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DETERMINATION OF THE PHARMACOKINETIC PARAMETERS OF ISONIAZID USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Tuberculosis is one of the most common diseases worldwide. The pharmacokinetics of isoniazid are unpredictable and vary widely in patients taking standard doses of the drug. In order to find the optimal dose of isoniazid, therapeutic drug monitoring should be carried out, determining the equilibrium concentration of the drug in blood plasma by HPLC.

The aim of this study is to determine the concentration of isoniazid in blood plasma by HPLC and calculate the pharmacokinetic parameters of isoniazid in patients with newly diagnosed pulmonary tuberculosis in the Republic of Sakha (Yakutia).

We determined the equilibrium concentration of isoniazid in blood plasma by high-performance liquid chromatography in 33 patients with pulmonary tuberculosis, using a Milichrome a-02 device manufactured by CI “Econova" LLC (Russia) using a ProntoSIL 120-3-C18 AQ column.

The results obtained confirm the high individual variability of pharmacokinetic parameters: the maximum equilibrium concentration of the drug, the area under the pharmacokinetic curve, the average stationary concentration of the drug, the degree of fluctuation in the concentration of isoniazid in the blood plasma of patients with tuberculosis. Individual differences in the pharmacokinetic parameters of isoniazid indicate the need for therapeutic drug monitoring when prescribing isoniazid.

Keywords: tuberculosis; pharmacokinetics, equilibrium concentration, isoniazid, high-performance liquid chromatography.

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Introduction. Tuberculosis is common in all countries and age groups. According to reports provided by the World Health Organization, 10 million people fell ill with tuberculosis in 2019, 1.4 million people died.

For the treatment of newly detected drug-sensitive tuberculosis, a highly active anti–tuberculosis drug isoniazid is used. Isoniazid disrupts the synthesis of mycolic acids and has a selective bacteriostatic effect on non-dividing and bactericidal effect on Mycobacterium tuberculosis (M. tuberculosis) in the breeding stage.

The pharmacokinetics of isoniazid are unpredictable and vary widely in patients taking standard doses of the drug. Individual differences in the pharmacokinetics of isoniazid depend on many factors: age, gender, body weight, race and ethnicity, the rate of acetylation, the nature and severity of the underlying and/or concomitant diseases, dysfunction of elimination systems, drug interactions, the presence of bad habits, etc. [1,5,12,16].

Isoniazid is a drug with concentration-dependent antimicobacterial action. The level of its concentration in plasma correlates with the speed of tuberculosis recovery, elimination of bacilli, the frequency of adverse drug reactions and drug resistance of M. tuberculosis [7,11,13,14]. In order to determine the optimal dose of isoniazid, it is necessary to know the "dose - concentration of isoniazid or the area under the pharmacokinetic curve" dependance. To do this, therapeutic drug monitoring is carried out with the determination of the equilibrium concentration of the drug in the blood plasma. Carrying out therapeutic drug monitoring of isoniazid will rationalize the treatment of tuberculosis, increase the effectiveness of treatment and minimize the development of undesirable drug reactions.

Currently, the method of high-performance liquid chromatography (HPLC) is widely used in monitoring the concentration of the drug in the blood plasma of patients. The advantage of the HPLC method from the rest is high sensitivity and versatility, the HPLC method simultaneously determines the concentrations of several medicinal substances with sufficient selectivity, accuracy and reproducibility [8]. However, in the Republic of Sakha (Yakutia), the use of the HPLC method for monitoring the concentration of isoniazid to determine the equilibrium concentration of the drug in blood plasma in patients with tuberculosis was not utilized.

In this regard, the purpose of our study was to determine the concentration of isoniazid in blood plasma by HPLC and calculate the pharmacokinetic parameters of isoniazid in patients with newly diagnosed pulmonary tuberculosis in the Republic of Sakha (Yakutia).

Material and methods. The protocol of the study was reviewed and approved by the Ethics Committee at the Scientific and Practical Center "Phthisiology" (Protocol No. 3 of 26.09.2018). The study involved 35 patients with newly diagnosed pulmonary tuberculosis (Table 1). Inclusion criteria: first onset of pulmonary tuberculosis, intensive phase of anti-tuberculosis chemotherapy, age of patients 18-60 years, the presence of signed informed consent. Exclusion criteria: generalized tuberculosis, HIV infection, malignant neoplasms and other concomitant diseases, taking any medication lasting more than a week during the last month, drinking alcoholic beverages, pregnancy.

For three days, isoniazid was injected into the vein 1 time a day at a dose of 10 mg/ kg (no more than 600 mg/day) (Clinical recommendations "Tuberculosis of the respiratory organs in adults" (approved By the Ministry of Health of Russia in 2018). Blood samples were obtained on the 4th day: 15 minutes before the injection of isoniazid, then 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours, 24 hours after it. Blood was centrifuged at 3000 g for 10 min, plasma was subjected to "shock freezing" with liquid nitrogen.

Blood plasma in the amount of 200 µl was placed in a 1.5 ml Eppendorf tube, 100 µl of 10% trichloroacetic acid was added, intensively shaken on a vortex for 10 minutes, centrifuged for 5 minutes at 12100 g, 100 µl was taken for analysis. The isoniazid concentration was determined by high-performance liquid chromatography (HPLC) on a Milichrome a-02 device manufactured by CI "Econova" LLC (Russia). Chromatographic examination was carried out on a ProntoSIL 120-3-C18 AQ column. The conditions for determining the level of isoniazid by HPLC were as follows: eluent A – 0,4 % articulant with 0.1 % trifluoroacetic acid, pH 2,2; eluent B: acetonitrile; gradient: regeneration – 700 µl 1% B, 1 tier – 1-60 % B for 2000 µl, 2 step – 100% B 2000-2800 µl; eluent flow rate of 150 µl; wavelength detector – 266 nm; time constant of the detector is 0.18 s; temperature – 40^{0}C; pressure - 2.5-5.5 MPa; sample volume - 20 µl. The chromatogram of the working blood plasma sample of a patient with pulmonary tuberculosis with intravenous administration of isoniazid obtained as a result of HPLC analysis is shown in Figure 1.

Based on the obtained concentrations of isoniazid the following pharmacokinetic parameters were determined: $AUC_{\tau,ss}$ – area under the curve within a dosing interval at steady-state conditions (ss) with repeated administration of the drug; $C_{max,ss}$ – maximum equilibrium concentration of drug in blood plasma; $C_{min,ss}$ – minimum equilibrium concentration of drug in plasma; T_{max} is the maximum measured concentration in blood plasma of the patient C_{av} – average steady-state concentration of drug in blood plasma; DF – degree of fluctuation of drug concentration in plasma; T½ is the half – life of the drug substance; k_{el} – constant of elimination of drug substances; $T_{aboveCav}$ – the period of time during which the concentration of medicinal substance exceeds C_{av} [2; 3].

Statistical processing of research results was carried out using the Microsoft Excel application software package and the IBM SPSS Statistics 24 statistical program. The Kolmogorov-Smirnov criterion was used to check the distribution form. The initial quantitative variables are presented in the form of Me [Q1-Q3] - median and interquartile interval (values of 25 and 75 percentiles). The Mann-Whitney U–test was used to compare two independent samples. When comparing the groups , the differences were considered statistically significant at p<0,05.

Table 1

Demographic and anthropometric indicators of patients included in the study

Parameter		n=35
Age, years (M±SD)		33.00±10.87
Height, cm (M±SD)		164.00± 9.58
Weight, kg (M±SD)		55.00± 8.24
Sex	male, % (person)	22 /35 (62.86)
	female, % (people)	13/35 (37.14)
Nationality	Yakuts, % (people)	31/35 (88.57)
	Russians, % (people)	4/35 (11.43)
Degree of obesity	Deficit, % (people)	5/35 (14.29)
	Norm, % (people)	28/35 (80.0)
	Excess, % (people)	2/35 (5.71)
Diagnosis	Infiltrative tuberculosis, % (people)	16/35 (45.71)
	Focal tuberculosis, % (people)	10/35 (28.57)
	Disseminated tuberculosis, % (people)	9/35 (25.71)

Note: BMI – body mass index; M - average value; SD - standard deviation.

Results and discussion. The patients (35) included in the studies did not have statistically significant demographic and anthropometric differences. On day 4, 2/35 (5.71%) patients developed adverse effects during parenteral administration of isoniazid: 1/14 (7.14%) patient complained of dizziness, 1/14 (7.14%) patient developed nausea, vomiting, drug administration was discontinued, patients were excluded from the analysis. Statistical analysis was performed on the data of 33 patients.

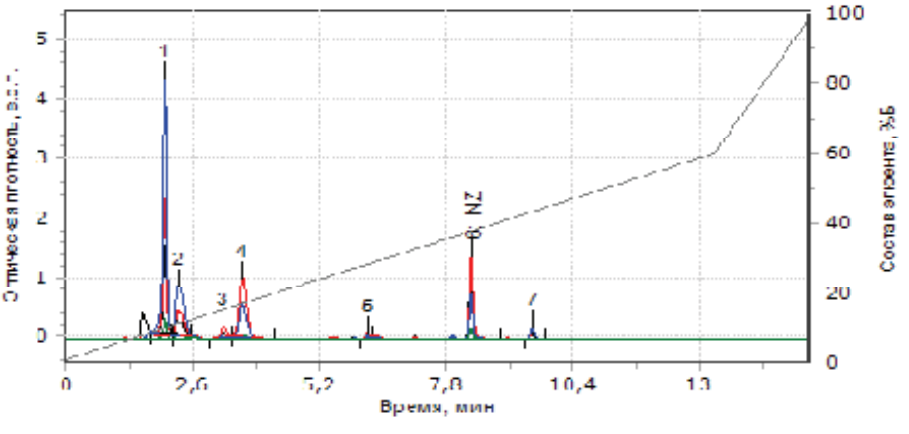

Fig. 1. Blood plasma chromatogram of a patient with pulmonary tuberculosis with intravenous administration of isoniazid (INH)

In accordance with the set goal and objectives, the concentration of isoniazid in blood plasma samples was determined during the study to construct pharmacokinetic curves. The profile "plasma concentration - time" after intravenous administration of isoniazid in the blood plasma of patients included in the study is shown in Figure 2.

Average values of pharmacokinetic parameters of isoniazid in patients included in the study: the area under the curve ($AUC_{t,ss}$) – of 37.69 (22,62-58,76) μg×h/ml; the maximum equilibrium concentration of isoniazid ($C_{max,ss}$) – 12,76 (10,02-16,29) μg/ml; the time to maximum plasma concentration (T_{max}) – 0,50 (0,50-0,50) h; the average steady-state concentration (C_{av}) – 1,57 (0,94-2,44) μg/ml; the degree of fluctuations of drug concentration in blood plasma (DF) – 753,20 (538,90-1149,00) %; the period of preliminarii ($T_{½}$) – 2,23 (1,71 was 3.79) h; the elimination constant (k_{el}) – 0,31 (0,18-0,40) h^{-1}; the time during which the concentration exceeds With$_{av}$ ($T_{aboveCav}$) – 5,50 (4,50-5,50) h

According to the dependence of the concentration of isoniazid on time, pharmacokinetic parameters were calculated, presented in Table 2.

A personalized analysis of the pharmacokinetic parameters of isoniazid showed their significant individual variability (Table 2).

The maximum plasma concentration of isoniazid (C_{max}) and the area under the pharmacokinetic curve ($AUC_{t,ss}$) are the most important pharmacokinetic parameters of isoniazid, determining its effectiveness and tolerability.

The optimal maximum concentration of isoniazid in blood plasma is in the range from 3 to 6 micrograms/ml [6,9] When prescribed 10 mg / kg / day (no more than 600 mg / day) the maximum equilibrium concentration (With $_{max, ss}$) of isoniazid in the blood plasma of all patients was determined above 6 micrograms/ml.

To ensure the necessary therapeutic effect and reduce the risk of adverse drug reactions in the treatment of tuberculosis, the average inpatient concentration (C_{av}) of isoniazid should be within the therapeutic range of 1-2 micrograms/ml [4.10]. The average inpatient concentration (C_{av},) of less than 1 mcg/ml was determined in 9/33 (27.27%) patients, was 0.73±0.17 mcg/ml, more than 2 mcg/ml - 13/33 (39.39%) patients, 4.22±4.45 mcg/ml.

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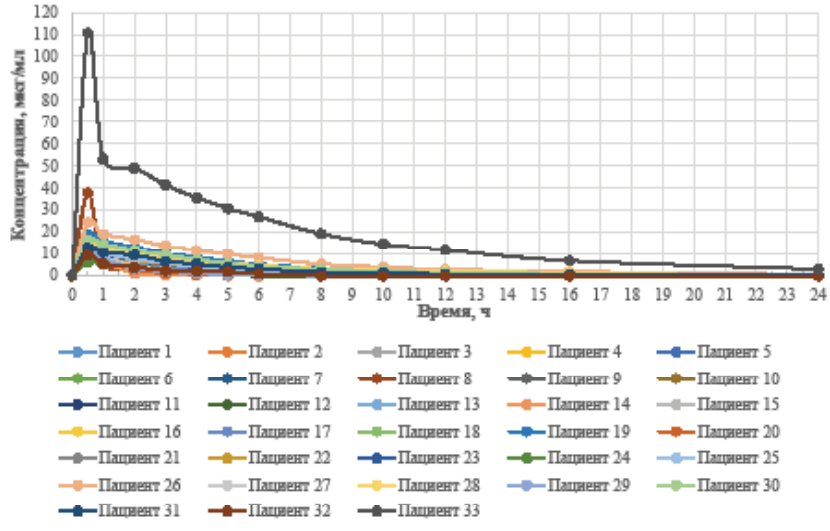

Fig. 2. Pharmacokinetic curves of isoniazid concentration in blood plasma after intravenous administration of the drug to patients included in the study

Table 2

Pharmacokinetic parameters of isoniazid in patients with pulmonary tuberculosis

Patient's No	$C_{max,ss}$, mcg/ml	T_{max}, h	AUC, mcg×h/ml	k_{el}, h^{-1}	$T_{1/2}$, h	C_{av}, mcg/ml	DF, %	$T_{aboveCav}$, h
1	10.72	0.50	29.11	0.40	1.74	1.21	883.91	4.50
2	13.64	0.50	39.17	0.12	6.02	1.63	836.06	4.50
3	18.52	0.50	72.28	0.29	2.44	3.01	614.87	5.50
4	19.22	0.50	54.50	0.37	1.87	2.27	846.50	5.50
5	11.83	0.50	37.69	0.32	2.14	1.57	753.22	5.50
6	6.63	0.50	33.90	0.06	11.33	1.41	469.60	5.50
7	7.85	0.50	24.42	0.42	1.66	1.02	771.31	5.50
8	37.84	0.50	35.12	0.13	5.30	1.46	2586.06	3.50
9	13.98	0.50	74.90	0.18	3.80	3.12	442.69	5.50
10	6.81	0.50	31.17	0.39	1.78	1.30	523.91	7.50
11	10.02	0.50	22.10	0.58	1.20	0.92	1087.82	3.50
12	8.79	0.50	14.30	0.82	0.85	0.60	1475.67	4.50
13	7.65	0.50	15.20	0.76	0.91	0.63	1208.92	4.50
14	8.07	0.50	10.18	0.95	0.73	0.42	1901.66	1.50
15	18.17	0.50	58.76	0.33	2.13	2.45	742.85	5.50
16	16.08	0.50	26.08	0.31	2.24	1.09	1479.47	4.50
17	13.94	0.50	27.29	0.40	1.72	1.14	1225.95	4.50
18	16.29	0.50	78.01	0.19	3.72	3.25	501.23	5.50
19	18.94	0.50	84.35	0.22	3.10	3.52	538.94	5.50
20	10.52	0.50	15.45	0.75	0.92	0.65	1633.89	3.50
21	14.47	0.50	51.64	0.33	2.08	2.15	672.62	4.50
22	10.17	0.50	43.29	0.22	3.21	1.80	563.63	5.50
23	11.17	0.50	49.54	0.19	3.64	2.06	541.29	7.50
24	6.40	0.50	17.88	0.42	1.67	0.75	859.46	4.50
25	13.04	0.50	44.55	0.26	2.64	1.86	702.43	5.50
26	24.48	0.50	131.93	0.14	5.00	5.50	445.30	5.50
27	10.82	0.50	22.62	0.43	1.60	0.94	1147.56	3.50
28	14.67	0.50	75.75	0.09	7.68	3.16	464.88	5.50
29	11.16	0.50	20.12	0.28	2.51	0.84	1331.03	3.50
30	16.46	0.50	79.12	0.17	4.20	3.30	499.12	5.50
31	12.76	0.50	57.24	0.07	9.49	2.39	534.99	5.50
32	9.46	0.50	19.76	0.32	2.14	0.82	1149.03	5.50
33	110.60	0.50	449.44	0.12	5.91	18.73	588.45	7.50

Note: Me [Q1-Q3] is the median and interquartile interval (values of 25 and 75 percentiles).

Table 3

The average values of the main pharmacokinetic parameters of isoniazid for both groups of patients

Parameter	Group 1, n=23	Group 2, n=10	p (Kraskel-Wallis criterion)
$C_{max,ss}$, mcg/ml	12.29 [10.12-16.33]	13.04 [9.46-16.07]	p = 0.98
$T_{max,}$ h	0.50 [0.50-0.50]	0.50 [0.50-0.50]	—
$AUC_{t, ss}$, mcg×h/ml	38.43 [26.57-61.00]	26.08 [19.76-58.76]	p = 0.51
k_{el}, h^{-1}	0.30 [0.17-0.40]	0.31 [0.26-0.32]	p = 0.98
$T_{½}$, h	2.28 [1.70-3.89]	2.23 [2.13-2.64]	p = 0.98
C_{av}, mcg/ml	1.60 [1.10-2.54]	1.08 [0.82-2.44]	p = 0.51
DF, %	712.90 [532.20-1102.80]	859.50 [702.40-331.00]	p = 0.25
$T_{aboveCav,}$ h	5.50 [4.50-5.50]	5.50 [4.50-5.50]	p = 0.65

Note: Me [Q1-Q3] — median and interquartile interval (values of 25 and 75 percentiles); group 1 - patients with body weight < 60 kg, group 2 - patients with body weight > 60 kg; p (Kraskel-Wallis criterion) - statistically significant differences at p.

acquired drug resistance M. tuberculosis [15]. AUC values of $_{T,ss}$ in 22/33 patients (66.67%) were determined below 52 mcg×h/ml for 24 hours, the average $AUC_{t\ ss}$ it was 28.66±11.90 micrograms ×h/ml.

According to the instructions for medical use, the half-elimination period ($T_{½}$) with repeated prescriptions of isoniazid is 2-3 hours. The indicator of the $T_{½}$ varies significantly among patients with fast and slow type of acetylation, is 0.5-1.6 hours and 2-5 hours, respectively (State Register of Medicines: [website]. URL:https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=019337ee-bfad-48fe-b9a7-02c7ac9e-109c&t=).

The half-elimination period ($T_{½}$) of isoniazid in 12/33 patients (36.36%) was less than 2 hours, was 1.39± 0.43 hours. A short period of half-elimination may be due to intensive biotransformation of isoniazid and indicate a rapid type of acetylation of the drug. In 13/33 (39.39%) patients, the half-elimination period was more than 5 h (5.56 ± 2.21 h), a decrease in the rate of acetylation of isoniazid is characteristic of patients with a slow type of acetylation.

When analyzing the pharmacokinetic parameters of isoniazid, a high concentration spread (DF, %) was found in patients, which does not allow maintaining a constant concentration of isoniazid in plasma in these patients.

Sharply distinguished values were found in patient No. 33: $AUC_{t\ ss}$, $C_{max,ss}$, $T_{1/2}$, C_{av} (Table 2). High values of the area under the pharmacokinetic curve ($AUC_{t\ ss}$) and the maximum plasma concentration (With $_{max,\ ss}$) of isoniazid correlate with the development of undesirable side reactions [13].

According to the study design, isoniazid was prescribed to patients at an estimated dose of 10 mg/ kg / day, but not 600 mg per day. We compared pharmacokinetic parameters among two groups of patients: group 1 - patients with body weight < 60 kg; group 2 - patients with body weight > 60 kg. The average values of the main pharmacokinetic parameters of isoniazid for the compared groups of patients are presented in Table 3.

According to the results of the comparison, no differences in pharmacokinetic parameters were found (Table 3).

Conclusions

1. The high specificity, accuracy, sensitivity and speed of the analysis make it possible to use the HPLC method to determine the concentration of isoniazid in blood plasma in order to conduct therapeutic drug monitoring in the treatment of drug-sensitive pulmonary tuberculosis.

2. For the first time, the equilibrium concentration of isoniazid in blood plasma was studied by HPLC in patients with pulmonary tuberculosis living in the Republic of Sakha (Yakutia).

3. High individual variability of pharmacokinetic parameters of isoniazid in the blood plasma of patients was established.

4. Individual differences in the pharmacokinetic parameters of isoniazid indicate the need for therapeutic drug monitoring when prescribing isoniazid.

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HEALTHY LIFESTYLE. PREVENTION

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STUDY OF THE MICRONUTRIENT COMPOSITION OF ACTUAL DIETS IN THE ELDERLY POPULATION OF YAKUTSK

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The data obtained allowed us to conclude that the elderly population had a deficit of vitamins, microelements in the diet of the actual consumption, especially there was a decrease with age. Gender differences in the content of some vitamins and minerals in the diet were revealed.

Keywords: nutrition, micronutrients, vitamins, minerals, old age, epidemiology.

Relevance. The most important of the national project "Demography" in the Russian Federation is to increase the healthy life expectancy of the population. There is no doubt that this task is inseparable, connected with the state of health of the elderly and senile aged population and becomes an important factor for achieving an increase in life expectancy. One of the important factors influencing both the state of health and well-being of the mentioned category of population is a balanced nutrition. It is known that a balanced diet is necessary for the physiological needs of the body in nutrients (macro- and micronutrients) and energy. Rational and balanced nutrition contributes to the body's resistance to the negative effects of environmental influences, reducing the risk of alimentary-dependent diseases and increasing life expectancy [4, 8, 12]. The elderly population is often considered to be at higher risk for a number of reasons, one of which is a decrease in food intake that can lead to the development of malnutrition (malnutritional deficiency) syndrome. Current nutritional problems in the elderly population are one of the important reasons for the formation of numerous geriatric syndromes (sarcopenia, senile asthenia, falls, bedsores, depression, cognitive decline, etc.), which worsen not only the quality of life, the functional status of the elderly person, but also worsen the forecast of morbidity and mortality indicators [5, 11, 12]. In this connection, it becomes relevant to study the actual nutritional status of this age group for the prevention and possible correction of geriatric syndromes in the elderly population living of the Republic of Sakha (Yakutia).

Aim: of this study was to study the micronutrient (vitamins and minerals) composition of the actual dietary intake in the elderly population of Yakutsk.

Materials and methods of research. This paper uses the materials of an epidemiological study conducted as part of the research work «Epidemiology of some chronic non-infectious diseases and risk-factors in the elderly population (including long-livers) of Yakutsk» by the Yakut Scientific Center of complex medical problems. The study design corresponds to a one-stage cross-sectional population study described in a previously published paper by the authors [1].

The population of the city of Yakutsk aged 60 and older was chosen for the study. The selected representative sample of the population aged 60 years and older was 5.3% of the total number of residents of the city. Data from 775 people were collected for the survey. The mean age of those surveyed was 75.7 years with a standard deviation of 9.4 years, and the response was 79.9%. Data from 244 men and 331 women were used to analyze micronutrients (vitamins and microelements) in the diet.

Validated questionnaires and questionnaires that included sociodemographic characteristics and data on actual nutrition were used for the study [1].

The method of analyzing the frequency of food consumption was used to assess actual nutrition. The database "Tables of the chemical composition of dishes and culinary products", taking into account losses during heat treatment, was used to determine the micronutrient composition of diets. Daily food rations were analyzed based on an assessment of both the quantitative content and the ratio of micronutrients. To analyze the data obtained, the norms of physiological need for nutrients and energy for different population groups were used [6].

Statistical processing and data analysis were performed using the SPSS software package (11.5 version). Values p <0,05 were considered authentic.

Results and discussion. The analyzed data assessing the average daily content of micronutrients (vitamins A, B1 and B2, β-carotene, PP, C and minerals - sodium, potassium, calcium, magnesium, phosphorus and iron) in the diet of the actual diet showed insufficient consumption at the level of the recommended physiological norms for men and women aged 65 and older.

Average levels of vitamin intake are shown in table 1. Deficiencies in dietary vitamin intake relative to recommended levels were noted in both groups. However, the average daily intake of vitamins was statistically significantly higher in the male population compared with the same

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