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Features of the Pharmacokinetics of Antipyrine in Patients with Uterine Myoma

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Annotation: Uterine myoma is one of the most common malignant tumor diseases of female genital organs. The aim of this study was to investigate the pharmacokinetic parameters of antipyrine in patients with uterine myoma. The study included 33 patients aged between 37 and 57 years, with an average age of 43.8±0.6 years old. Among women of this group, 56.3% had gastrointestinal diseases and 69% had respiratory system diseases. We analyzed the most significant changes in antipyrine pharmacokinetics in the patients of the third group. Among them, the T1/2 and AUC indicators increased by 212.2% and 17%, respectively, while the MCR and Kel indicators decreased by 57.4% and 68.1%, respectively. According to the results of antipyrine test, the functional activity of MOS is clearly reduced in women with uterine fibroids. The decrease of the activity of MOS in patients with uterine fibroids also worsens in patients with hepato-biliary and respiratory system's pathologies on the background of anemia.

Keywords: myoma, pharmacokinetics, antipyrine, uterine fibroid.

Introduction. It has been established that uterine myoma is accompanied by distinct violations of antipyrine pharmacokinetic parameters, especially serious in women with concomitant diseases of hepatobiliary and respiratory systems against the background of anemia. Therefore, it was corroborated a relation between a concomitant pathology and an expression MOS functional activity disturbance that should be taken into consideration for choice of treatment.

Uterine myoma is one of the most common malignant tumor diseases of female genital organs [1], [2], [3], [4]. This pathology significantly disrupts childbearing, and causes anemia (following loss of fertility) and the development of genital malignant tumors. Currently, there is not enough information to fully describe all stages of the pathogenesis of the disease. However, the leading role in its development is attributed to hyperestrogenemia and disruption of hormone-receptor relations [5], [6], because estrogens are traditionally considered the main promoter of neoplastic growth of the endometrium and myometrium. In this case, uterine fibroids are accompanied by an increase in the amount of estradiol and progesterone in the regional blood stream. These conditions is not only an increase in hormone synthesis and storage, but also a result of their biotransformation and removal from the body. It is known that the liver provides important aspects of the biodynamics of sex hormones, that is, in metabolism, production of special transport proteins that bind hormones in blood plasma; It plays a key role in the synthesis of cholesterol and its absorption in the composition of lipoproteins (for biosynthesis of androgens, estrogens and progestin's) by the gonads. Mono-oxygenaseenzymesystem (MOS) of hepatocytes plays a central role in these processes. However, Additionally, studying chemical hemostasis may help prevent or treat other gynecological conditions, such as endometriosis or fibroids. By understanding how these conditions are related to disruptions in blood clotting, researchers may be able to develop new therapies that target these underlying mechanisms. In clinical practice antipyrine test widely used to determine MOS functional activity.

The aim of this study was to investigate the pharmacokinetic parameters of antipyrine in patients with uterine myoma.

Material and methods. The study included 33 patients aged between 35 and 57 years, with an average age of 43.8±0.6 years old. The duration of the disease from first diagnosis ranged from a few months to six years. In five patients, myoma size did not exceed 6-8 weeks of pregnancy, just at some patient it

was 9-10 weeks and while in three patients, it was found at 10 weeks (9.1%). Most of the patients examined had a body weight slightly above the physiological norm (first-degree obesity). The menstrual cycle had an average of 28-30 days, and menstruation lasted for five or more days, often accompanied by heavy bleeding. Reproductive activity was preserved in all cases, but infertility was found in the anamnesis of three women: primary infertility in two (three years and five years) and secondary infertility in one woman (more than six years). In the past medical history, there were 8 patients with chronic adnexitis, 8 patients with erosion of the cervix, 2 patients with colitis, 2 patients with ovarian cyst, 3 patients with chronic end metritis, 2 patients with premenstrual syndrome. The ratio of birth and childbirth was 1:1.5.

The diagnosis was verified on the basis of a bimanual gynecological examination, ultrasound, clinical and laboratory tests, etc. The combinations of extragenital and genetic diseases were in more than 2/3 observed patients.

The functional activity of liver MOS was assessed using an antipyrine test [7]. Freshly prepared antipyrine solution was given orally at the dose of 10 mg/kg in the morning and after 3, 12 and 24 hours and quantity of antipyrine in blood was determined by the spectrophotometric method. The principle of the method is based on the fact that antipyrine in the presence of sulfuric acid with sodium nitrite forms 4 - nitrosoantipyrine, the optical density of it measured on a spectrophotometer with wavelength 350 nm. After that, the elimination half-life ($t_{1/2}$), the volume of apparent distribution (aVd), the metabolic clearance of the drug (MCR), the rate of elimination constant (Kel) and the area under the pharmacokinetic curve (AUC) were calculated. The control group consisted 6 healthy volunteer women in reproductive age.

The obtained data were processed by the method of variation statistics using the paired Student's test and one-way analysis of variance using the standard software package BIOSTAT 2009 with an assessment of the significance of indicators (Mean ± Std error). Differences in the compared groups were considered significant at a significance level of 95% $p < 0.05$.

Results and discussion. In the control group (healthy), the half-life of antipyrine was 9.0 ± 0.86 hours. This value was close to the literature data - 10.1 ± 0.27, 9.75 ± 0.62 [8] and 9. 23±0.11 [9]. In the group of patients with uterine myoma, this indicator was high by 107.8%. As can be seen from the data in Table 1, such an increase in the half-life of antipyrine was accompanied by a two-fold decrease in the value of the elimination constant and the intensity of the metabolic clearance of the drug by 43.1%, which led to an increase in the value of the integral indicator of the pharmacokinetics of antipyrine - the area under the pharmacokinetic curve by 88.6%.

Against this background, the volume of the apparent distribution of the drug did not undergo statistically significant changes. The revealed disturbances of the pharmacokinetics of antipyrine clearly indicate the inhibition of the functional activity of MOS in patients with uterine myoma, since antipyrine is quickly and completely absorbed from the digestive tract, evenly distributed throughout the body fluid, slightly binds to tissue and blood plasma proteins, and is completely metabolized by cytochrome P-450 isoenzymes [10]. Therefore, the antipyrine test has found wide acceptance in clinical practice as the most reliable, simple, and informative test in assessing the functional activity of MOS [7], [8], [9]. With a low activity of MOS, the oxidation (biotransformation) of endogenous compounds and xenobiotics slows down sharply and their concentration in body fluids, including blood, increases, which leads to an increase in their toxic or fibiological effect. The results of this study suggest that hyperestrogenemia observed in patients with uterine myoma may be not only their hyperproduction, but also the result of a slowdown in their elimination, since inactivation and conjugation of estrogens occurs in the liver by its monooxygenase system [11], [12]. A low activity of the MOS causes increase in the free fractions of the hormone, which probably have a more pronounced ability to stimulate hyperplastic processes in the target organs. In the literature there are single works (information) indicating the suppression of liver function in uterine fibroids. At the same time, it is noted that the development of the disease was preceded by chronic diseases of the gastrointestinal tract in every second patient with uterine myoma, and in every 3rd - pathology of the heptobiliary system

[13]. It should be noted that conservative treatment with synthetic progestins worsened the functional state of the liver [14]. Based on this and taking into account the invaluable role of the liver in metabolism, when managing patients with hyperplastic diseases of the uterus, it is recommended to pay special attention to the correction of concomitant metabolic disorders due to extragenital pathology [13] and to use drugs that improve the functions of the gastrointestinal tract [15].

Analysis of the variation series of the results of studying the pharmacokinetics of antipyrine in patients with uterine myoma revealed their heterogeneity, which made it possible to distribute them according to the severity into 3 groups according to the severity of disturbances of the pharmacokinetic parameters of antipyrine. As can be seen from the data in Table 1, in 13 patients (Group 1), the degree of disturbances of the pharmacokinetic parameters of antipyrine was moderate: there was an increase in $t_{1/2}$ by 44.4% and AUC - by 43.5%, with a decrease in MCR by 30.1% and K_{el} – by 32.1%. Among women 81% of patients in this group had grade 1 anemia, 46.2% of patients had pathology of the respiratory organs, 54% of patients had diseases of the gastrointestinal tract, and 30.8% of patients had diseases of the hepatobiliary system. At the same time, many patients had a combination of two or more extragenital pathologies.

We found a stronger disturbance of antipyrine pharmacokinetic parameters in patients of 2nd group, compared to patients 1st group. In group 2 patients, $t_{1/2}$ and AUC indicators increased by 124.4% and 98.8%, and indicators of VCR and Kel were low by 48.5% and 56.9% respectively. Among women of this group, 37,5% had gastrointestinal diseases, 56.3% had diseases of hepato-biliar system and 69% had respiratory system diseases. The most significant changes in antipyrine pharmacokinetics were in the patients of the third group. Among them, the $T_{1/2}$ and AUC indicators increased by 212.2% and 174%, respectively, while the MCR and K_{el} indicators decreased by 57.4% and 68.1%, respectively. Half of the patients had 2-3 degrees of anemia, all had hepato-biliary system diseases, 75% had respiratory system diseases, and 25% had gastrointestinal tract diseases. It is evident that there was a greater disruption in the pharmacokinetics of antipyrine in groups with extragenital diseases such as respiratory and hepatobiliary system pathologies, as well as anemia.

Through this analysis, a comprehensive description of the systemic damage to the female body in benign hyperplastic diseases of the uterus can be obtained. The dystrophic changes in myoma that occur due to microcirculation disturbances and increased tissue hypoxia are not considered to be complications of myoma or secondary changes but rather links of one process [16], [17].

Considering this, hypoxia developed as a result of microcirculation disturbance can be considered a factor inducing local myometrial hypertrophy [18]. These two factors are an important link in liver and MOS damage. Besides, respiratory system diseases and anemias can

Table 1. The parameters of antipyrine in patients with uterine myoma

Groups	$t_{1/2}$, hour	aVd, ml/kg	MCR,ml×kg /hour	K_{el}, hour^{-1}	AUC,mkg/ml× hour^{-1}
Healthy	9,0±0,86	536,9±75,8	40,8±2,59	0,08066±0,00772	250,8±17,7
Patients	18,7±1,00	592,9±25,3	23,2±1,19	0,04038±0,0022	473,1±35,6
1st group	13,0±0,56*	534,5±34,5	28,6±1,49*	0,05478±0,00265*	359,9±19,2*
2ndgroup	20,2±0,57*	604,7±27,0	21,0±1,02*	0,03475±0,00095*	498,7±25,9*
3rdgroup	28,1±1,56*	682,0±120,0	17,4±3,72*	0,02491±0,00140*	687,1±135,1*

Note: * —statistical difference between healthy group P<0.05;

cause a sharp decline in the body's oxygen saturation, leading to tissue hypoxia.Liver pathology can also lead to a sharp decrease in hormone metabolism against the background of MOS damage. This can enhance their effect on target organs and is probably an important factor in tumor development. It is important to consider the sensitivity of liver MOS in patients with respiratory and cardiovascular diseases that lead to organ and tissue hypoxia, anemia, and a clear disturbance in antipyrine pharmacokinetics [10], [19]. These findings suggest a possible correlation between hepatobiliary system pathology and MOS functional activity in women with uterine fibroids. A decrease in MOS

activity may reduce the liver's ability to detoxify, leading to endogenous intoxication syndrome that can negatively impact the disease's course and outcome. Therefore, using drugs that restore MOS functional activity could improve the effectiveness of conservative treatment for uterine fibroids. This approach addresses key pathogenic factors associated with the disease while correcting metabolic disorders and endogenous intoxication, ultimately promoting regression of the pathological process.

Conclusion

1. According to the results of antipyrine test, the functional activity of MOS is clearly reduced in women with uterine fibroids.
2. The decrease of the activity of MOS in patients with uterine fibroids also worsensin patients with hepato-biliary and respiratory system’s pathologies on the background of anemia.
3. Timely evaluation of MOS system is very necessary in choosing the conservative treatment plan. Antipyrine test can be used directly in this case.

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