Digoxin-Uke Immuno-Reactive Substance: Is It Important in Preeclampsia Etiology?

DİGOKSİN-BENZERİ İMMÜN-REAKTİF MADDE: PREEKLAMPSİ ETYOLOJİSİNDE ÖNEMLİ Mİ?

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SUMMARY

Objective: To determine serum and amniotic fluid Digoxin-Uke immuno-reactive substance (DLIS) concentrations of preeclamptic and non-preeclamptic pregnant women and to investigate whether DLIS has an etiologic role in preeclampsia.

Institution: Ege University Medical Faculty, Department of Obstetrics and Gynecology and Department of Pharmacology.

Material and Methods: 15 preeclamptic and 15 non-preeclamptic pregnant women were investigated serum and amniotic fluid Digoxin concentrations were measured. The statistical analysis was evaluated by student's t test.

Findings: The mean serum and the amniotic fluid digoxin concentrations were measured as 0.15+0.01 and 0.59+0.19 ng/ml in preeclamptic patients and 0.12+0.01 and 0.57+0.09 ng/ml in non-preeclamptic patients, statistically non-significant (p>0.05).

Results: Digoxin-like immuno-reactive substance concentrations are not elevated in preeclampsia in the third trimester, it is very unlikely that this test will be helpful in predicting preeclampsia and may play a major role in the development of preeclampsia.

Key Words: Digoxin-like, Immuno-reactive substance, Preeclampsia, Hypertensive disease of pregnancy

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ÖZET

Amaç: *Preeklamptik ve normal gebelerde Digoxin benzeri immün-reaktif maddenin (DBİM) serum ve amniotik sıvı konsantrasyonlarını saptamak ve DBİM'in preeklampsi etyolojisinde rolü olup olmadığını araştırmak.*

Çalışmanın Yapıldığı Yer: Ege Üniversitesi Tıp Fakültesi Kadın Hast, ve Doğum ABD ve Farmakoloji ABD

Materyal ve Metod: 15 preeklamptik ve 15 normal gebede serum ve amniotik sıvı Digoksin konsantrasyonları ölçüldü, istatistiksel değerlendirme Student t testi ile yapıldı.

Bulgular: Ortalama serum ve amniotik sıvı DBİM konsantrasyonları preeklamptik hastalarda 0.15+0.01 ve 0.59+0.19 ng/ml, normal gebelerde ise 0.12+0.01 ve 0.57±0.09 ng/ml olarak bulundu (İstatistiksel olarak anlamsız, p>0.05).

Sonuç: DBİM preeklamptik hastalarda gebeliğin 3. trimesterinde yükselmediği için, bu testin preeklamptik gebelerin önceden belirlenmesinde bir test olarak kullanılamayacağı ve preeklampsi etyolojisinde önemli bir rolünün olmadığı kanısına varıldı.

Anahtar Kelimeler: Digoksin-benzeri, İmmün-reaktif madde. Preeklampsi, Gebeliğin hipertansif hastalıkları.

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Hypertensive disease of pregnancy is still one of the most important causes of maternal deaths and it is also responsible for a large proportion of perinatal mortality (1,2). Despite this fact; the etiology of this syndrome is unclear and its treatment still remains symptomatic. Recently, an endogenous "Digoxin-like Immuno-reactive subtance" (DLIS) has been measured in the serum of pregnant patients (1,3). In subsequent studies, higher concentrations of DLIS were measured in the serum of preeclamptic patients and investigations have suggested that DLIS may play an etiologic role in the development of preeclampsia (1,4).

The study aimed to determine serum and amniotic fluid concentrations of preeclamptic and non-preeclamptic pregnant women and to investigate whether DLIS has an etiologic role in preeclampsia or not.

MATERIAL AND METHODS

15 preeclamptic and 15 non-preeclamptic pregnant women who were admitted an delivered in the department of Obstetrics and Gynecology of Ege University Medical Faculty were investigated. All patients

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Table 1. The data and results of patients with and without preeclampsia.
Tablo 1. Preeklamptik ve kontrol grubu hastaların veri ve sonuçları.

	Preeclamptic Group (n=*15)	Control Group (n=15)	P value
1- Age (year)			
-Mean+SEM	29.2±1.8	27.3H.5	NS"
-Median	31 (16-40)	28(18-38)	
2- Systolic blood pressure (mm Hg)	183.0±5.1	119.0±2.7	p<0.01*
3- Diastolic blood pressure (mm Hg)	117.6+2.4	73.3+2.1	p<0.01*
4- Gestational age (weeks)	34.9±0.7	38.5+0.5	p<0.01*
5- Infant weight (gram)	2200±186	3347+123	p<0.01*
6- Digoxin-like immunoreactive Substance (ng/ml)			
-Serum	0.15±0.01	0.12+0.01	NS*
-Amniotic fluid	0.59+0.19	0.57+0.09	NS*

Statistically significant
NS: Statistically non-significant.

studied were primigravid. None of them had a history of chronic hypertension of chronic renal failure and none had used digoxin or similar drugs during the previous three months. The gestational ages of patients were determined by last menstrual period, obstetric examination and ultrasound. 15 women in the third trimester of pregnancy were admitted to the hospital with preeclampsia as defined by a blood pressure of 140/90 mm Hg or an increase of 30 mm Hg systolic or 15 mm Hg diastolic over baseline values on at least two occasions, 6 or more hours apart, and proteinuria and/or edema (2).

A blood sample was taken and centrifuged before starting treatment in any patient. When amniotomy was performed during labor, an amniotic fluid sample was taken and sent for DLIS measurement. Serum and amniotic fluid digoxin concentrations were measured by using commercial digoxin kits utilizing flouresans-polarization immunoassay method. (TUx-abbott).

The statistical analysis of the study was evaluated by student's t test in the center of computer sciences, Ege University and the results are expressed as mean ± SEM.

RESULTS

The mean age of the 15 pregnant women in the preeclamptic group (group I) was 29.2+1.8, while it was 27.3±1.5 in the 15 non-preeclamptic pregnant women as control group (group II), statistically non-significant (p>0.05). As can be expected, the mean systolic blood pressure at the time of admittance was significantly different in the two group, 183.0+5.1 mm Hg in group I, as opposed to 119.0±2.7 mm Hg in group II. The difference between two groups was statistically significant (p<0.01). The mean diastolic blood pressures were 117.6±2.4 mm Hg and 73.3±2.1 mm Hg in groups I and II respectively and the difference was statistically significant (p<0.01).

The mean gestational age was 34.9±0.7 weeks and the mean birth weight was 2200+186 gm in the preeclamptic group compared to 38.5+0.5 weeks and 3347±123 gm In the control group, again significant (p<0.01). The mean serum and the amnitoic fluid digoxin concentrations were measured as 0.15±0.01 anJ 0.59+0.19 ng/ml in group I, while these measurements were found to be 0.12±0.01 and 0.57±0.09 ng/ml in group II, statistically non-significant (p>0.05).

Table I shows the data and results from the two groups indicating whether the difference between them was statistically significant or not.

DISCUSSION

Recently, several investigators reported the presence of "digoxin-like immuno-reactive substance" in sera from neonates, in human amniotic fluid, umbilical cord blood and placental homogenates (4-8). Although purification of this factor has not yet been achieved and its precise biochemical structure is still unclear; Gruber et al (9) suggested that this substance might be "an endogenous natriuretic hormone" which cross-reacts with antibodies against digoxin.

In early pregnancy; DLIS is undetectable in the serum of patients, it begins to appear during the second trimester and is present in almost all third trimester patients (6,10). In a study reported by Phelps et al (6) in 1988, DLIS levels In all trimesters of pregnancy were investigated. They found that none of the patients in first trimester had detectable serum DLIS levels. The mean serum concentrations of DLIS were found to be 0.02±0.01 ng/ml and 0.29+0.01 ng/ml in second and third trimester patients respectively. In conclusion, they evaluated the relationship between increasing gestational age and DLIS levels and suggested a non-linear model that shows DLIS levels during pregnancy.

Higher concentrations of DLIS have been found in the sera of preeclamptic patients (1,4). The mechanism responsible for the development of preeclampsia has not been delineated, however, many causes (i.e. vascular, placental, renal and hematologic) have been proposed (2). Because digoxin-like immuno-reactive substance activity includes natriuresis, natrium/kalium adenosine triphosphatase (Na^+ / K ATP'ase) and vasoconstriction, it has been speculated that DLIS may be a causative agent in the development of preeclampsia (1,3,4,7). Gusdon and collègues (1) investigated 10 preeclamptic and 10 non-preeclamptic pregnant women in third trimester. They found that serum DLIS concentrations were 0.14+0.01 and 0.07±0.01 ng/ml respectively, a significant difference.

Despite these findings reported by Gusdon (1); Phelps and colleagues (6) studied 27 preeclamptic and 27 non-preeclamptic pregnant women in the third trimester of pregnancy. The mean serum DLIS concentrations were found to be very similar (0.30±0.02 ng/ml in the preeclamptic group and 0.32±0.02 ng/ml in the control group). There was no statistically significant difference between the two groups ($p>0.05$). Gonzalez and colleagues (10) found that DLIS concentrations in preeclamptic patients even lower than control group (0.22+0.12 and 0.32±0.15 ng/ml respectively.). An explanation of this controversy could be that mean gestational age and birth weights in the preeclamptic group was lower than the control group. When two groups were matched for geastational age, there was no statistically significant difference. In our study, the mean DLIS concentration in sera of preeclamptic patients was measured as 0.15±0.1 ml compared to 0.12±0.01 ng ml in the control group ($p> 0.05$, non-significant). Our findings were similar to those of Phelps (6) and Gonzalez (10).

Most research on DLIS focused on the use of radioimmunoassay cross-reactivitiy with anti-digoxin antibodies to detect presence of DLIS in serum (3,5,6,8). Howerr, DLIS cross-reacts with antibodies in each immunoassay to varying degrees, making comparison of results by various authors difficult (3,11). Therefore, direct measurement of Na^+/K ATP*'ase inhibition may be a more reliable way to assess the biologic presence or activity of DLIS. Kuhnert et al (12) reported no difference in in-vitro maternal eryhtrocyte Na^+/K^+ ATP'ase inhibition in patients with or without preeclampsia admitted for delivery. Although a biologic assay was not used in our study, our findings supported these investigators since we found no difference in the serum concentration of DLIS between patients with or without preeclampsia.

Because digoxin-like immuno-reactive substances are rarely detected in the first and second trimesters and the concentrations are not elevated in preeclampsia in the third trimester, it is very unlikely that this test will be helpful in predicting preeclampsia and may play a major role in the development of preeclampsia.

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