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Can We Tame Glucocorticoids? Blood Tyrosine as a New Laboratory Test

Irma Th. Rass*

Center of Theoretical Problems of Physico-chemical Pharmacology, Russian Academy of Sciences (Until 2007), Moscow, Russia

***Corresponding author:** Irma Th. Rass, Center of Theoretical Problems of Physico-chemical Pharmacology, Russian Academy of Sciences (Until 2007), Moscow, Russia, E-mail: irma2@kmail.ru

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Abstract

Glucocorticoid (GC) preparations are used in medicine for about 70 years as the most powerful anti-inflammatory drugs also possessing immunosuppressive, anti-allergic and antitoxic properties. However, application of these unique preparations is associated with nearly inevitable serious adverse effects and a difficulty of their withdrawal. It is very important that the adverse effects are caused not by toxic action of GC preparations but by their hormonal nature. Glucocorticoid hormones directly or indirectly control virtually all metabolic and physiological processes in the body. However, for these virtually omnipresent and vitally important hormones there is no representative specific index of action similar to blood content of glucose for insulin. The present paper considers specific features of tyrosine metabolism that allows us to consider changes in blood tyrosine content as manifestation of regulatory action of GCs. Changes in blood tyrosine content were compared with using GC preparations in two typical cases: in systemic lupus erythematosus and in congenital adrenal virilizing dysfunction in children. Blood tyrosine behavior was also considered in rats after adrenalectomy and on injecting them with hydrocortisone. Based on these observations, it is proposed to use blood content of tyrosine as a laboratory test for reasonable prescribing GC preparations and monitoring their dose. Blood tyrosine behavior in comparison with adrenocortical response is also considered in influenza.

Keywords: Safety of glucocorticoids; Hormonal provision of tissues; Blood tyrosine; Systemic lupus erythematosus; Congenital adrenal hyperplasia; Adrenalectomy in rats; Influenza

Introduction

Glucocorticoid (GC) preparations are the most powerful anti-inflammatory drugs also possessing immunosuppressive, anti-allergic and antitoxic properties, i.e., the range of their therapeutic activities is much wider than of all modern non-steroidal anti-inflammatory preparations. GC preparations are used in all fields of medicine and in veterinary. However, application of these preparations is associated with virtually inevitable adverse effects and the difficulty of their withdrawal. Although GC preparations were introduced in medicine for nearly 70 years ago [1,2] and influence many clinical and laboratory parameters, up to now there is no specific index of their action that would allow clinicians to assess the real need of a patient in these preparations and predict their efficiency.

It is very essential that the adverse effects of GC preparations and the difficulty of their withdrawal are caused not by their toxic action but are associated with the hormonal nature of these preparations. Glucocorticoid hormones generated in the adrenal cortex are hormones of total action and directly or indirectly control virtually all metabolic and physiological processes. Moreover, in healthy humans and animals production of GC hormones sharply increases in various stress situations. The adverse effects of GC therapy are caused either by excess of GC preparations, or by disturbance of normal negative feedback connection between the pituitary gland and adrenal cortex.

From the very birth of GC therapy, chemists and pharmacologists had a problem of separating the therapeutic efficiency of GC preparations from undesirable manifestations of their hormonal features, in particular, from their influence on the carbohydrate and mineral metabolism and suppression of the pituitary–adrenocortical system. This problem has been partially solved by addition to the natural hormone structure of some atoms and groups of atoms. The anti-inflammatory efficiency of such derivatives (prednisolone, methylprednisolone, dexamethasone, etc.) is stronger than that of their natural prototype; however, the adrenal cortex suppression also is deeper and more prolonged. The search and synthesis of new drugs based on these "classic" GC preparations is continued.

For clinicians the problem was more difficult. GC preparations were effective in various diseases, but not in all patients with the same disease. GC preparations influenced the general condition of patients and many clinical and laboratory parameters, but neither change could be definitely ascribed to action of the GC preparation given. Moreover, GC preparations could be helpful on the different background of a patient's own GC hormones and even at their increased content in blood.

These difficulties resulted in a "natural selection" of diseases which had to be treated with GC preparations. Schemes of their application have been developed empirically, and these schemes are reproduced in countless guidebooks and papers up to now without essential changes. Special protocols of GC therapy and the well-timed pharmaceutical prevention of the adverse effects allowed clinicians to decrease their frequency and gravity.

The medical approach for using GC preparations may be resumed as two commandments: 1) GC preparations must be given considering not the diagnosis but the general condition gravity; 2) The minimal effective dose of GC preparations must be prescribed.

But what is this "minimal effective dose"?

I would like to discuss an essentially new approach for determination of this "minimal effective dose". If problems of using GC

preparations are associated with their hormonal nature, it seems reasonable to use a manifestation of the regulatory action of GC hormones. The present paper shows that tyrosine content in blood can be considered as such a manifestation and be used as a representative index of tissue provision with GC hormones or preparations that would allow clinicians to predict the efficiency of GC therapy for a given patient and to realize the dose monitoring.

This idea was published by me in Russian in 1978 [3] based on observations on blood tyrosine behavior in GC-treated patients with SLE in comparison with specific features of dependence on GCs of tyrosine catabolism. The works testing the hypothesis on clinical and experimental models were published also in Russian, as well as the generalizing paper [4]. The main results of these works and the corresponding references were republished rather in detail in English much later [5,6]. Nevertheless, because safety of GC therapy is still urgent, it seems reasonable to attract attention to this problem and reproduce briefly the most important results of these works.

GC Preparations and Tyrosine Content in Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease of connective tissue grasping virtually all organ systems: joints, skin, kidneys, gastro-intestinal tract, lungs, cardiovascular system, central nervous system, blood system, etc. Multiple autoantibodies are found in blood of the patients, therefore, SLE is also considered a typical autoimmune disease.

Before appearance of GC preparations the life duration of 84% of patients with SLE was no more than 3 years, and GCs radically changed the fate of patients with this most severe collagenosis: Now 90% of patients live for no less than 10 years, and in some cases even the capacity for work can be retained. At present, GC preparations in SLE are used in combination with cytostatics, nonsteroidal anti-inflammatory drugs, etc., but in all schemes GCs remain basic preparations, especially on generalization of the process or on exacerbations. However, even in SLE GC preparations are efficient not in all patients, complications can be very severe, and to abolish them is impossible.

For the first time disorders in tyrosine metabolism in collagen diseases were found by Japanese physicians [7] in 1958, but later such disorders were found by different authors in other diseases.Our work was performed within three years in the Clinic of Therapy and Occupational Diseases, First Moscow Medical Institute. Eighty patients with SLE were observed during hospitalizations, some of them were hospitalized repeatedly.

Tyrosine content was determined spectrophotometrically [8] in blood samples taken for biochemical analysis in the morning on empty stomach. After the patients' discharge from the Clinic, the results of tyrosine measurements were compared with clinical and laboratory data recorded in the case histories. Special attention was paid to the regimen of using GC preparations as the main curative agent. The most interesting results of this "retrospective experiment" were as follows:

In 32 patients GC preparations were prescribed (or the daily dose was increased) because of exacerbations in the dose of 40-60 mg (calculated for prednisolone). The retrospective comparison of the case records written by clinicians as usually with tyrosine measurements revealed that 20 patients were given GCs on the significantly increased tyrosine content (49.1 ± 0.8 as compared to 16.2 ± 0.9 μg/ml in 16 healthy donors).

The clinical and laboratory parameters were significantly improved in 17 of 20 patients and in 13 of 17 this improvement was accompanied by a decrease in the blood tyrosine content, whereas in 4 of these 17 patients with a pronounced liver damage hypertyrosinemia remained. It was very interesting that the decrease in blood tyrosine to normal values outstripped the appearance of signs of Cushing's syndrome. In 12 patients GC preparations were given on the background of normal tyrosine content and were ineffective in 9, with a rapid appearance of "side effects" in 4 of them. A slight improvement was recorded in 3 patients of 12 that could be associated with other drugs (immunosuppressors, antibiotics, heparin, anti-allergic drugs, etc.) given concurrently.

Clinical steroid-dependence in some patients was characterized by a sharp increase in the tyrosine content on attempts to even slightly lower the dose of GCs; the most dramatic was the case of "withdrawal syndrome" at the forced withdrawal of GC preparations because of aseptic osteonecrosis of femoral bone heads–this withdrawal was accompanied by a sharp increase in blood tyrosine content along with a severe aggravation of symptoms (Figure 1).

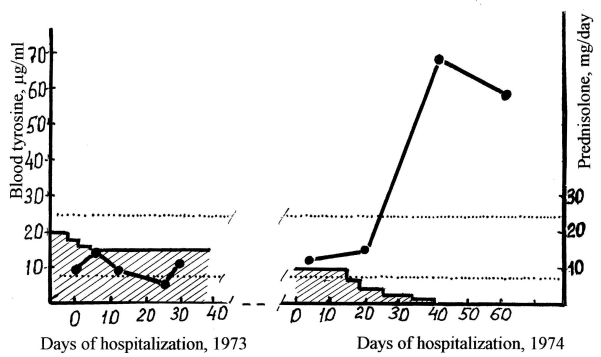

Figure 1: Tyrosine content in blood of a 22-year-old woman with sub-acute SLE and doses of GC preparations (hatched). "Withdrawal syndrome" at the forced abolishment of GC preparations because of aseptic osteonecrosis of femoral bone heads. Dotted lines show the normal limits of blood tyrosine.

Some Features of Tyrosine Catabolism

Tyrosine is produced in the body as a result of hydrolysis of food protein. About 30% of the resulting free tyrosine is used for synthesis of catecholamines, melanin, and thyroid hormones, a portion of it is used for renewal of tissue proteins. More than 60% of tyrosine enters the liver where it is oxidized. The first reaction in this major oxidation pathway of tyrosine is its transamination with alpha-ketoglutaric acid under the influence of the hepatic enzyme tyrosine aminotransferase (TAT) with production of p-oxyphenylpyruvic acid. The terminal products of this quantitatively major pathway of tyrosine oxidation are acetoacetic and fumaric acids (Figure 2).

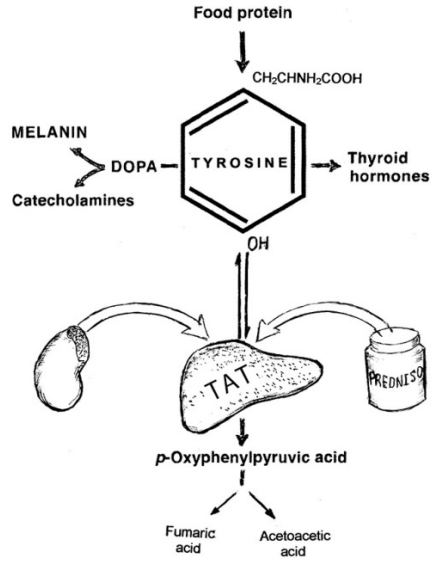

Figure 2: Major pathways of tyrosine conversions in the body (the initial stages).

TAT is an adaptive enzyme synthesized by the liver cells in response to entrance of its substrate tyrosine into the liver, but for the substrate induction of TAT GC hormones or preparations also must enter the liver [9]. The synthesis of hepatic TAT seems to be the most demonstrative example of the so-called gene-mediated action of GCs. It should be noted that the synthesis of TAT quantitatively depends on GCs and, therefore, is also used for testing the efficiency of GC preparations on cell cultures or animals. However, the hepatic enzyme TAT cannot be determined in blood, but the activity of TAT inevitably determines the content of non-transaminated free tyrosine.

Thus, free tyrosine content in blood virtually depends on two factors: the functional competence of the liver cells (i.e., their ability to synthesize TAT, as well as other hepatic enzymes) and the GC entering the liver. As a result, blood tyrosine content is virtually the same in healthy humans and does not depend on sex and age. Moreover, blood samples taken from the same 61 subjects four times during the period of 3.5 years displayed virtually the same value of tyrosine content [10,11]. We also observed the same value of blood tyrosine in the samples taken repeatedly from the same healthy donors, as well as in patients with SLE in remission.

Thus, it seems that in the absence of pronounced damage of the liver an increased tyrosine content should indicate an insufficient provision with GC hormones (or preparations). Remind that synthesis of GC hormones increases under stress conditions or in disease, therefore, an increased tyrosinemia in exacerbations of SLE could indicate a relative insufficiency of GC hormones (or preparations) because of an increased requirement for GGs in disease (the stress situation).

Then, the efficiency of GC preparations observed in SLE on the background of the increased tyrosine content could be due to their prescription at the relative hormonal insufficiency not corresponding to the increased requirements. In this case blood tyrosine content can serve an index of tissue provision with GCs, similarly to blood glucose content for insulin.

It was necessary to test this hypothesis.

Testing the Hypothesis on Clinical and Experimental Models

This hypothesis could be tested on patients with glucocorticoid insufficiency treated with GC preparations as substitutive therapy. To test the hypothesis, Prof. M.A. Zhukovsky proposed to perform the study on children with congenital adrenal hyperplasia, or adrenogenital syndrome (AGS). The main results of this work and also of the experiment were republished [5,6].

AGS, or hereditary virilizing adrenal dysfunction, is caused by a genetically determined deficiency of enzyme(s) responsible for biosynthesis of GC hormones in the adrenal cortex and the resulting shift to overproduction of androgens. The insufficient production of GC hormones induces an increased synthesis of adrenocorticotropic hormone (ACTH) in the pituitary gland that leads to an uninterrupted stimulation of the adrenal cortex causing a continuous surplus synthesis of androgens.

This syndrome is manifested by a characteristic clinical picture: An abnormal structure of external sex organs, an early arresting of growth because of premature ossification of tubular bones and closing the growth zones, etc. The affected girls have masculine features (pseudohermaphroditism) and boys display an early sexual maturation.

In AGS GC preparations must be prescribed as early as possible and be taken during the whole life. GC preparations break the vicious circle: They recompense the synthesis of GC hormones that prevents the surplus synthesis of ACTH and the overproduction of androgens.

The correct and strictly individualized dose of GC preparations allows endocrinologists to obtain the normal physical and sexual development of the affected children–up to normal pregnancy and childbirth in the girls. The dose must be corrected regularly based on the growth and sex maturation rate and character–but the same parameters may be considered as indices of the GC dose correspondence to real requirements of the organism.

Thus, AGS in children seems to be the only clinical situation when a physician can more or less objectively assess the adequacy of the substitutive use of GC preparations. In other cases of GC insufficiency, including adult patients with AGS, there is no objective parameter of the dose adequacy. The only orientation is the normal average content of GC hormones in healthy people and a patient's feeling but both these registration points are rather conventional. There is no laboratory parameter of tissue provision with GC hormones or preparations and of the patient's real need in them.

The study was performed in the Pediatric Department of the Institute of Experimental Endocrinology and Chemistry of Hormones, the USSR Academy of Medical Sciences. Tyrosine content was determined in blood samples taken on empty stomach from 38 children with AGS (33 girls and 5 boys, of 3-18 years old). The data were compared with the clinical picture. The results are presented in Figure 3.

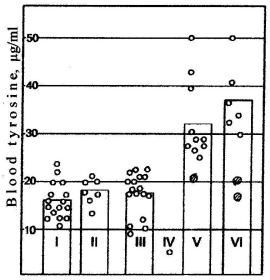

Figure 3: Tyrosine content in blood of healthy donors and of children with AGS. The columns present arithmetic means for the corresponding groups, the circles present individual values. I) Healthy adults; II) Healthy children; III) Patients with a complete clinical compensation; IV) An affected girl with overdosed GCs; V) Patients with incomplete compensation; VI) Untreated patients. The hatched circles in the columns V and VI indicate blood tyrosine contents in patients with melanodermia (compare with Figure 2).

Blood tyrosine values were the same in healthy adults and children. Tyrosine values were also normal in children with the complete clinical compensation (the column III). Note that blood tyrosine transiently increased during acute respiratory disease (stress and a resulting need in GCs–compare with recommendations to increase the dose of GC in occasional infections). Blood tyrosine values were increased in patients with incomplete compensation (the column V) and in untreated patients (the column VI). Normal tyrosine values were recorded in three children (the hatched circles in the V and VI columns) which appeared "sunburned". However, this "sunburn" disappeared upon prescribing GC preparations. Obviously, this "sunburn" was melanodermia, i.e., a part of free tyrosine took not the major pathway of the catabolism but was converted into the pigment melanin (compare with Figure 2). In a girl with signs of Cushing syndrome blood tyrosine was below the normal value. Thus, blood tyrosine seems to characterize an adequacy of the substitutive GC therapy in children with AGS.

Two untreated girls were prescribed GC preparations and repeated measurements of blood tyrosine allowed the pediatrician to choose an adequate dose within two weeks.

This hypothesis was also tested experimentally. Young Wistar rats were subjected to bilateral adrenalectomy. Changes in blood contents of corticosteroids and of tyrosine after adrenalectomy are presented in Figure 4a. According to the literature data [12], corticosteroid content became undeterminable on the 4th day after the operation and then began to increase presumably due to beginning of its synthesis in the brown fat tissue activated by an increased production of ACTH. After the operation, blood tyrosine content was increasing and reached the maximum on the 5th day at the most pronounced weight loss and death of 15-20% of animals in different series of the experiment. Thus, the blood tyrosine maximum corresponded to the minimum of own corticosteroids and to critical conditions of the animals after removal of the adrenals (considering the 6-h interval between the GC entrance into the liver and synthesis of TAT). In the survived rats tyrosine content began to decrease and reached the normal level by the 10th day due to synthesis of GC hormones in the brown fat tissue. The weight also began to increase. Obviously, in this experiment changes in the blood tyrosine content depended on production of endogenous hormones.

In another experiment intraperitoneal injections of hydrocortisone in the dose of 2 mg/kg per day were started on the 7th day after the adrenalectomy. This dose approximately corresponded to the daily supporting dose of 15 mg prednisolone in humans. Hydrocortisone was injected for 20 days, was withdrawn for 5 days, and then injected for three days in the dose of 5 mg/kg. Figure 4b shows that blood tyrosine behavior was "a mirror" of the entry of exogenous GCs.

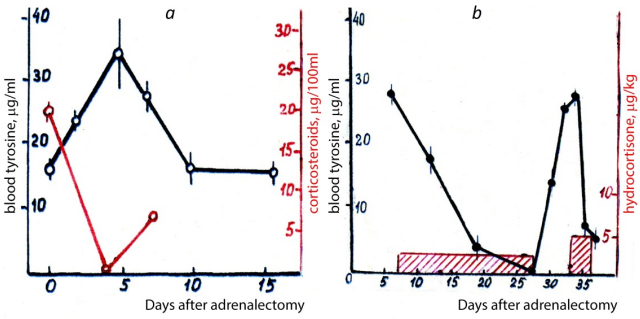

Figure 4: a) Changes in blood contents of corticosteroid hormones (red curve) and tyrosine (black curve) after bilateral adrenalectomy. b) Changes in blood content of tyrosine in adrenalectomized rats subjected to daily injections of hydrocortisone (2 mg/kg, hatched), upon withdrawal of them and on the recommencement of hydrocortisone injections in the dose of 5 mg/kg.

Thus, data obtained on the clinical and experimental models allow us to consider blood tyrosine content a representative index of tissue provision with GCs. The normal tyrosine content corresponded to the normal hormonal provision (due to natural hormones of preparations), whereas an elevated content of this amino acid evidenced an insufficiency of GCs.

Adrenocortical Response and Blood Tyrosine Behavior in Influenza

Although influenza is a disease when GC preparations are used rather seldom, concurrent measurements of blood tyrosine and 11-oxycorticosteroids during the disease seem interesting not only for clinicians but also for physiologists. This work published in Russian [13] was not reproduced later.

The work was performed during the influenza epidemic in Moscow in winter 1977-1978. Blood samples were taken from patients hospitalized because of their severe condition in one of Moscow usual hospitals. Contents of tyrosine and 11-oxycorticosteroids were determined in the same samples. According to the course of influenza, the patients were subdivided by the clinicians into two groups: 11

patients with a severe complicated course of the disease (the 1st group) and 22 patients with a relatively light course of the disease. Results of the measurements obtained for these two groups were processed separately.

In the 1st group blood tyrosine content was significantly increased in all patients and in nearly all samples during the hospitalization. In the 2nd group significantly increased values of blood tyrosine (higher than the doubled upper normal value (M+3δ)×2, i.e., 26.5×2=53 μg/ml) and only at the beginning of the disease were recorded in 9 patients.

We supposed that very high values of blood tyrosine can be a result not only of a probable hormonal insufficiency, but also of intoxication of the liver. Thus, we admitted that 11 patients with the severe course of influenza and these nine patients of the 2nd group with a relatively light course of the disease had virtually the same "intoxication start". However, the blood tyrosine behavior during the disease was essentially different: during the observation period tyrosine content remained high in all the "severe" patients and soon decreased nearly to normal level in the 2nd group patients (Figures 5a and 5b; black curves).

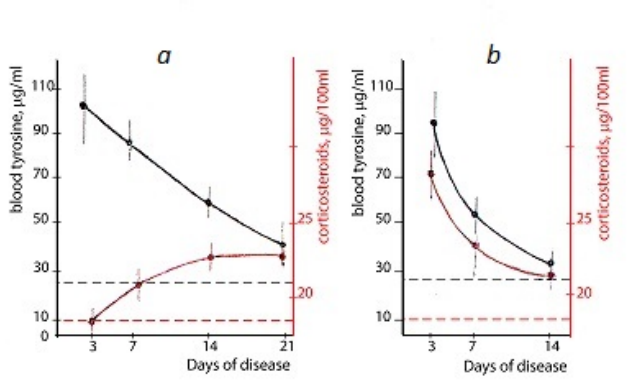

Figure 5: Changes in blood contents of tyrosine (black curves) and 11-oxycorticosteroids (red curves) in patients with influenza. Interrupted lines indicate upper normal limits of tyrosine (black) and corticosteroids (red). a) Patients with severe complicated course of the disease; b) Patients with relatively light course of the disease.

Changes in the content of 11-oxycorticosteroids characterized the adrenal cortex response during the disease (Figures 5a and 5b; red curves). This response was dramatically different. In the "severe" patients the level of hormones in the beginning of the disease was normal and began to increase later. In the "relatively light" patients the content of hormones at the first measurement was significantly increased and remained elevated during the acute period of the disease.

Thus, at the severe course of influenza there was no normal adrenocortical response, whereas the relatively light course of influenza was associated with an active and well-timed response of the adrenal cortex in the beginning of the disease.

Sometimes GC preparations are given in the first days at a severe toxic influenza, just as it is recommended in the first "Commandment": To give GCs considering not the diagnosis but the severity of the disease. Our data justified the prescription of GCs but certainly this does not exclude prescription of usual antiviral agents and antibiotics. In this case hormonal preparations have to support the patient's organism and more or less imitate the adrenocortical response required under stress (or an acute disease) conditions.

Discussion

The present paper seems to be rather old-fashioned on the background of many brilliant achievements of modern medicine due to methods of gene engineering and molecular genetics. Nevertheless, GC preparations are widely used as before and the problem of GC therapy safety exists as before–it is only preserved and considered an inevitable evil.

Blood tyrosine up to now seems to be the only rather specific and representative index of regulatory action of GCs and, as a consequence, of tissue provision with these hormones (or preparations). Therefore, it can be used as a clinical parameter for determination of a real need in GC therapy in various diseases and for monitoring the dose. In the review articles [5,6] some real cases of SLE were considered and the imaginary tyrosine-based monitoring of hormonal therapy. Tyrosine values at GC therapy in a patient with SLE were successfully used by Dr. I.A. Borisov (the case is re-described in [6]). Imagine the tyrosine-based monitoring in the case presented in this paper in Figure 1: In 1973 the patient was in remission, blood tyrosine was rather low–therefore, the prednisolone dose of 10 mg could be decreased carefully step-by-step (under the control of tyrosine determination).

The parallelism of the therapeutic effectiveness of GC preparations in SLE and their influence on the blood tyrosine content, i.e., the manifestation of the regulatory effect of GCs makes it reasonable to think that the powerful and many-sided therapeutic effect of GC preparations can be caused not by a unique combination of pharmacological properties but by their ability to act through usual pathways of these hormones and to normalize the multiplicity of processes depending on them. In particular, their anti-inflammatory and anti-allergic effects can be associated with triggering the natural protective mechanisms.

It seems that using GC preparations is reasonable and efficient as much as it can imitate a well-timed and full-value response of the adrenal cortex of a given human in disease which is a stress situation for the body. GC therapy has to compensate an insufficient adrenocortical response. It seems that GC preparations are unique and efficient just because they act in the role of their natural prototypes which under stress conditions act as a natural doping.

Blood tyrosine content can serve an index of tissue provision with GCs, similarly to blood glucose content for insulin, and be used as a laboratory parameter for determination the real need in GCs (except acute situations) and for prescribing and monitoring the dose of GC preparations in various diseases.

Conclusions

1. GC preparations can be favourable at relative insufficiency of own natural GC hormones.

2. Blood content of tyrosine shows the tissue provision with GC hormones or preparations.

3. Tyrosine determination in blood (considering the functional capability of the liver) can be used as a laboratory parameter on

prescribing GC preparations and monitoring their dose in various diseases and in insufficiency or some dysfunctions of the adrenal cortex.

4. Measurement of blood tyrosine allows realizing the second commandment: to give the minimal effective dose of GC.

5. Glucocorticoid preparations can be tamed, if blood tyrosine measurement will be introduced in practice of clinical laboratory.

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