intoxication in 53 per cent of cor pulmonale patients. J. Morrison and T. Killip (12) find out a digitalis intoxication at 1.2 ng/ml in 8 patients with pO_2 of 39 mm Hg. G. Koren and R. Parker (13) investigate 47 children aged between 2 and 16

years and emphasize that the very high serum digoxin concentrations exert not always a toxic effect. R. Goldmann and D. Harrison (14) report that while hypoxemia possesses an indirect effect hypercapny acts directly on sympathico-adrenal stimulation. The fact that we have not investigated blood-gas parameters in most of our patients does not enable us to associate ourselves with this concept, still more, that heart frequency reduction is best experessed in cases with the highest serum digoxin concentration.

We can draw the following conclusions:

1. Digoxin has a good enteral resorption in patients with chronic respiratory insufficiency and cor pulmonale.

2. Both moderately rapid saturation and continuous maintenance therapy together with missing electrolyte balance disturbances does not create any risk of intoxication.

3. Excessive elevation of serum digoxin levels is clinically manifested as a bradycardic effect and ST-T-changes of the electrocardiogram.

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СЫВОРОТОЧНЫЕ КОНЦЕНТРАЦИИ ДИГОКСИНА ПРИ ЛЕЧЕНИИ ХРОНИЧЕСКОГО ЛЕГОЧНОГО СЕРДЦА

Х. Цеков, Б. Каназирев, Т. Русева

РЕЗЮМЕ

При помощи радиоиммунологической методики прослеживался сывороточный уровень дигоксина у 35 больных хронической обструктивной легочной болезнью и хроническим легочным сердцем. Установлено, что умеренно быстрое насыщение и непрерывное поддерживающее лечение не создают риска интоксикации. Эксцессивно повышенный уровень дигоксина вызвал брадикардию у одного больного. У шести больных наблюдались ST-T изменения дигиталисового типа. Получение терапевтических сывороточных концентраций к пятому дню умеренно быстрого насыщения (3.02±1.35 нмол/л) и к десятому дню (2.14±0.25 нмол/л) свидетельствует о хорошей энтеральной резорбции дигоксина. Умерено быстрое насыщение статистически достоверно замедляет сердечную деятельность ($P<0.001$). Низкий исходный уровень, установленный у больных, не получающих дигоксина до исследования (0.19±0.07 нмол/л), доказывает отсутствие дигоксиноподобных субстанций и определяет высокую специфичность радиоиммунологического метода. Определение сывороточных концентраций дигоксина дает представление о некоторых особенностях его фармакокинетики. Это подчеркивает также, что страх интоксикации дигиталисом у больных хронической обструктивной легочной болезнью и хроническим легочным сердцем неоснователен.