

Serum α_1 -acid glycoprotein, sialic acid, and protein binding of disopyramide in normal subjects and cardiac patients

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KEY WORDS glycoproteins; myocardial infarction; congestive heart failure; disopyramide; sialic acids

AIM: To study influence of congestive heart failure (CHF) and acute myocardial infarction (AMI) on α_1 -acid glycoprotein (AGP) and sialic acid (SA) concentration, and binding of AGP to disopyramide (Dis). **METHODS:** Sera from 85 healthy subjects, 6 patients with CHF, and 6 patients with AMI were determined by immunochemistry for AGP, by HPLC method for sialic acid (SA), and by ultrafiltration and HPLC for the free fraction of Dis. **RESULTS:** Serum AGP concentrations ($\text{g}\cdot\text{L}^{-1}$) were 0.74 ± 0.16 (healthy), 1.18 ± 0.40 (d 1, CHF) and 0.90 ± 0.24 (d 14, CHF), 1.53 ± 0.26 (d 5, AMI) and 1.08 (d 14, AMI). The free Dis were 1.76 ± 0.62 (d 1) and 2.14 ± 0.48 (d 14), in CHF patients, 1.66 ± 0.52 (d 5) and 1.77 (d 14) in AMI patients. The changes of serum SA and AGP concentrations showed the same tendency. **CONCLUSION:** The free Dis in serum was affected by the change of AGP binding in CHF and AMI patients.

α_1 -Acid glycoprotein (AGP) takes part in coagulation, immunological, and tissue repair processes^(1,2). Its concentration in plasma increases from $0.5 \text{ g}\cdot\text{L}^{-1}$ normal up to $3.0 \text{ g}\cdot\text{L}^{-1}$ in acute inflammation, cancer, and myocardial infarction. Disopyramide (Dis) is used in the treatment of supraventricular and ventricular arrhythmias⁽³⁻⁶⁾ at $6-15 \mu\text{mol}\cdot\text{L}^{-1}$. Since binding to AGP diminishes free drug fraction, rapid or large change in the concentration of AGP could confound the interpretation of the total drug concentration in plasma. The AGP concentrations in serum vary markedly in patients associated with various bindings of basic drugs^(1,4).

Heart diseases may influence the AGP concentration in serum. This study was to examine the influence of congestive heart failure (CHF) and acute myocardial infarction (AMI) on AGP, sialic acid (SA), and binding of AGP to Dis in Japanese.

MATERIALS AND METHODS

Chemicals Dis was from Nippon Roussel K K (Japan). SA (*N*-acetyl neuraminic acid, NANA) (lot MST4140) was from Nakarai Lab (Japan), 1,2-diamino-4,5-dimethoxybenzene (DDB) (lot AW323) was from Dojindo Lab (Japan). Other chemicals were of AR.

The serum samples were obtained from Japanese. Group A: 85 healthy subjects (M: 46, F: 39, aged 20-69 a) one blood sample was drawn; Group B: 6 patients with CHF (M: 4, F: 2, aged 43-79 a), blood samples were collected on the day of admission and 2 wk later; and Group C: 6 patients with AMI (M: 5, F: 1, aged 54-71 a), blood samples were collected on the day of admission and at least 4 consecutive days during hospitalization. Blood samples were spun at $1000 \times g$ at 4°C for 30 min. Sera were stored at -20°C .

Apparatus and chromatographic condition The chromatographic system for assay of Dis consisted of a Hitachi L6000 Pump, Hitachi 638-41 UV detector set at 270 nm at 0.005 AUFS and a reverse-phase column (Hitachi 3053, 4 mm \times 250 mm) at 55°C . The chromatographic system for the determination of SA (NANA) was a Hitachi 655A pump, Hitachi F1000 fluorescence spectromonitor at λ_{ex} 369 nm; λ_{em} 453 nm, and a reverse-phase column (Licorsorb RP-18, 4 mm \times 125 mm).

Analytical method The NANA concentration was determined by the modification method of Hara *et al*⁽⁷⁾. The serum AGP concentration was determined by radial immunodiffusion (RID) plate method.

The protein binding of Dis was measured by ultrafiltration using an ultrafree C₃ LGC (Millipore ultrafiltration membrane, nominal molecular weight limit: 10 000, Millipore Co, Bedford MA, USA) and by HPLC method⁽⁸⁾.

Statistical significance was analyzed by *t* test.

RESULTS

There was a two-fold increase in the serum concentration of AGP in patients with AMI during the

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stages of d 4 - 6 in comparison with normal subjects. This was accompanied by a reduction in the free Dis fraction. In AMI patients, the serum AGP concentration was increased to the maximum on d 4 and d 5. But the free Dis was decreased to the lowest. The changes of NANA, AGP, and Dis binding (C_b) concentrations in sera of AMI patients showed the same tendency during the course of the diseases (Tab 1).

Tab 1. AGP and NANA concentration, free Dis, and C_b of Dis in serum, $^bP < 0.05$, $^cP < 0.01$ vs d 0.

	n	AGP /g·L ⁻¹	Free Dis /mg·L ⁻¹	NANA /g·L ⁻¹	C_b of Dis /mg·L ⁻¹
Healthy subjects					
	85	0.74±0.16	2.9±0.6	0.61±0.16	2.1±0.6
CHF patients					
d 1	6	1.2±0.4	1.8±0.6	0.88±0.25	3.2±0.6
d 14	6	0.90±0.24	2.1±0.5	0.77±0.15	2.9±0.5
AMI patients					
d 1	6	0.81±0.18	2.6±0.5	0.61±0.19	2.4±0.5
d 2	5	0.99±0.07	2.28±0.09	0.66±0.18	2.72±0.09
d 3	5	1.25±0.17 ^b	2.21±0.29	0.67±0.13	2.79±0.29
d 4	5	1.38±0.28 ^b	1.8±0.4 ^b	0.85±0.17 ^b	3.2±0.4 ^b
d 5	6	1.53±0.26 ^c	1.7±0.5 ^c	0.82±0.21	3.3±0.5 ^c
d 6	4	1.3±0.4	1.5±0.8	0.74±0.08	3.4±0.8
d 7	3	1.3±0.3	1.7±0.8	0.78±0.09	3.3±0.8
d 14	2	1.08	1.77	0.65	3.23

C_b and NANA concentration increased with the rise of AGP concentration (Fig 1).

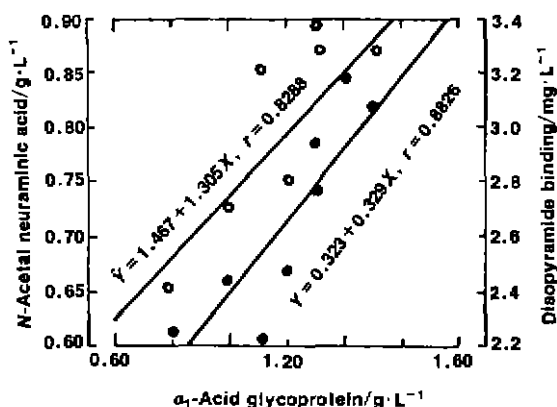


Fig 1. Effect of AGP concentration on C_b (○) and NANA (●) concentration in 8 patients with AMI.

DISCUSSION

The toxicity of Dis is apparently to be related to free plasma concentration, and the use of total plasma concentration of Dis to dose adjust problem patients may fail if binding variations are not taken into account. The study showed the same results as reports^(3,4,8,9) that Dis is binding with serum AGP, and that AGP concentration in serum increased in the patients with AMI and CHF. The change of serum AGP concentration results in alteration in the distribution and metabolism of Dis which will complicate the interpretation of the relationship between total drug concentration and drug efficacy or toxicity for the reason of binding of AGP to Dis. So more dose must be given in order to attain the curative effect in CHF and AMI. Use some physiology index to predict the free of Dis like AGP concentration or direct measurement of Dis free may improve its clinical use. The results indicated that there was a linear relation between C_b , NANA, and AGP serum concentration in AMI patients samples, and that there was a marked individual difference in CHF patients.

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正常人和心脏病患者血清 α_1 -酸性糖蛋白、
唾液酸及丙吡胺蛋白结合率

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心肌梗死

关键词 糖蛋白类; 心肌梗死; 充血性心力衰竭;

丙吡胺; 唾液酸类 蛋白结合率

目的: 研究日本人充血性心力衰竭 (CHF) 和急性心肌梗塞 (AMI) 病人对血清 α_1 -酸性糖蛋白 (AGP)、唾液酸 (SA) 浓度及 AGP 与丙吡胺 (Dis) 结合的影响。方法: 对正常人、CHF 及 AMI 患者血清样本 97 例, 采用免疫化学法测定 AGP 浓度, 高效液相层析法测定 SA 浓度及超滤膜技术和高效液相层析法测定 Dis 的体外游离浓度。结果: CHF 及 AMI 患者血清 AGP 浓度较正常人升高, Dis 药物游离浓度降低。血清 SA 浓度的变化与血清 AGP 浓度的变化趋势一致。结论: CHF 和 AMI 病人血清药物游离浓度受血清 AGP 结合的影响而变化, 应进行临床监测。

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