THE EFFECT OF ANABOLIC STEROIDS ON THE COURSE OF UREMIA

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Before pathogenetically based treatment of acute renal failure can be given, new methods must be found for dealing with disturbances of water, salt, and protein metabolism in uremia.

The rational search for preparations influencing protein metabolism has been aided by Kochakian's investigations [3]. These yielded experimental verification of clinical observations showing that the male sex hormone – testosterone – possesses along with its specific androgenic action the property of stimulating weight and growth.

The results of further investigations showed that some derivatives of the male sex hormone have a less marked androgenic and a more marked anabolic action, and that this is associated with their chemical structure. This acted as a stimulus to the use of testosterone and its derivatives for the treatment of diseases accompanied by increased protein breakdown.

The therapeutic efficacy of testosterone in experimental uremia was first described by Selye [5] in 1940. He noted an increase in the mean survival period of nephrectomized mice treated with testosterone by 33% compared with the value of this index in control animals. Gerber and Cottier [2], however, who used anabolic steroids (derivatives of the three main compounds: testosterone, androstenediol, and 19-nortestosterone) to treat experimental uremia in rats, came to the conclusion that hormone therapy did not increase the mean survival period of the animals and had no effect on the changes in the blood urea concentration. Different results were obtained by Szold [6], although he used the same anabolic agents and rats were used as test objects. It may be that in this case the effect of treatment depended on the dose of the preparation.

In the present investigation an attempt was made to analyze the efficacy of anabolic hormones in uremia depending on the dose of the preparation, and to study the effect of Dianabol (methandienone) on the changes in the water, salt, and protein metabolism in uremia.

EXPERIMENTAL METHOD

Experiments were conducted on male chinchilla rabbits weighing from 2500 to 3000 g, kept in identical conditions and on the same diet. First, the optimal therapeutic dose of Dianabol was determined from the maximal increase in the mean survival period of the animals after bilateral nephrectomy. For this purpose 25 rabbits were divided into five groups: one control and four experimental. After a one-stage bilateral nephrectomy, the animals of the control group received no preparations whatever. After a similar operation the animals of the experimental groups received Dianabol daily by mouth in the form of an oily emulsion in a predetermined dose for each group (3, 5, 7, and 15 mg/kg body weight per animal respectively).

In this manner the optimal therapeutic dose of Dianabol was determined: it was 5-7 mg/kg body weight. The next part of the investigation was carried out on two groups of animals (25 rabbits in each group). In the animals of the first group the uremia was produced by one-stage bilateral nephrectomy, in the rabbits of group 2 by ligation of both ureters. The control group consisted of 20 rabbits which did not receive Dianabol during the course of development of the uremia.

The electrocardiogram (ECG) was recorded daily in the rabbits before and after the operation. In the course of the experiments the following determinations were made during the development of uremia: the blood nonprotein nitrogen (by Kjeldahl's method), the electrolytes in the blood plasma and myocardium (by flame photometry), and the changes in body weight.

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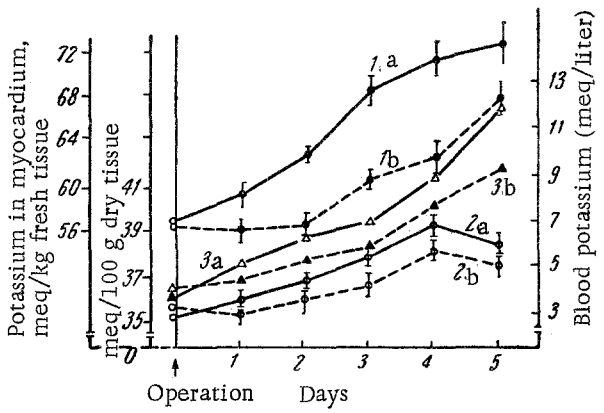

Fig. 1. Changes in concentration of potassium in the blood plasma and myocardium in the process of development of uremia in experiments without and with administration of Dianabol. 1a) Potassium concentration in fresh myocardial tissue in experiments without administration of Dianabol; 1b) with the administration of Dianabol; 2a) potassium concentration in dry myocardial tissue in experiments without the administration of Dianabol; 2b) with administration of Dianabol; 3a) potassium concentration in blood plasma in experiments without the administration Dianabol; 3b) with administration of Dianabol.

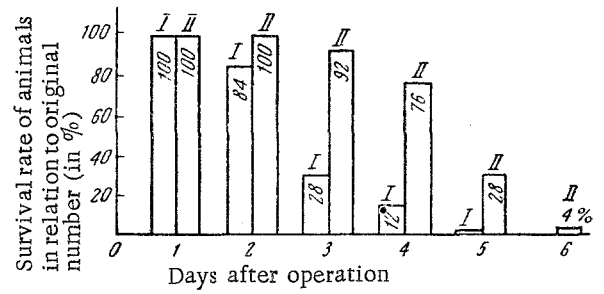

Fig. 3. Changes in mean survival period of animals in the process of development of uremia during administration of Dianabol. I) In experiments without administration of Dianabol; II) with administration of Dianabol.

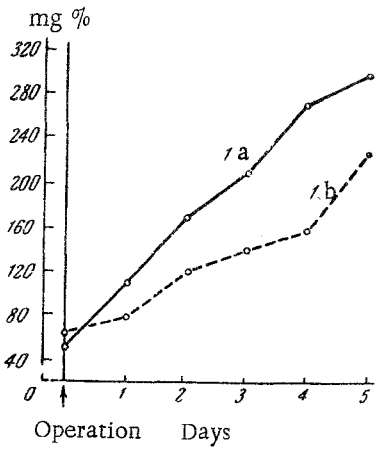

Fig. 2. Dynamics of changes in the nonprotein nitrogen concentration in the blood during the development of uremia. 1) In experiments without the administration of Dianabol; 1b) with the administration of Dianabol.

EXPERIMENTAL RESULTS

The efficacy of Dianabol depended on its dosage. In a dose of 3 mg/kg, for example, Dianabol had no effect on the mean survival period of the nephrectomized animals. A dose of 5-7 mg/kg was most effective, and an increase in the administered dose above this level gave a less satisfactory result, possibly on account of its action on the liver, with a disturbance of its antitoxic activity [1]. In addition, the effect of the anabolic agent on the adrenals cannot be excluded. Large doses of anabolic hormones give rise to excessive activation of the adrenal function. The adrenals in these circumstances secrete a vast amount of endogenous corticosteroids, the action of which exceeds the effect of the anabolic preparation, so that the combined effect becomes negative [4]. For this reason the dose of 5 mg/kg, determined as the optimal therapeutic level, was chosen for the subsequent experiments.

By giving its anabolic effect and accelerating the synthesis of protein, Dianabol lowered the movement of potassium from the cells into the blood and thus slowed the increase in the kaliemia observed in the course of development of uremia. Administration of Dianabol for 3 days before the operation was not reflected in the potassium concentration in the blood plasma. However, from the moment of develpment of uremia, the disturbance of the electrolyte balance in the experimental animals was less severe in its course than in the controls. The differences were statistically significant ($P < 0.02$).

A similar and significant difference was also observed in relation to the changes in the potassium content of the heart muscle (dry tissue). Although its concentration also rose when Dianabol was given, it did so much more slowly than in the rabbits of the control group. So far as differences in relation to the plasma sodium level are concerned, these were statistically significant only on the 5th day, when the sodium level in the blood plasma of the control animals showed a sharp decrease ($P < 0.001$).

The changes in the potassium content in the blood plasma and the myocardium are illustrated in Fig. 1, which clearly reveals the difference between the increase in potassium in the weighed sample of fresh and dried heart muscle of the experimental and control rabbits. The more marked increase in the potassium concentration in the weighed sample of fresh myocardial tissue of the control animals is attributable to dehydration of the heart muscle

cells, intensified during the development of experimental uremia. When Dianabol was used, no dehydration of the myocardium was observed in the process of development of uremia.

In the animals of the control groups of both series, after 24-48 h abnormalities were recorded on the ECG, consisting mainly of changes in the frequency of the nomotopic rhythm. In addition, at these times changes were observed in the voltage of the peaks of the ECG, together with a slight slowing of the heart rate within the limits of 16% of the original rate. In most experiments changes of different types appeared in the P wave in both the standard and the chest leads (in half the animals the P waves disappeared in leads 1-2). More constant changes were recorded in relation to the T wave of the ventricular complex of the ECG, which was increased (most commonly in two leads, mainly standard). This pattern of the electrocardiographic changes following administration of Dianabol was observed only on the 3rd-4th days after the operation.

More marked changes were observed in the ECG of the control animals on the 3rd-4th days of development of the uremia. These changes were mainly associated with a progressive disturbance of the conductivity of the heart and with the appearance of ectopic foci of excitation. On the 4th day after the operation in most animals the nomotopic rhythm was replaced by an atrioventricular and a polytopic ventricular rhythm. The heart rate slowed to 180 beats/min (normally 250-300 beats/min). Changes of various types were observed in the ventricular complex, in the form of the appearance of indentation, splitting, or a considerable widening of the QRS complex to 0.07.

The sharp fall in the voltage of the P waves in all leads, the deviation of the S-T segment from the isoelectric line, and the appearance of giant T wave reflected the severe damage to the myocardium in these conditions. In the animals receiving Dianabol, identical electrocardiographic changes were recorded only on the 5th-6th days.

It may be concluded from the results of these investigations that the fact that the electrocardiographic changes appeared later in the experimental animals than in the controls was due to the normalizing effect of the Dianabol on the potassium metabolism and also, possibly, on other types of electrolyte balance in the animals.

Administration of the anabolic hormone likewise influenced the intensity of nitrogenous catabolism, as reflected by the nonprotein nitrogen level in the blood. The nonprotein nitrogen level in the blood of the experimental animals rose much more slowly than in the controls, and its maximal concentration did not exceed 250 mg%, whereas in the animals not receiving Dianabol it reached 300 mg% or even higher (Fig. 2).

The severe anabolic effect thus manifested also influenced the changes in the body weight of the experimental animals. As a result of the action of Dianabol, the experimental rabbits gained weight by comparison with the controls.

In consequence of its normalizing influence of the fundamental aspects of the metabolic processes in the organism, Dianabol increased the mean survival period of the rabbits by 35-40% (Fig. 3).

It may thus be concluded that Dianabol has a distinct influence on the course of uremia, regardless of how it is produced (by bilateral nephrectomy or by bilateral ligation of the ureters).

SUMMARY

Uremia was induced in rabbits by bilateral nephrectomy or bilateral ligation of the ureters. This surgical procedure was followed by an increase in the potassium content of the blood plasma and myocardium, a disturbance of the atrioventricular and intraventricular conductivity of the heart. The animals died on the 3rd-4th day after the operation.

In the application of Dianabol the best therapeutic effect was produced by a dose of 5-7 mg/kg of body weight (daily). The life of the animals was thus prolonged by 35-40%. Changes in the electrolyte metabolism and ECG disturbances occurred later. This effect is attributed to the anabolic action of the hormone.

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