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Immunologic Effect of Antihypertensive Therapy in Patients with Essential Hypertension

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ESANSİYEL HİPERTANSİYONDA ANTİHİPERTANSİF TEDAVİNİN İMMÜN SİSTEM ÜZERİNE ETKİLERİ

ÖZET

Esansiyel hipertansiyonu olan kişilerde hipertansiyonun bazı immünolojik bozuklarla birlikte bulunabileceği gösterilmiştir. Antihipertansif tedavinin immün sistem üzerine etkisini araştıran çalışmalar sınırlıdır. Bu çalışmada farklı antihipertansif ilaçların immün sistem üzerine etkileri araştırılmıştır.

Kalsiyum kanal blokeri (nifedipine), alfa bloker (prazosin), ACEİ (kaptopril), diüretik (hidroklortiyazid) ve beta bloker (praplanolol) ile tedavi edilen 169 hipertansif hastada tedavi öncesi ve sonrası oluşan immün değişiklikler immünglobülin, T, B ve O lenfosit ve CIC tayini yapılarak araştırılmıştır. Tedavi öncesi hipertansif kişilerdeki immün değişiklikler aynı yaş ve cinsiyetteki 20 normal birey ile karşılaştırılmıştır.

T lenfosit düzeylerde kontrol grubuna kıyasla hipertansiflerde tedavi öncesi ve sonrasında belirgin azalma görülürken ($p<0.01$) O-lenfosit düzeylerinde belirgin artış saptanmıştır ($p<0.01$). B lenfosit düzeyleri kontrol grubu ve hipentansiflerde farklılık göstermemiştir. Hipertansiyonu olan kişilerde IgA ve IgG düzeyleri kontrol grubuna kıyasla anlamlı olarak yüksek bulunmuş ($p<0.01$), IgM düzeyi farklılık göstermemiştir. Yine hipertansiyonu olan kişilerde inisiyal CIC seviyesi kontrol grubuna göre anlamlı yüksektir ($p<0.05$). Farklı antihipertansiflerle tedavi sonrasında kalsiyum kanal blokerleri ve alfa blokerlerin immün sistem üzerine nötr, beta blokerler ve özellikle ACEİ'nin pozitif, diüretiklerin ise negatif etkilerinin olduğu saptanmıştır. Diüretik tedavi görenlerde T lenfosit değeri belirgin olarak azalmış ($p<0.001$), B lenfosit miktarında belirgin artış ($p<0.001$) saptanmıştır. IgA, IgG ve CIC seviyelerinde de anlamlı artış olduğu görülmüştür.

Anahtar kelimeler: *Esansiyel hipertansiyon, immün sistem, antihipertansif tedavi.*

The presence of certain immunologic disturbances for essential hypertension had been confirmed by the reports of published papers in the past ten years. The increase of concentration of blood serum of different Ig classes [1,2], revealing organospecific autoantibodies [3,4], change of immunocompetent cell activity [5-8] refer to them.

However, information on the effect of antihypertensive therapy on the immune system is scanty and contradicting [9,10]. We aimed our investigation at the study of the effect of antihypertensive drugs of different groups on immune state values of hypertensive patients.

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MATERIALS and METHODS

169 patients with stage II esential hypertension (96 - males, 73 - females) aged 38-62 years and 20 normal subjects comparable by age and sex were under observation. The study was performed before and after treatment. Blood pressure was measured by generally accepted methods. Besides clinical and laboratory investigations, all patients underwent immunologic study involving the determination of T-lymphocytes by M. Jondal spontaneous E-RFC methods, B-lymphocytes - By G. Statophulos, E.Elliot spontaneous E-RFC methods with mice erythrocytes before and after a course of treatment. The level of IgA, IgM, IgG in blood serum had been measured by radial immunodiffusion method in agar by G.Manclini et al. V.Hashkova's method had been used to determine CIC content.

Depending on the treatment, all patients were subdivided into 5 groups: group I consisted of 32 patients and received nifedipine - calcium channel blocker at a dose of 10-60 mg/day; group II consisted of 28 patients and received prazosin - alpha-blocker at a dose of 4-12 mg/day; group III comprised 42 patients and received captopril - ACE inhibitor - 25-150 mg/day, group IV - 31 patients taking hydrochlorthiazide - diuretic - 25-100 mg/day; group V - 36 patients taking propranolol - beta-blocker - 60-240 mg/day. The dosage of drugs was individual for each patient. In all cases the administration of other drugs was excluded.

Statistical evaluation of digital data was performed using standard methods of variation statistics.

RESULTS

The initial blood pressure was on average: systolic - 186.4±4.5 mm Hg, diastolic - 106.5±2.56 mm Hg.

Complex immunologic study of the observers revealed marked change of cellular as well as humoral immune values in hypertensive patients before treatment (Table).

Statistical significant reduction of percent T-lymphocytic content ($p<0.01$), significant increase of indifferent 0-lymphocytic level had been observed throughout the study. B-lymphocytic average level was not significantly different from the values of control group and was 8.6±0.2% in all groups.

Hypertensive patients showed disimmunoglobulinemia characterized by the increase of IgA ($p<0.01$) and IgG levels ($p<0.01$). The concentration of IgM in blood serum of the observers was not different from the values of normal sujects.

The initial CIC level in hypertensive patients had significantly been increased on average by 21% ($p<0.05$). A close correlative dependence between the duration of disease and T-lymphocytic content ($r=-0.6$; $p<0.01$), duration of disease and Ig: G/r=0.8; $p<0.01$), A/r=0.6; $p<0.01$); between the duration of a disease anad CIC level ($r=0.8$; $p<0.01$); between age and T-lymphocytic content ($r=-0.5$; $p<0.01$); age and Ig level: G/r=0.8; $p<0.01$, A/r=0.05; $p<0.01$); between age and CIC level ($r=0.8$; $p<0.01$) was observed while studying the dependence of immune values on hereditary aggravation, age, duration of disease, sex and blood pressure level.

After the treatment group I patients had systolic blood pressure reduced by 16.9%, diastolic - 17.1%. A course of treatment found to be effective in 71% of patients. There were no significant changes of immune values on the background of treatment with nifedipine (Table).

67% of group II patients taking prazosin showed marked antihypertensive effect after the effective individual dosage had been selected. An average systolic blood pressure reduction from the initial level in all groups was 18.2%, diastolic - 18.9%. Significant difference of immune state in group II patients was not observed after a course of treatment (Table).

78% of group III patients taking captopril developed a distinct antihypertensive response. They had systolic blood pressure reduced by 22.7%, diastolic - 19.9%. This group of patients showed positive effect of immune state (Table). A distinct T-cellular link stimulation of the immunity was observed on the background of treatment with captopril. An average 19.5% ($p<0.001$) significant increase of T-lymphocytic percentage was observed. At the same time we observed the reduction of indifferent 0-cell level ($p<0.001$). Normalization of B-cell content ($p<0.05$) was observed after a course of treatment. Mean values of IgA and IgG levels were reduced: IgA - by 24.1% ($p<0.001$), IgG - 26.2% ($p<0.01$). The value of IgM had not significantly been changed though we observed a tendency to its reduction. The study of CIC showed their level reduction on average by 7.1% in the group after a course of treatment though it was insignificant.

The treatment with hydrochlorthiazide in group IV patients found to be effective in 59% of patients and coexisted with the reduction of systolic blood pressure by 12.8%, diastolic - 9.6%. As seen in the table, hydrochlorthiazide taking was concomitant with unfavourable changes of immune values. T-lymphocytic content was reduced by 10.8% ($p<0.001$). After a course of treatment the patients of this group showed percent B-lymphocytic content to be significantly increased on average by 9.6% ($p<0.01$).

Mean values of IgA, IgG levels in blood serum had been concurrently increased by 15.6% ($p<0.001$). The level of CIC had been increased by 17.5% after a course of treatment. However, its average increase in the group was insignificant.

A course of treatment with propranolol turned out to be effective in 69% of group V patients. Systolic blood pressure was reduced by 18.9%, diastolic - 11.6%. The study of immune values on the background of treatment with propranolol showed a tendency to their improvement (table). Only the content of of T-lymphocytes was significantly increased on average by 11.5% and the content of IgA was reduced by 11.6%.

DISCUSSION

The results obtained show that hypertensive patients had changes of immune system of cellular as well as

Table: Comparative Immunologic Efficacy of Different Antihypertensive Drugs in Hypertensive Patients

	Control group n=20	Before treatment n=169	Nifedipine n=32	Prazosin n=28	Captopril n=42	Hydrochloro-thiazide n=31	Propranolol n=36
T-lymphocytes, %	70.0±3.4	52.6±0.86[b]	53.9±0.83	53.1±0.9	62.9±0.81[a]	46.9±0.78[a]	60.8±0.78[a]
B-lymphocytes, %	8.8±0.4	8.3±0.16	8.5±0.2	8.4±0.17	8.8±0.18[a]	9.1±0.26[a]	8.4±0.22
0-lymphocytes, %	21.2±2.0	39.1±0.8[b]	37.6±0.9[a]	38.5±0.6	28.3±0.75[a]	44.4±0.9[a]	30.8±0.82[a]
Immunoglobulins, mg/ml, A	1.66±0.05	2.24±0.06[b]	2.19±0.03	2.22±0.04	1.70±0.02[a]	2.59±0.05[a]	1.98±0.04[a]
M	1.15±0.05	1.16±0.01	1.15±0.02	1.16±0.02	1.15±0.01	1.17±0.03	1.15±0.02
G	9.12±1.4	13.7±0.65[b]	13.4±0.5	13.4±0.6	10.1±0.28	15.9±0.52[a]	12.8±0.46
CIC, CU	66.0±4.0	79-.9±4.2[b]	78.9±3.25	79.1±3.8	74.2±2.1	81.3±4.1	76.4±3.2

a - significant difference as compared with that of the values before treatment
b - significant difference of initial values as compared with that of the values of control group

humoral links that required their further study for the interpretation of genesis and determination of the necessity of immunocorrection.

The study carried out using traditional antihypertensive drugs in hypertensive patients demonstrated that their effect on immune state ranged from potentially unfourable-to-potentially "useful" effect. Thiazide diuretics possess unfavourable effect on immune system values that necessiated the use of immunocorrection combined with antihypertensive drugs in this group. We observed no significant difference of immune values after treatment of patients taking prazosin - alpha-blocker as well as in the group of patients taking nifedipine - calcium channel blocker. Hence, these drugs do not possess a significant effect on immune state, we may consider them to be "immunoneutral" drugs. Favourable effect of captopril - ACE inhibitor and propranolol - beta-blocker on immune values proved to be similar and different from the effect of hydrochlorthiazide. The patients taking captopril showed more marked positive immunologic effect enabling the modulation of cellular as well as humoral immunity. We feel the participation of prostaglandin-dependent mechanisms as prostaglandins E_2 modulate immune response [9]. At the same time we obtained data indicating a participation of ACE and A-II in the development of immunologic reactions [11]. It was stated that A-II increased the addition of ^{3}H-thymidine in lymphocytes-suppressors (cytoxines CD8) induced by phytohemagglutinine while in helper-cells (inductors CD4) we did not observe such a circumstance. Thus, A-II immunosuppressor effect may relate to CD8 activation [12]. Captopril had a certain structural similarity with D-penicilamine, a drug possessing marked antiinflammatory activity and immunomodulating feature [9].

In the light of the above, the results of study of M.Ya. Vilchinskaya et al. [9] showing on the background of captopril therapy that has sulfhydrile group developed a tendency to a reduction of Ig concentration in blood during prolonged treatment which are of particular interest.

Thus, different antihypertensive drugs had different effect on immune system that is important to consider for the treatment of hypertensive patients as the potential benefit of blood pressure reduction may be compromised if immune system parameters are deteriorated. Thiazide diuretics result in unfavourable changes of the immune system; in contrast to them, calcium channel blockers possess favourable effect of varying degrees on immune state of hypertensive patients.

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