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IS THE CONCENTRATION OF POTASSIUM IN EJACULATE CAPABLE TO BE THE PREDICTOR OF CLINICAL EFFICACY OF TADALAFIL IN MEN WITH CHRONIC PROSTATITIS 3B?

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Abstract

Introduction. For objective assessment of the functional status of prostatic tissue, the «**KA**lium **P**arameter of **L**aboratory analysis, **E**valuating in **E**jaculate (**KAPLEE**)» was offered. KAPLEE is the concentration of K^+ ions, measuring with the help of potentiometry in 42 ml of water solution, which contains 1 ml of ejaculate, 39 ml of distilled water and 2 ml of special buffer solution. **The aim –** to check the hypothesis that the deviation of KAPLEE from the normal range towards reduction or towards increase is the predictor of less efficacy of tadalafil in patients with CP3B. **Materials and methods:** In trial 36 patients with the diagnosis of CP3B, who received tadalafil 5 mg once a day for 30 days as monotherapy, took part. During first stage each patient evaluated the efficacy of this pharmacotherapy in his case; it varied from 1 point (absolute non-efficacy) to 5 points (absolute efficacy). Then each patient ejaculated into container, and the concentration of KAPLEE was measured. Thus, the data of each patient were placed in two-axial system of coordinates: axis of abscisses was the concentration of KAPLEE, axis of ordinates was the mark of efficacy. Then the cluster analysis of these data was made. **Results and conclusion.** The concentration of kalium in ejaculate is the predictor of tadalafil efficacy in men with CP3B. Normal values of KAPLEE are associated with high efficacy of tadalafil, its deviations are predictors of low efficacy.

Keywords: *tadalafil; prostatitis; chronic pelvic pain syndrome; pharmacotherapy; ejaculate; KAPLEE nomogram.*

Introduction

The problems of pharmacotherapy of chronic prostatitis 3B (CP3B) have not lost their relevance for many decades [1, 2]. The complexity and multifactorial nature of the etiology and pathogenesis, the scarcity of detected pathological changes make researchers expand the diagnostics through procedures that go beyond "traditional" methods. This highlights the fact that CP3B is an interdisciplinary problem [3]. In recent years, the volume of scientific data has been growing, convincingly testifying to the important role of ischemic processes in the pathogenesis of CP3B [4, 5]. Therefore, there is a need to find those parameters that could become objective markers of inflammatory and/or ischemic damage to the prostate. There are no unambiguous physical and chemical laboratory tests and indicators in the available literature.

The ideal method would be one that would allow **to assess the functional status of prostate cells noninvasively** and thus predict the effectiveness or inefficiency of pharmacotherapy before it begins. As, for example, electrocardiography (ECG) in cardiology.

This need is very relevant when prescribing tadalafil to patients with lower urinary tract symptoms (LUTS) associated with CP3B. Today, the mechanism of action of tadalafil on prostate tissue is not clearly understood [6]. The results of prescribing tadalafil to patients with CP3B are contradictory [3, 7, 8].

Comparison of the myocardium and the "second heart of a man" – the prostate – is not included in the objectives of this article. We only note that the ECG allows physicians to objectively and firmly distinguish between many clinically similar conditions caused by ischemia and inflammation, and to evaluate the functional status of myocardial **cells**; while the size and volume of the organ are not so important. With mild ischemia, which manifests itself only during exercise, the prognosis is favorable. And in patients with total transmural post-infarction cardiosclerosis the prognosis is poor [9, 10].

The classic of medicine is the thesis that ECG is based on the registration of transfer processes of potassium, sodium and chlorine ions inside and outside myocardial cells [9, 10]. In other words, an ECG is a non-invasive assessment of the ionic composition of the intra- and extracellular fluid in the myocardium. In this case, the potassium ion (K^+) plays a leading role [9, 10].

A healthy person with a body weight of about 70 kg contains 3150 mmol of potassium. Only 50-60 mmol of potassium is located in the extracellular space, the rest of it is distributed in the intracellular space. That is why a very narrow normal range of serum potassium concentration – from 3.5 mmol/L to 5.0 mmol/L – is traditionally considered one of the most important constants of water-electrolyte balance [11].

An objective registration of deviations from this normal range underlies electrocardiography (ECG), the identification of metabolic disorders in therapeutic and surgical practice, and resuscitation [9-11].

That's why we showed interest in studying the concentration of potassium in ejaculate. At the planning stage of the presented research, our hypotheses were based on the following logic. The ejaculate is a mixture of spermatozoa and prostate secretion, and prostate secretion is much more prevalent in it. The secretion of the prostate is produced by the cells of the prostate and is, in fact, an "extracellular fluid" in relation to the cells of the prostate. Potassium is a classic intracellular ion, which concentration is high inside of cells and is low outside of cells. By analogy with the myocardium, if prostate cells are in an unsatisfactory functional status, then, more precisely, their enzyme systems are not able to maintain adequate potassium concentrations inside and outside the cells. Therefore, it should be expected that the concentration of potassium outside the cells, and therefore in the secretion of the prostate and in the ejaculate will deviate from the norm [12].

We were the first to propose the use of the «Potassium parameter of laboratory analysis evaluating in ejaculate (**KA**lium **P**arameter of **L**aboratory analysis, **E**valuating in **E**jaculate – **KAPLEE**)» [12]. The most suitable and comfortable variant of pronunciation is «'kɑ:pli». There is a play on words here. Traditionally, In Russian language the Latin word «***ka****lium*» – «***ка****лий*» – is used to designate «*potassium*». The Russian word «***'kɑ:****pli*» –

«***ка**плu*» – «***КА**PLEE*» means «*the drops*». So, KAPLEE are «the drops of ejaculate» [12].

KAPLEE is the concentration of potassium ion (K^+), measured by the potentiometric method in 42 milliliters (ml) of water solution that contains 1 ml of ejaculate, 39 ml of distilled water and 2 ml of special buffer solution [12].

The discussed KAPLEE technique is based on the potentiometric measurement of potassium ions (K^+) in water, standardized in Russia, based on the use of the dependence of the electric signal (potential) of a special sensor, called a measuring electrode, on the composition of the analyzed solution. The measurements are carried out using two electrodes: a measuring potassium selective electrode and a reference electrode (electrode pair (EP)). This EP is connected to the "EXPERT-001" device (manufacturer – "ECONIX", Russia) and immersed in a plastic disposable container with a volume of 60 ml, in which the **studied solution with a volume of 42 ml is preliminarily prepared.** The sequential keystrokes are performed on the device and the molar concentration of potassium ion is measured in micromoles per liter (microMol/L) [12].

Based on our studies, we created the KAPLEE nomogram, or Lobkarev nomogram (Figure 1) [12].

See Figure 1.

The logic of the nomogram is simple. The KAPLEE parameter obeys the law of normal distribution. The arithmetic average $\overline{x}$ of the KAPLEE parameter is 770 microMol/L and is equal to the mode and to the median. Accordingly, the interval from $\overline{x} - 3\sigma$ to $\overline{x} + 3\sigma$ is from 623 to 917 micromol/L. This range of values, i.e. from 623 microMol/L to 917 microMol/L, was proposed to be considered the normal KAPLEE range [12]. It was proposed to measure the deviation from the arithmetic average $\overline{x}$ in standard deviations (σ), which is reflected in the KAPLEE nomogram (Figure 1) [12].

Objective: Using the method of cluster analysis, to check the hypothesis that the deviation of KAPLEE from the normal range towards reduction or towards increase is the predictor of less efficacy of tadalafil in patients with LUTS associated with CP3B.

Methods

The study involved 36 patients with a diagnosis of CP3B, who had been taking tadalafil 5 mg per day as monotherapy for the first time in order to correct LUTS before that. The work was carried out in two stages.

At the first stage, according to the principle of "case-control", each patient answered the following question: "Dear patient! You have taken tadalafil 5 mg per day for one month to attenuate complaints related to your illness. How can you characterize the efficacy of this medicine in your case?" This score ranged from 1 point (absolute inefficacy) to 5 points (absolute efficacy).

Then the patient ejaculated into a standard sterile, disposable container.

Then we determined the concentration of KAPLEE. It was graphically represented on the KAPLEE nomogram.

In order to optimize the size of the article, we show the results of five men (man 1 (M1), man 2 (M2), etc.) on one nomogram and give a brief description of the clinical picture of each man (Figure 2).

See Figure 2.

M 1 – a man without complaints. KAPLEE = 750 microMol/L.

M 2 – a man who periodically notes moderate LUTS associated with chronic prostatitis (approximately, 17-20 points on the scale "System for the comprehensive assessment of chronic prostatitis (CAS-XII) [1]). KAPLEE = 845 microMol/L. LUTS in this patient are successfully stopped by tadalafil 5 mg/day.

M 3 – a patient suffering from chronic prostatitis for many years. The KAPLEE value is 475 microMol/L. With almost no effect, he sequentially took α_1-blockers, tadalafil and many other drugs. He notes a weak effect of prostate massage.

M 4 – a patient suffering from chronic prostatitis 3B/chronic pelvic pain syndrome for many years. The KAPLEE value is 425 microMol/L. A small effect is noted only from prostate massage.

M 5 – a patient suffering from chronic prostatitis for many years. The KAPLEE value is 990 microMol/L. He notes a minor effect of taking tadalafil.

M 6 – a patient suffering from chronic prostatitis for many years. The KAPLEE value is 1110 microMol/L. He does not note the effect of taking tadalafil.

The second stage of the work was an iterative cluster analysis of the data obtained during the first stage. The k-means algorithm was used. In accordance with it, based on the purpose of our study, the hypothesis of the existence of three clusters was tested:

1. Patients who underwent treatment of CP3B (tadalafil 5 mg/day), with a **normal** value of the KAPLEE parameter (from 623 to 917 microMol/L). They noted the highest efficacy of tadalafil **(9 men)**.

2. Patients who underwent treatment of CP3B (tadalafil 5 mg/day), with a **low** value of the KAPLEE parameter (lower than 623 microMol/L). They evaluated the efficacy of tadalafil as low or zero **(13 men)**.

3. Patients who underwent treatment of CP3B (tadalafil 5 mg/day), with a **high** value of the KAPLEE parameter (higher than 917 microMol/L). They evaluated the efficacy of tadalafil as low or zero **(14 men)**.

For this, all patients were distributed in the appropriate cluster depending on the KAPLEE value.

Thus, each patient's result was localized in biaxial coordinate system (in cluster analysis it is called a "dispersion diagram of variables X and Y"):

1) the abscissa axis (X) is the KAPLEE value (microMol/L);

2) the ordinate axis (Y) is the patient's assessment of the efficacy of the course of taking tadalafil 5 mg/day, which ranged from 1 point (absolute inefficacy) to 5 points (absolute efficacy) (Figure 3).

See Figure 3.

Next, the hypothesis of the "isolated" existence of three different clusters was tested. The criterion for determining the similarity and difference of the clusters was the distance between the points on the scattering diagram.

According to the principle of the k-means method, in the case of good clustering, very different means should be obtained for all measurements, or at least most of them. The statistical significance of these differences was checked using the non-parametric Dunn test according to the formula:

$$Q = \frac{\overline{R_A} - \overline{R_B}}{\sqrt{\frac{N\,(N+1)}{12}\left(\frac{1}{n_A} + \frac{1}{n_B}\right)}},$$

where $\overline{R_A}$ and $\overline{R_B}$ are the average ranks of the two compared samples, n_A and n_B are their volumes, and N is the total volume of all compared samples [13].

Results

Graphically, the results of an iterative cluster analysis of the obtained data are shown in Figure 3.

See Figure 3.

As we can see, the men who make up the 2nd cluster (they are the men with normal KAPLEE parameter values) are significantly more satisfied with the course of taking tadalafil than the representatives of the first and third clusters.

We used the Dunn test to evaluate the statistical significance of these differences.

The difference between cluster 1 and cluster 2:

$$Q = \frac{32 - 13.6}{\sqrt{\frac{36\,(36+1)}{12}\left(\frac{1}{9} + \frac{1}{13}\right)}} = 4.$$

The obtained value Q = 4 exceeds the critical Q = 2.936, therefore, the difference is statistically significant ($p < 0.01$) [13].

The difference between cluster 2 and cluster 3:

$$Q = \frac{32 - 14.4}{\sqrt{\frac{36\,(36+1)}{12}\left(\frac{1}{14} + \frac{1}{9}\right)}} = 3.9.$$

The obtained value Q = 3.9 also exceeds the critical Q = 2.936, so the difference is statistically significant ($p < 0.01$) [13].

The difference between cluster 1 and cluster 3:

$$Q = \frac{14.4 - 13.6}{\sqrt{\frac{36\,(36+1)}{12}\left(\frac{1}{14} + \frac{1}{13}\right)}} = 0.2.$$

The obtained Q value is lower than the critical Q= 2.394, so there is no difference between cluster 1 and cluster 3 ($p > 0.05$) [13].

Discussion

The question that became the title of this article, in our opinion, is organically integrated with the problems of modern urology. During professional meetings, much attention is paid to the study of the quality of life of patients with CP3B, individualization of pharmacotherapy in each case.

The subjective factors of the doctor's choice of the medical drug (MD), the patient's preferences, the patient's expectations of taking MD, of course, play an important role in the treatment of intimate voiding disorders, discomfort in the perineum, combined with sexual problems. This is a huge difficulty for the doctor. In this subjectivity we are forced to work daily.

What is the relationship of the doctor and the patient who takes tadalafil with a good result? What does the patient think and say? "A doctor is a wonderful person, a true professional, he cures me successfully with just one tablet per day. I will continue to take the same medicine. There's no reason in going to the doctors now". Soon he will forget his doctor's name. He will forget the doctor's recommendations.

In other words, in this case the doctor and the patient, without much effort, won a brilliant pharmacological victory over the disease.

And the patient, who evaluates the efficacy of tadalafil as low or zero (because the desired effect was not achieved), will look at life and at the doctor in a completely different way. "The doctor – this scumbag in a white coat – once again robbed me, received money from me and sent me to the pharmacy for useless tadalafil. A pharmacy employee, of course, in collusion with a doctor, sold an ineffective medicine…" Such people, as a rule, remember well all their doctors. They then ask for surgery because "the pills still do not help". They force the healthcare system to incur large expenses for their treatment and are forced to spend a lot of money themselves.

There is a reason to believe that there is a material, materialistic factor that fundamentally influences the clinical efficacy of tadalafil in CP3B [2, 3, 12].

A big scientific problem that needs to be solved, we consider insufficient attention to the functional status of the prostate tissue and cells at the time of the start of taking a particular drug.

The results of our cluster analysis show that the administration of tadalafil to patients with CP3B is the most effective in cases where the concentration of KAPLEE is within normal values, i.e. from 623 to 917 microMol/L ($p < 0.05$). The deviation of KAPLEE from the normal range towards reduction or towards increase is the predictor of less efficacy of tadalafil in patients with LUTS associated with CP3B (Figure 3).

This unexplored phenomenon, first identified by us, has no explanation today. We assume that there is an individualized degree of damage of prostatic cells. In patients who have KAPLEE value in the normal range, there is no cellular damage to the prostate (or it is expressed weakly), therefore, the administration of tadalafil leads to a significant improvement in the patients' quality of life. In the case when the concentration of KAPLEE deviates from the normal range, the patient has metabolic disorders of the prostate cells, serious changes in homeostasis of prostate, damage to energy processes of various etiologies. Therefore, the administration of tadalafil does not always achieve the desired result in such "difficult" patients.

In recent years, much attention has been paid to the problem of individualization, personalization of pharmacotherapy, but according to standards. In our opinion, the study of the concentration of potassium in ejaculate can allow us to combine these two opposite trends, to predict the efficacy of the drug administration even before it starts. And, thereby, to facilitate significantly the work of the doctor with the patients with a diagnosis of "CP3B".

Conclusion

The normal KAPLEE value is a predictor of the high efficacy of tadalafil in patients with CP3B. The deviation of KAPLEE from the normal range towards reduction or towards increase is the predictor of less efficacy of tadalafil in patients with LUTS associated with CP3B. Thus, we can affirmatively answer the question that has become the title of this article. The concentration of potassium in the ejaculate can be a predictor of the clinical efficacy of tadalafil in CP3B. This subject requires further comprehensive study.

Authors declare the lack of the possible conflicts of interests

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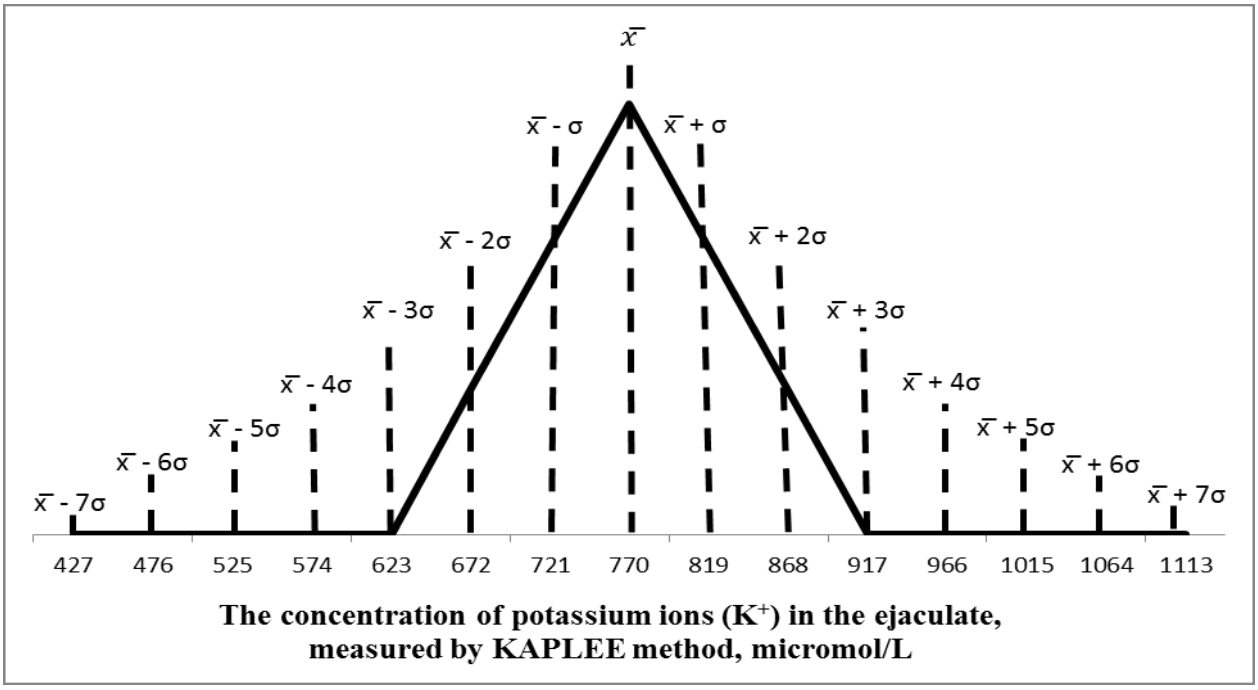

Figure 1. The KAPLEE nomogram.

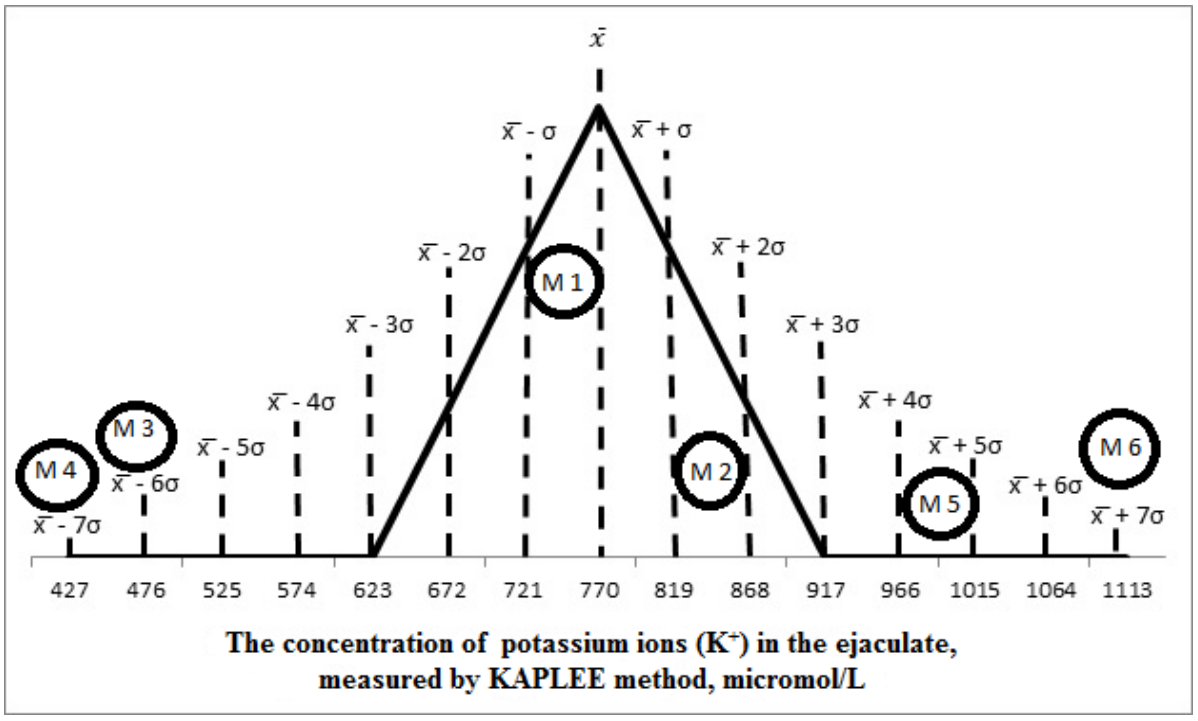

Figure 2. The examples of clinical using of KAPLEE nomogram.

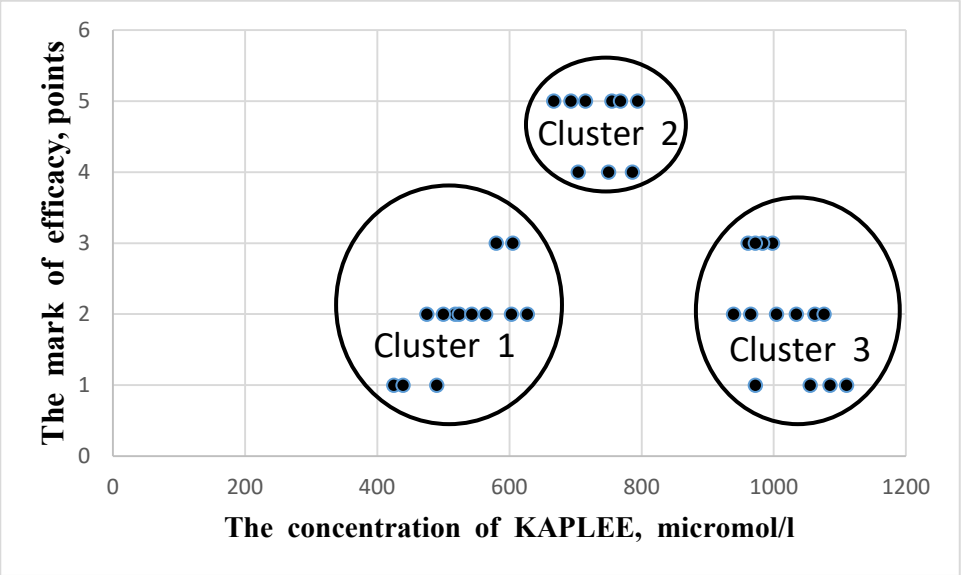

Figure 3. The results of the cluster analysis. It is easy to distinguish three groups of associated objects – three clusters.