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Study of the distribution of the coordinating compound $C_{11}H_{12}N_2O_2•(C_{11}H_{13}N_2O_2)^+•NA^+•2H_2O•(I_4)^{2-}$ in mice organism by radioisotope method

Abstract. The paper presents the results of studies on the effect of a new synthesized coordination compound based on an amino acid-tryptophan and iodine compounds on bacterial DNA and the kinetics of its distribution in mice tissues after a single intravenous or oral administration. A radiochemical study of the quantitative content of the coordination compound labeled with iodine-131 in the system of laboratory mice after intravenous and oral administration showed the presence of an isotopic label in the tissues and organs under study. The coordination compound has the ability to accumulate in internal organs and tissues in various concentrations with a further decrease by 24 hrs (study period) and clearance of the drug from the body. The effect of a solution of a coordination compound labeled with the ^{131}I isotope on the *E. coli* culture ATCC 25922 showed that DNA halogenation occurs due to the breakdown of the tryptophan-tetraiodide iodine complex in the cell with the formation of molecular iodine.

Key words: coordination compound of tryptophan and iodine, drug distribution, elimination, radiochemistry.

Introduction

Despite increase in the number of new antibacterial drugs on the market, the emergence of antibiotic resistance is currently a global medical and social problem [1]. In this regard, the development and creation of fundamentally new antimicrobial drugs for the treatment of infectious diseases caused by multiply resistant microorganisms is an urgent problem.

Compounds of chlorine, iodine and other halogens are characterized by a strong bactericidal effect on gram-positive and gram-negative bacteria, and also increase the lipophilicity of drugs and facilitate their passage through biomembranes [2]. The creation of complexes of coordination compounds (derivatives of carbohydrates and amino acids) with halogens results in the emergence of new types of bioactivities or a noticeable increase in existing ones. Thus, in our early studies, we showed that the coordination compound of lithium and iodides with biologically active organic ligands (amino acids and oligosaccharides) can be used to obtain materials with different optoelectric and magnetic properties [3; 4]. Iodine compounds are arousing growing interest due to the expansion of the range of applications and the presence of a special spatial molecular configuration. In the works of Yuldasheva G.A. et al. it was found that such compounds inside the dextrin helix contain three active centers – molecular iodine coordinated by the polypeptide and lithium halide, lithium triiodide and halides. These iodine compounds inhibit the active site of topoisomerase I through the effect on the amino acid residues of arginine and tyrosine [5].

Earlier, the Scientific Center for Anti-Infectious Drugs JSC synthesized a new *coordination compound based on the amino acid of tryptophan and iodine* with the gross formula $C_{11}H_{12}N_2O_2•(C_{11}H_{13}N_2O_2)^+•Na^+•2H_2O•(I_4)^{2-}$ (hereinafter referred to CCTI). We have determined the chemical structure by X-ray diffraction analysis. It was found that four iodine atoms are coordinated in CCTI (Figure 1). The bond length in the iodine molecule (I1-I2) is 2.762 Å, and the bond length of the I3- and I4- ions attached to the molecule is as follows: I1-I3 – 3.431 Å, I2-I4 – 3.628 Å. In the polyanion I_{4-} is realized a rare case where two iodide anions polarize the electrons of the iodine molecule with the formation of a partially positive charge on each atom I- 3.431Å Iδ + 2.762Å Iδ + 3.628ÅI- [6].

Microbiological methods established the low toxicity of CCTI and determined bactericidal

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activity against both sensitive and multi-resistant bacterial strains of *S. aureus, P. aeruginosa and E. coli*. [6] In this work, in order to study the properties of CCTI, we have studied the effect of CCTI on bacterial DNA and the kinetics of CCTI distribution in the mice tissues after a single intravenous or oral administration. For the study, a radiochemical method – liquid scintillation β-spectrometric analysis was used, and the isotope of iodine ^{131}I was used as an indicator of the isotope label, since iodine is a part of the compound under study.

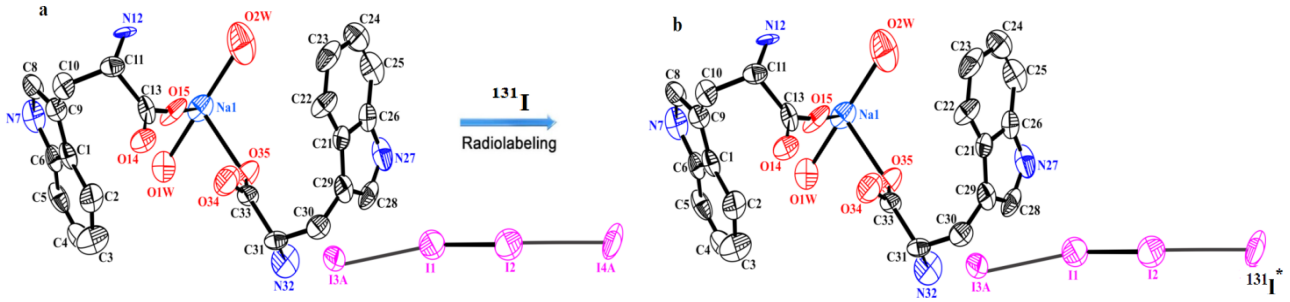

Figure 1 – Schematic isotope tagging process

Materials and methods

Materials. CCTI is a dark yellow powder with a specific odor. Na^{131}I, used for isotopic labeling, is an isotonic NaI solution, a clear and colorless liquid with a pH of 6.5-7.5. Radiochemical purity is not less than 95.0%. The volumetric activity is 20 MBq/ml at the date of synthesis. The ^{131}I isotope decays with a half-life period of 8.06 days; the most intense component of gamma radiation has an energy of 364.0 keV (81.2%), β-radiation is 606.0 keV (89.7%).

Test-Systems Used. The studies used white outbred rats and white outbred mice of both sexes. The research site was the rooms for keeping laboratory animals of the Scientific Center for Anti-Infectious Drugs JSC and the vivarium of the Scientific and Practical Center for Sanitary and Epidemiological Expertise and Monitoring RNE.

All animals were kept in cages with bedding for laboratory animals, previously incubated under the exposure to UV rays. The bedding was changed twice a week. Housing conditions for the animals corresponded to generally accepted standards: the ambient temperature was (21±2) °C, humidity (50 ± 10)%, artificial light conditions (12:12).

A diet was selected for the animals, including the complete pelleted autoclavable SSNIFF feed for laboratory rodents. The animals were fed twice a day, at the same time of day. Water was at the disposal of the animals *ad libitum*. Group allocation was carried out after randomization and labeling of animals. Marking was carried out by marking a patch of hair on the limbs, back and head with a marker.

The animals were withdrawn from the experiment in compliance with the rules of humane treatment of laboratory animals by decapitation after inhalation with air containing 70% CO_2 at a flow rate of 30 L/min in a chamber, and biomaterial was collected.

CCTI labeling method with Iodine-131 radioactive isotope. The CCTI synthesis was carried out using the method described in [6]. For the introduction of an isotope label in CCTI at a temperature of 18-22 °C, a Na131I solution is added, considering the final activity of the radionuclide of 500 kBq/ml. The total volume of the preparation is brought up to 1000 ml. This labeled CCTI preparation is left for 3-5 hrs to complete isotope exchange (Figure 1). Subsequently, for simplicity, the preparation labeled with the ^{131}I isotope will be presented in the form of CCTI (^{131}I).

Microbiological Research. The test strains used in the study were obtained from the American Type Culture Collection (ATCC). Cultivation and preparation of a suspension of *E. coli* ATCC 25922 at a concentration of 1.5x10^8 CFU/ml was carried out in accordance with [6; 7]. In tubes containing 1.5x10^8 CFU/ml *E. coli* ATCC 11229, the CCTI(^{131}I) was added at a concentration of 500 μg/ml (which is 1/2 of the MIC) and incubated for 1 h at 37°C. 1/2 MIC was determined by us in work [6].

DNA isolation using the Lisates Mini Kit test systems was carried out in accordance with the instructions for the PureLink Genomics DNA Mini Kit. Determination of the amount of isolated DNA was carried out on a NanoDrop 2000C spectrophotometer (Thermo Scientific, USA, wavelength in the range of 190-840 nm).

Study of the CCTI Pharmacokinetics. 0.5 ml of an aqueous solution of CCTI (^{131}I) was injected into a mouse in accordance with the injection methods of procedure (Figure 2) with a specific activity of 500 kBq/g. Considering the animal weight, this activity was considered equal to the concentration of the administered drug.

β-spectrometric analysis of biological samples. For β-spectrometric analysis of the isolated DNA, the entire isolated DNA sample was transferred into special vials (containers) and brought to 5 ml with the Ultima Gold LLT scintillation cocktail. Measurement parameters for ^{131}I 500 keV, measurement time – 5 min. β-spectrometric analysis was carried out according to [8]

For β-spectrometric analysis of animal organ samples, the organs were homogenized and transferred into special vials (containers), and brought to 10 ml using the Ultima Gold LLT scintillation cocktail. Measurement parameters for ^{131}I 500 keV, measurement time 5 min. β – spectrometric analysis was performed with a HIDEX-300SL instrument.

During the study with radioisotopes, the radiation situation in the room was monitored, and protective measures for the exposure of personnel were prepared. The results of measurements of the room and the equipment involved before and after the experiments showed the background values of radiation dose (0.14 – 0.19 μSv/h).

Results and discussion

Study of the CCTI effect on the modification of bacterial DNA by radiochemical research methods. To study possible penetration of the coordination compound $C_{11}H_{12}N_2O_2•(C_{11}H_{13}N_2O_2)^+•Na^+•2H_2O•(I_4)^{2-}$ into bacterial cells, a study was carried out to determine the localization of coordination compounds with a radioactive label of ^{131}I in test cells of *Escherichia coli* ATCC 25922 culture. For this purpose, a spectrophotometric analysis was performed of DNA isolated from the cell culture of the test system using a NanoDrop 2000C device. The test culture was cultured in three separate Petri plates. The absorption of light at 260/280 nm was measured by placing a 100μl DNA drop on a standing module of the device.

Table 1 shows the indicators of spectrophotometric analysis of DNA samples and data on the quality coefficients of the sample.

When recalculating the amount of DNA from different plates, the above sample quality factors were taken into account (Table 2).

The data obtained from the study of DNA samples during spectrophotometric analysis were recalculated considering the quality factor as a percentage (Table 3).

Then, β-spectrometric analysis of the isolated DNA of *E. coli* ATCC 25922 was carried out. DNA of the *E. coli* culture treated with $Na^{131}I$ solution under the same cultivation conditions (without CCTI content) was used as a reference sample. The value of ^{131}I activity in the reference sample was 39 Bq/ml (Table 4). In DNA samples of cultures treated with CCTI (^{131}I), the value of radioactivity increased by an average of 6-7 times. This suggests that the active substance CCTI (in particular iodine) binds to DNA.

Table 1 – Quality of the sample obtained by DNA isolation

Sample No.	the quality of the sample obtained during the extraction of DNA (coefficient)			
	the 1st repeat	the 2nd repeat	the 3rd repeat	
1	1.83	1.9	1.8	Norm 1.8–2.0 (coefficient) (260/280 nm)
2	1.83	1.9	1.8	
3	1.83	1.9	1.8	
Mean	1.83	1.9	1.8	

Table 2 – The amount of DNA in the isolated sample, μg/ml

Sample No.	the quality of the sample obtained during the extraction of DNA (coefficient)			
	the 1st repeat	the 2nd repeat	the 3rd repeat	
1	1.83	1.9	1.8	Norm 1.8–2.0 (coefficient) (260/280 nm)
2	1.83	1.9	1.8	
3	1.83	1.9	1.8	
Mean	1.83	1.9	1.8	

Table 3 – Amount of DNA (%)

Sample No.	Amount of DNA (%)			
	the 1st repeat	the 2nd repeat	the 3rd repeat	
1	91.5	95	90	Norm 90 – 100% when recalculated considering the quality factor
2	91.5	95	90	
3	91.5	95	90	
Mean	91.5	95	90	

Table 4 – Radioactivity of DNA samples

Sample No.	Activity of DNA samples, Bq/ml			
	the 1st repeat	the 2nd repeat	the 3rd repeat	Background (control)
	The mean value of the concentration of DNA 14.5 μg/ml	The mean value of the concentration of DNA 15 μg/ml	The mean value of the concentration of DNA 14.3 μg/ml	
1	284	267	266	41
2	251	281	201	32
3	284	230	260	44
Mean	273.0±19.1***	276.0±51.1*	219.0±35.6*	39.0±6.25
Note: * – reliable compared to control ($p< 0.05$), *** – reliable compared to control ($p< 0.0005$)				

Taking into account that C_0 (CCTI (^{131}I)) in terms of molecular iodine is 54,4g/ kg, and also taking for A0 = 5000 Bq/ml according to formula (1), the concentration of CCTI (^{131}I) bound to the DNA of microbial cells was determined (table 5).

$$C\ (CCTI\ (^{131}I)) = A(I^{131})*C_0(CCTI\ (^{131}I)) / A_0(I^{131}) \quad (1)$$

where:

$A(I^{131})$ – specific activity of I^{131}, determined by measurements of samples with a β-spectrometer;

C_0(CCTI (^{131}I)) – the initial concentration of CCTI (131I) introduced into the cell culture;

$A_0(I^{131})$ is the initial specific activity of I^{131} resulting from the CCTI labeling.

Table 5 – Concentration of the active component CCTI (^{131}I) bound to DNA of *E.coli*

Repeat No.	The amount of DNA, μg/ml	Concentration of the active component CCTI (131I), g/kg
1	14.5	2.9
2	15.0	3.0
3	14.3	2.4
Mean	14.6± 0.28	2.8±0.23

The presence of a significant activity of the ^{131}I isotope in DNA samples of the *E. coli* ATCC 25922 culture cultivated with the addition of CCTI (131I) showed that there is a halogenation of the DNA of the microbial cell culture. DNA halogenation occurs due to the breakdown in the tryptophan-tetraiodide iodo complex cell ($C_{11}H_{12}N_2O_2$•($C_{11}H_{13}N_2O_2$)$^+$•Na^+•$2H_2O$ •$(I_4)^{2-}$) with the formation of molecular iodine. This is evidenced by the high values of the radioactivity of DNA treated with CCTI (131I) against the background of a reference sample – DNA of *E. coli* culture treated with $Na^{131}I$ solution. Unlike the iodide ion, molecular iodine, being an oxidizing agent, is capable of interacting with all classes of biological macromolecules, including

proteins, lipids, polysaccharides, and nucleic acids, to form iodine-derived biomolecules, the properties of which vary over a wide range. The high rate of iodination reaction leads to the degradation of proteins and nucleic acids, dissociation of membrane lipids, disruption of the native structure of enzymes, polysaccharides of the walls of bacteria and fungi.

Pharmacokinetic studies of the CCTI (^{131}I). Pharmacokinetic studies of the CCTI (^{131}I) were carried out in laboratory mice weighing 22 ± 10% g. For the CCTI study at a dose of 25,0 mg/kg, 36 white mice were used. The test substance CCTI (^{131}I) was administered in two ways: intravenously and orally (Figure 2).

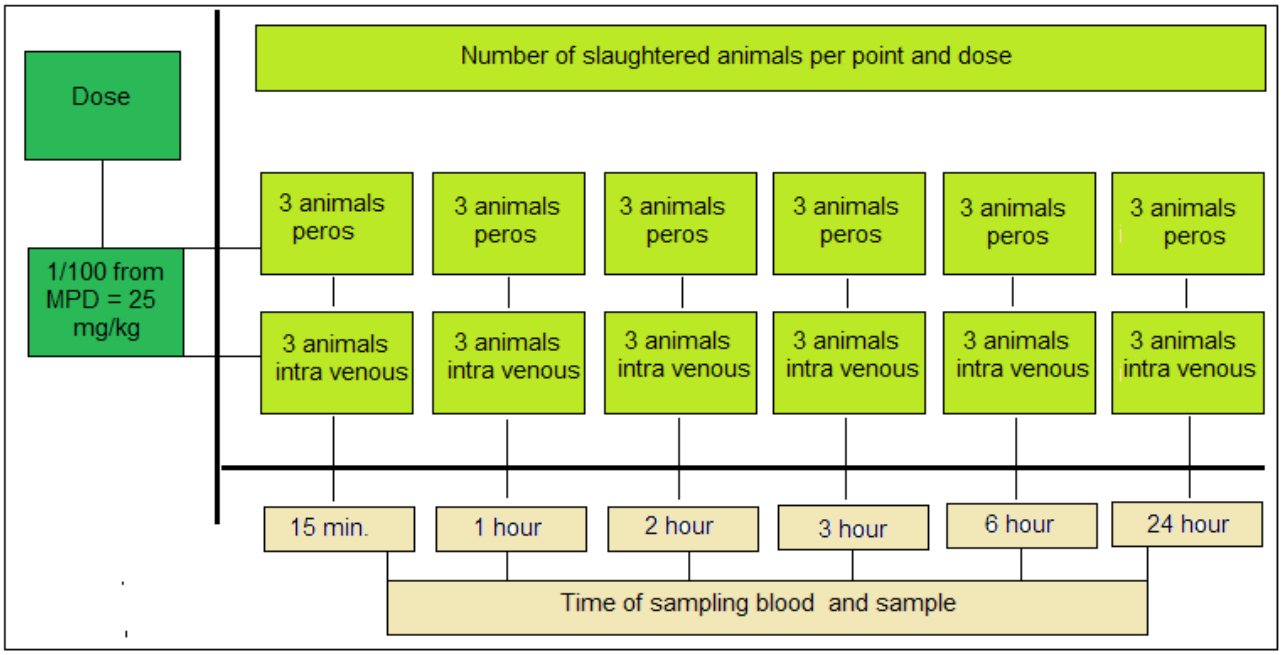

Figure 2 – Algorithm for studying the pharmacokinetics of CCTI (^{131}I) at a dose of 25.0 mg/kg with intravenous and oral administration

Experimental animals were sacrificed by decapitation (blood was collected) and organs (liver, kidneys, spleen, lungs, stomach, part of the femoral muscle) were placed into special vials, and after that the obtained samples were weighed. The sampling was carried out at 6 time points: 15 min; 1, 2, 3, 6, and 24 hrs (after 0.25, 1, 2, 3, 6, and 24 hrs after drug administration).

Pharmacokinetics of CCTI (^{131}I) injected. intravenously. Investigation of the distribution of radioactive ^{131}I in organs after intravenous administration of CCTI (^{131}I) at a dose of 25.0 mg/kg showed that at all times (time points) the highest concentration of the test substance was observed in the stomach. At the same time, the amount of CCTI (^{131}I) increased from 1.2 mg/kg after 15 min to 3.9 mg/kg by 2 hrs after administration. Then it decreased slightly and remained stable from 3 to 6 hrs and amounted to 2.2 and 2.4 mg/kg, respectively (Figure 3).

The amount of CCTI (^{131}I) in the lungs when administered intravenously at a dose of 25.0 mg/kg varied from 0.64 to 0.5 mg/kg with a maximum peak of 0.8-0.74 mg/kg at about 2-3 hrs after administration (Figure 3).

In the blood, already 15 min after intravenous administration of CCTI (^{131}I) at a dose of 25.0 mg/kg, a peak concentration of 0.52 mg/kg was noted, then its amount remained stable in the time interval from 1 to 6 hrs and was 0.31 and 0.30 mg/ml, respectively. A similar distribution pattern was observed in muscles – a peak at 15 min (0.46 mg/kg) followed by a decrease by 24 hrs to 0.07 mg/kg (Figure 3).

In the kidneys and spleen, the concentration peak occurred at 3 hrs and was 0.49 and 0.44 mg/kg, respectively. It should be noted that the concentration indicators of the drug were within the range of 0.36-0.49 mg/kg for kidneys and 0.32-0.44 mg/kg for spleen in the time range 15 min-6 hrs and dropped to 0.09-0.1 mg/kg by 24 hrs (Figure 3).

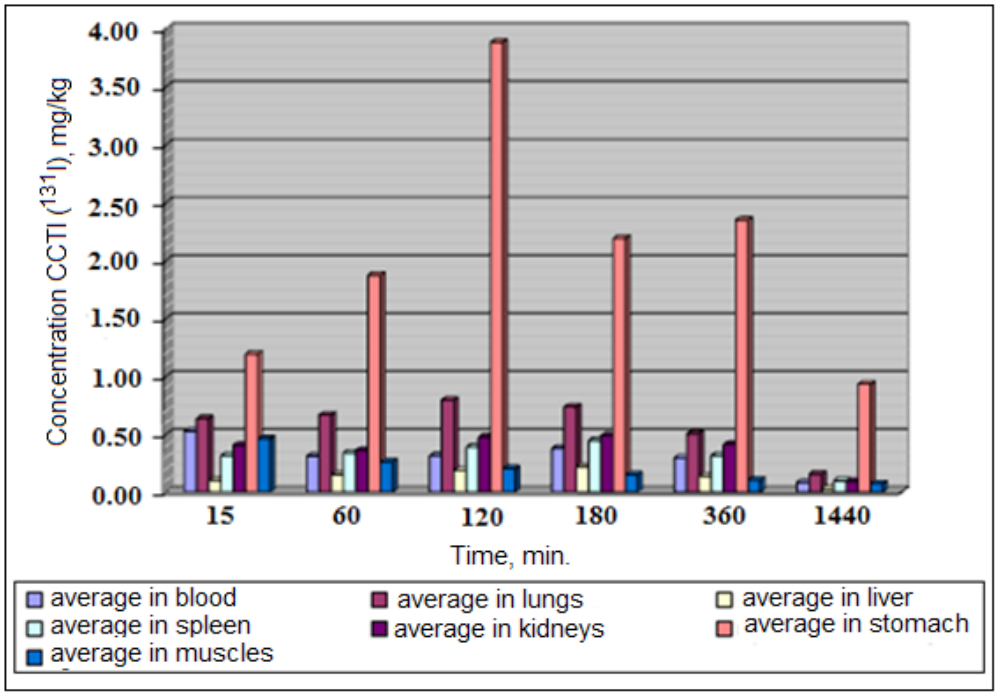

Figure 3 – Dynamics of CCTI (^{131}I) distribution after intravenous administration at a dose of 25.0 mg/kg in organs (0.133 mg/ml for total iodine)

The lowest CCTI concentration (^{131}I) was observed, compared with other organs, in the liver for all time points with a maximum of 3 hrs (0.22 mg/kg) and a minimum of 24 hrs (0.03 mg/kg) (Figure 3).

Analysis of the data on the total content of the drug with intravenous administration of CCTI (^{131}I) at a dose of 25.0 mg/kg showed that the maximum peak occurs at 2 hrs and is 6.25 mg/kg. Then the amount of CCTI (^{131}I) gradually decreases, remaining almost the same at 3-6 hrs and is in the range of 4.12-4.6 mg/kg, and by the end of the day it drops to 1.47 mg/kg (Figure 4).

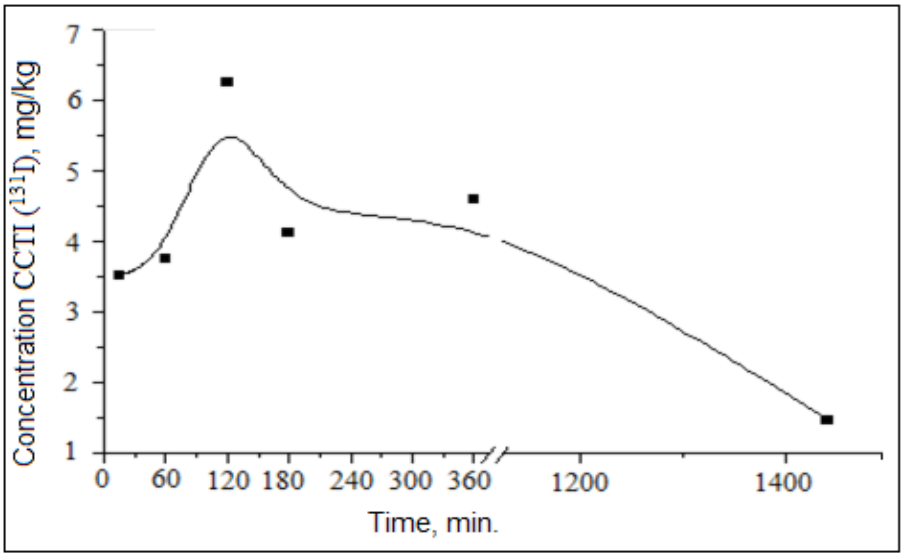

Figure 4 – Total CCTI (131I) when administered intravenously at a dose of 25.0 mg/kg

Pharmacokinetics of the oral drug CCTI (^{131}I). The organ distribution study of CCTI (^{131}I) when administered orally at a dose of 25.0 mg/kg showed that the highest concentration of the test substance was observed in the stomach, regardless of the time of sampling. The amount of CCTI (^{131}I) 15 min after administration was 4.39 mg/kg. 1 hr after administration, the iodine concentration dropped by 0,8 mg/kg and reached 3.59 mg/kg, and after 3 and 6 hrs – 3.23 and 3.22 mg/kg, respectively. That is, for 1-6 hrs, the concentration of the test substance in the stomach remains stable (Figure 5).

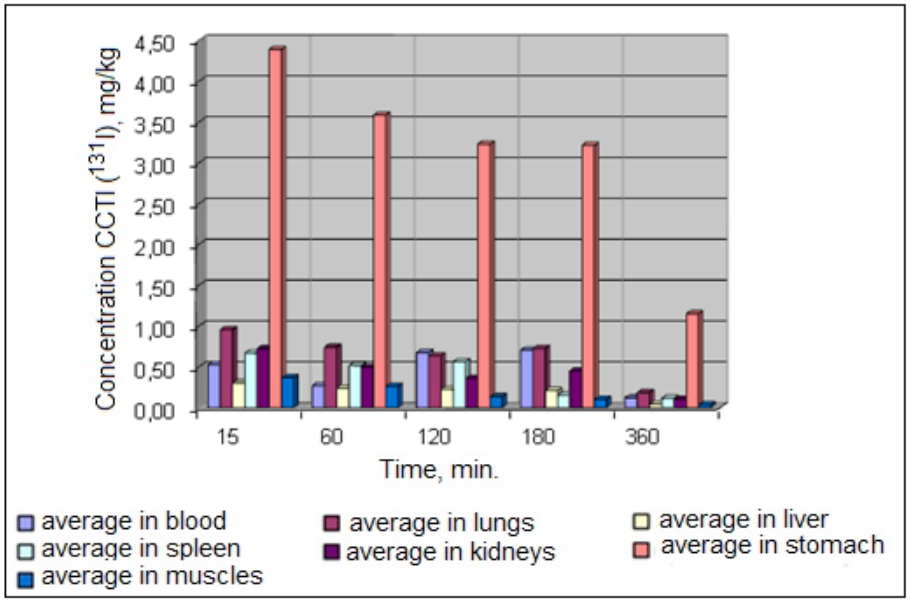

Figure 5 – Dynamics of distribution of CCTI (^{131}I) in organs after oral administration at a dose of 25.0 mg/kg (0.133 mg/ml for total iodine).

A similar dynamic of CCTI (^{131}I) distribution of is observed in the lungs after oral administration: a maximum of 15 min (0.96 mg/kg), then after 1 hr a gradual decrease with a plateau reaching up to 6 hrs (0.74-0.63-0.73 mg/kg) and a decrease by the end of the day to 0.18 mg/kg (Figure 5).

In the blood after oral administration of CCTI (^{131}I) at a dose of 25.0 mg/kg, the maximum iodine concentration of 0.68-0.71 mg/kg occurs at 3-6 hrs. In the muscles, the peak appeared at 15 min and gradually decreased with no abnormalities by 24 hrs (Figure 5).

An identical pattern was observed in the kidneys and spleen: the concentration peak occurred at 15 min and was 0.72 and 0.67 mg/kg, respectively. In the time range from 1 to 6 hrs, the CCTI (^{131}I) concentration in kidneys ranged from 0.36 to 0.5 mg/kg. In the spleen, the concentration was 0.52-0.56 mg/kg in the period from 1 to 3 hrs and then decreased by 6 hrs to 0.15 g/kg. One day after the administration of CCTI (^{131}I), the amount in the kidneys and spleen was the same and amounted to 0.11 mg/kg (Figure 5).

The lowest concentration of CCTI (^{131}I) compared to other organs, was observed in the liver at all time points, and was 0.3-0.04 mg/kg for 15 min and 24 hrs, respectively. For 1-3-6 hrs, a plateau was also observed with concentrations of 0.24-0.22-0.21 mg/kg (Figure 5). Analysis of the data on total iodine after oral administration of CCTI (^{131}I) at a dose of 25.0 mg/kg showed that the maximum concentration peak (7.94 mg/kg) falls on 15 min. Then CCTI (^{131}I) concentration drops, reaching a plateau, and practically does not change in the period from 1-3-6 hrs and amounts to 6.11 mg/kg; 5.82 mg/kg; 5.57 mg/kg, respectively, and by 4 hrs drops to 1.75 mg/kg (Figure 6).

The results of calculation of pharmacokinetic parameters of CCTI (^{131}I) are presented in Table 6. In the mathematical calculations, we used a two-compartment model, where blood and well-perfused organs (stomach, heart, lungs, liver, kidneys, and spleen) were taken as the central compartment and the muscle was taken as the peripheral compartment, as a poorly perfused organ.

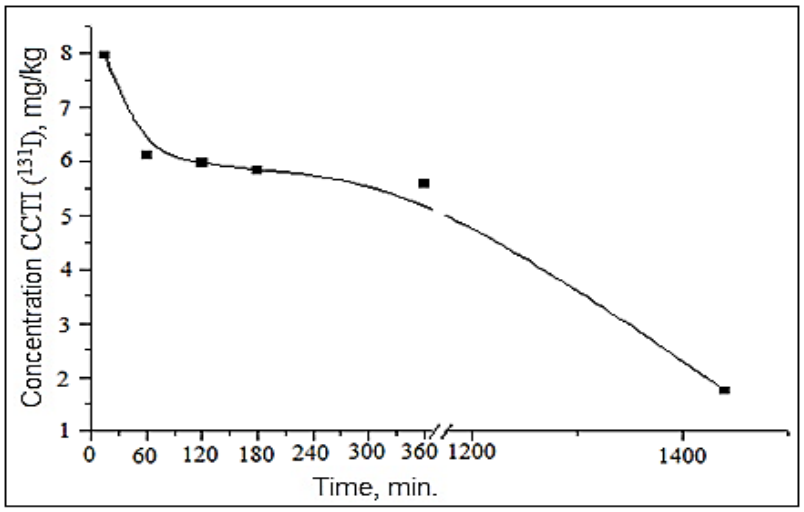

Figure 6 – Cumulative CCTI (^{131}I) when administered orally at a dose of 25.0 mg/kg.

With a total iodine being 0.133 mg/ml CCTI (^{131}I), the area under the concentration-time curve (AUC) is in the range of 5.5 mg/ml*h for intravenous administration and 10.8 mg/ml*h for intragastric administration.

Clearance (Cl) is used to calculate the dose required to maintain an equilibrium concentration in the blood. The clearance for CCTI (^{131}I) was 0.01-0.02 ml/h, depending on the route of drug administration.

Table 6 – Toxic and pharmacokinetic parameters calculated for a single intravenous and oral administration of CCTI (^{131}I) to mice

Toxic and pharmacokinetic parameters	CCTI (^{131}I) 25.0 mg/kg	
	intravenous (0.133 mg/ml by total iodine)	per os (0.133 mg/ml by total iodine)
AUC, (mg/ml*h)	5.46	10.84
Cl, (ml*h)	0.02	0.01
$k_{el,}$ (h^{-1})	0.081	0.098
V (ml/kg)	0.30	0.13
C_{max} (mg/kg)	0.52	0.71
t_{max} (h)	0.25	6
C_{max} / AUC (mg/kg)	0.09	0.06
$T_{1/2}$ (h)	8.52	7.07

The elimination constant k_{el} serves to quantify the rate of elimination of the drug from the body: for CCTI (^{131}I) it was about 0.09 (h^{-1}).

In clinical practice, the volume of distribution (V) is used to calculate the loading dose of the drug, which is required to achieve the required concentration in the blood. In our case, the volume of distribution ranged from 0.13-0.3 ml/kg at a total iodine concentration of 0.133 mg/ml CCTI (^{131}I).

The maximum concentration (C_{max}) and the time of the highest concentration (t_{max}) in the body with intravenous and intragastric administration of CCTI (^{131}I) was 0.5-0.7 mg/kg at 0.3 and 6 hrs.

The elimination of drugs from the body is judged about by the half-life (half-elimination) period, $T_{1/2}$ (h), which is defined as the time for the drug concentration in the blood to decrease by 50%

of the administered amount of the drug. For CCTI (^{131}I) $T_{1/2}$ is 8.5 hrs and 7.1 hrs for intravenous and oral administration, respectively. It is during these periods of time that the equilibrium concentration of the test substance in the blood is reached.

Bioavailability is an important parameter of pharmacokinetics – the amount of the drug entering the systemic circulation in relation to its administered dose, as well as the speed of this process. The bioavailability of a medicinal substance after intravenous administration is always 100%; however, with other modes of administration (for example, oral), for a number of reasons it will be less than 100%. Therefore, the ratio of AUC IV to AUC per os testifies its bioavailability and is equal to 2.

Thus, regardless of the route of administration of CCTI (oral or intravenous), it is noted that the main target organs are the stomach and lungs. Such a distribution of the active substance suggests the possibility of treating diseases of the gastrointestinal tract and lungs with this drug. It should be noted that the smallest amount of active substance is distributed to the liver.

Conclusion

1. Radiochemical study of the effect of the organic iodine coordination compound $C_{11}H_{12}N_2O_2 \bullet (C_{11}H_{13}N_2O_2)^+ \bullet Na^+ \bullet 2H_2O \bullet (I_4)^{2-}$ on the *E.coli* ATCC 25922 culture showed that DNA halogenation of microorganisms occurs due to the decomposition of the iodine complex of tryptophan-tetraiodide with the formation of a molecular iodine. The high rate of the kinetic reaction of iodination leads to the breakdown of nucleic acids, thereby preventing reproduction of pathogenic microorganisms.

2. The pharmacokinetic parameters calculated for a single intravenous and oral administration of the iodine coordination compound $C_{11}H_{12}N_2O_2 \bullet (C_{11}H_{13}N_2O_2)^+ \bullet Na^+ \bullet 2H_2O \bullet (I_4)^{2-}$ to mice were determined.

3. Regardless of the route of administration of CCTI (^{131}I) (oral or intravenous), it is noted that the main target organs are the stomach and lungs. Such a distribution of the active substance suggests the possibility of treating diseases of the gastrointestinal tract and lungs with these drugs.

Compliance with the ethical standards

Experiments on animals are approved by the local ethical commission of the Scientific Center for Anti-Infectious Drugs. The studies were carried out in accordance with the current regulatory documents (Order of the Minister of Health and Social Development of the Republic of Kazakhstan No. 392 "On the approval of good pharmaceutical practices" from May 27, 2015).

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