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Evaluation of the suitability and safety of the radiopharmaceutical MDP^{99m}Tc (methylene diphosphonate) used for the diagnosis of bone pathology in nuclear medicine

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ABSTRACT: This study investigated the functional suitability of the radiopharmaceutical MDP^{99m}Tc for skeletal radionuclide imaging under both normal and pathological conditions. The primary objectives were to evaluate its diagnostic efficacy, the specificity of drug accumulation in bone tissue, and its clinical applicability for early detection of bone pathology of various origins. A pharmacokinetic study was conducted in female rats following intravenous administration of MDP^{99m}Tc to assess its biodistribution and potential for osteoscintigraphy. One hour after injection, up to 52.4% of the radiopharmaceutical localized in the skeleton, indicating strong osteotropism. Differential accumulation coefficients (bone pathology/normal tissue and skeleton/blood) confirmed the radiopharmaceutical's potential for imaging osteoblastic activity, supporting its role in diagnosing bone tissue disorders. The optimal imaging time was determined to be 1–3 hours post-injection. The MDP-Sn(II) kit, in lyophilized form, maintained its biological efficacy for up to 1 year under recommended storage conditions, and the reconstituted radiopharmaceutical remained stable for 5 hours post-preparation. No significant differences in general health, behavior, body weight, or hematological and biochemical parameters were observed between experimental and control groups, indicating the safety and biocompatibility of the drug. The MDP^{99m}Tc preparation was confirmed to be sterile and apyrogenic. These findings supported the clinical applicability of the MDP-Sn(II) kit for bone imaging and recommended its use in clinical trials.

KEYWORDS: radiopharmaceutical; substance; radionuclide; technetium-99m.

I.INTRODUCTION

Radionuclide diagnostics play a crucial role in the evaluation of pathological processes in the skeletal system due to their high sensitivity and ability to detect changes at early stages, before radiological signs appear. One of the most widely used methods in clinical practice is osteoscintigraphy, using radiopharmaceuticals based on technetium-99m (^{99m}Tc) labeled with phosphate-containing ligands that possess osteotropic properties [1-2].

The pharmacological effectiveness of osteotropic radiopharmaceuticals depends on their chemical structure, in vivo stability, specificity of accumulation in bone tissue, and clearance pathways. Initially, ^{99m}Tc complexes with inorganic phosphates, including pyrophosphates, were used. These complexes are characterized by their ability to bind with hydroxyapatite. However, the presence of the P–O–P bond makes them vulnerable to enzymatic hydrolysis by alkaline phosphatase, reducing the stability of the radiocomplexes in vivo. Additional limitations include slow clearance from the bloodstream, moderate accumulation in bone tissue, and pronounced nonspecific distribution, particularly in the liver (up to 10–15% of the administered activity).

Significant progress was made with the introduction of ^{99m}Tc-containing bisphosphonate complexes. Due to the presence of the stable P–C–P bond, which is resistant to hydrolysis, these compounds demonstrate high chemical and biological stability. Bisphosphonates exhibit strong affinity for the mineral phase of bone, especially in areas of osteoblastic activity, ensuring selective accumulation of the drug in pathologically altered areas. This is particularly important for visualizing metastatic bone involvement, osteomyelitis, microfractures, stress, and degenerative changes [3-7].

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The most widely used radiopharmaceuticals in osteoscintigraphy are ^{99m}Tc-methylene diphosphonate (MDP) and ^{99m}Tc-hydroxyethylidene diphosphonate (HEDP). Both preparations are characterized by rapid clearance from the blood plasma, high accumulation in the skeleton within 60 minutes after intravenous injection, and low nonspecific distribution in soft tissues. Excretion occurs primarily via the kidneys, which further reduces background activity and improves image contrast.

Due to their combination of high sensitivity, availability, safety, and pronounced osteotropism, osteoscintigraphy with ^{99m}Tc-bisphosphonates remains the standard method for radionuclide imaging of skeletal pathologies in modern clinical practice.

The objective of this study is to evaluate the functional suitability of the radiopharmaceutical MDP^{99m}Tc for radionuclide imaging of the skeletal system in both normal and pathological conditions. The study aims to determine the diagnostic efficacy, specificity of drug accumulation in bone tissue, as well as to verify its clinical applicability as an early detection tool for bone pathology of various origins. Additionally, the study assesses the safety of the drug based on sterility, apyrogenicity, and its ability to cause adverse reactions when administered intravenously to animals.

II. METHODS, MATERIALS AND REAGENTS.

Preparation of MDP^{99m}Tc.

For the research, five batches of the MDP-Sn(II) lyophilized kit for the preparation of the radiopharmaceutical MDP^{99m}Tc were used.

The lyophilized kit for preparing the intravenous solution has the following composition per 1 mL:

- Technetium-99m: 370 MBq - 1110 MBq (10 mCi - 30 mCi)
- Methylene diphosphonic acid: 9.0 mg - 11.0 mg
- Stannous chloride dihydrate: 0.9 mg - 1.1 mg
- Ascorbic acid: 1.9 mg - 2.1 mg
- Transparent colorless liquid

The pH of the lyophilized solution (in 5 mL of 0.9% NaCl) is 5.0 - 7.0. Purity (RCH) > 98%.

To prepare the MDP^{99m}Tc radiopharmaceutical, 5.0 mL of sodium pertechnetate 99mTc solution from the generator is injected into the vial containing the MDP-Sn(II) lyophilized kit by piercing the rubber stopper with a syringe needle. After that, the vial is shaken and left for 20 minutes. The preparation is now ready for use.

Methodology and Experimental Animals.

The pharmacokinetics of the drug were studied on 300 intact albino rats and rats with a bone pathology model, weighing 170–240 g. The bone pathology was simulated by inducing a fracture of the right femur. Animal manipulations were performed under ether anesthesia. Over the next 14 days, a bone callus was formed, which served as the model for bone pathology.

The drug under investigation was administered intravenously into the tail vein in a volume of 0.2 mL. Animals were euthanized by decapitation at 1, 3, and 24 hours post-injection. The radioactivity in the organs and tissues was determined by direct radiometry using an automatic spectrometer NK-350 (Hungary). The results were calculated as a percentage of the administered dose. In the blood, the concentration was calculated as a percentage of the administered dose per gram, with the total blood volume assumed to be 7% of the animal's body weight.

Additionally, the differential accumulation coefficients (DAC) were calculated as the ratio of the concentration of the drug in the fractured femur to the concentration in the healthy femur, and the skeletal/blood ratio was determined as the ratio of the drug accumulation in the skeleton to its content in the blood. For each time point, 3-5 animals were used in parallel.

Statistical analysis was performed using the Student's t-test, calculating the arithmetic mean (M) and standard error of the mean (m).

All animal experiments were conducted in accordance with the applicable standards and regulations [6-7].

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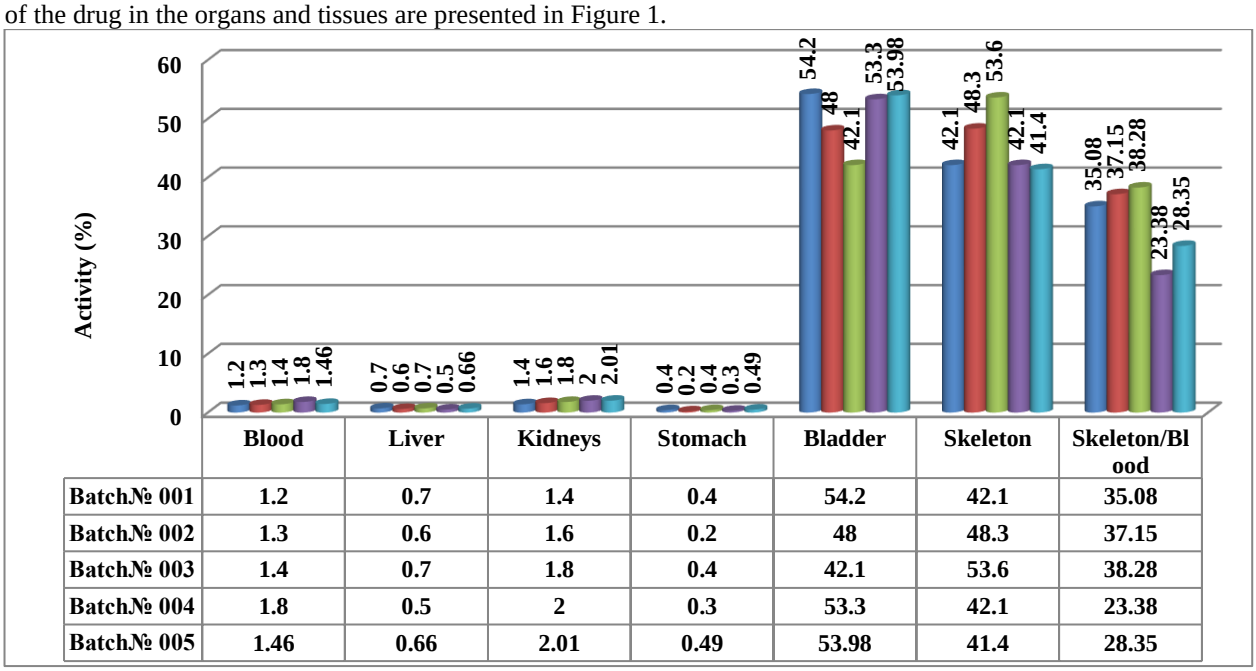
Principles of Animal Group Formation and Dosage of the Drug in Acute and Subchronic Toxicity Studies.

For the study of acute toxicity, 4 groups of animals were formed, with 6 animals in each group. The average weight of the female rats was 163 g, and the average weight of the male rats was 170 g. Animals in 3 experimental groups were injected with the MDP^{99m}Tc drug from the corresponding batch, prepared by diluting the lyophilized powder in 1 mL of 0.9% sodium chloride solution. The control group animals were injected with 0.2 mL of physiological saline. For the study of subchronic toxicity, 7 groups of female animals, each containing 6 rats, were formed by random selection. The animals were intravenously injected with 0.2 mL of the drug, prepared by diluting the lyophilized powder in 5 mL of 0.9% sodium chloride solution. The control group animals were injected with 0.2 mL of physiological saline. In both acute and subchronic toxicity studies, the solutions were prepared by diluting the lyophilized powder to achieve concentrations that, when injected intravenously, delivered doses of 70 and 14 times the recommended diagnostic dose for humans, respectively.

III. RESULTS AND DISCUSSION

Study of the Accumulation of MDP^{99m}Tc in Organs and Tissues of Healthy Uninbred Rats.

In this study, the accumulation of MDP^{99m}Tc in the organs and tissues of healthy uninbred rats was examined. Five batches of the MDP^{99m}Tc drug were used for the experiment, which were administered intravenously. Distribution analyses of the substance in various organs and tissues of the animals were conducted. The results of the accumulation of the drug in the organs and tissues are presented in Figure 1.



	Blood	Liver	Kidneys	Stomach	Bladder	Skeleton	Skeleton/Blood
Batch№ 001	1.2	0.7	1.4	0.4	54.2	42.1	35.08
Batch№ 002	1.3	0.6	1.6	0.2	48	48.3	37.15
Batch№ 003	1.4	0.7	1.8	0.4	42.1	53.6	38.28
Batch№ 004	1.8	0.5	2	0.3	53.3	42.1	23.38
Batch№ 005	1.46	0.66	2.01	0.49	53.98	41.4	28.35

Figure 1. Histogram of MDP^{99m}Tc Accumulation in Organs and Tissues of Healthy Female Rats 1 Hour After Intravenous Injection (% Dose/Organ).

As shown by the obtained data, the drug exhibits pronounced osteotropism. One hour after intravenous administration, an average of 45.6% of the MDP^{99m}Tc accumulates in the skeleton. Approximately 50.31% of the MDP^{99m}Tc is excreted from the body via urine. Thus, the level of drug accumulation in the skeleton provides satisfactory visualization for osteoscintigraphy.

Study of Pharmacokinetics of MDP^{99m}Tc in Rats with Femoral Fracture.

Increased accumulation of osteotropic bisphosphonates reflects the intensity of metabolic processes at the site of bone damage, and therefore serves as an important indicator of pathological activity. Any bone disease, including tumor

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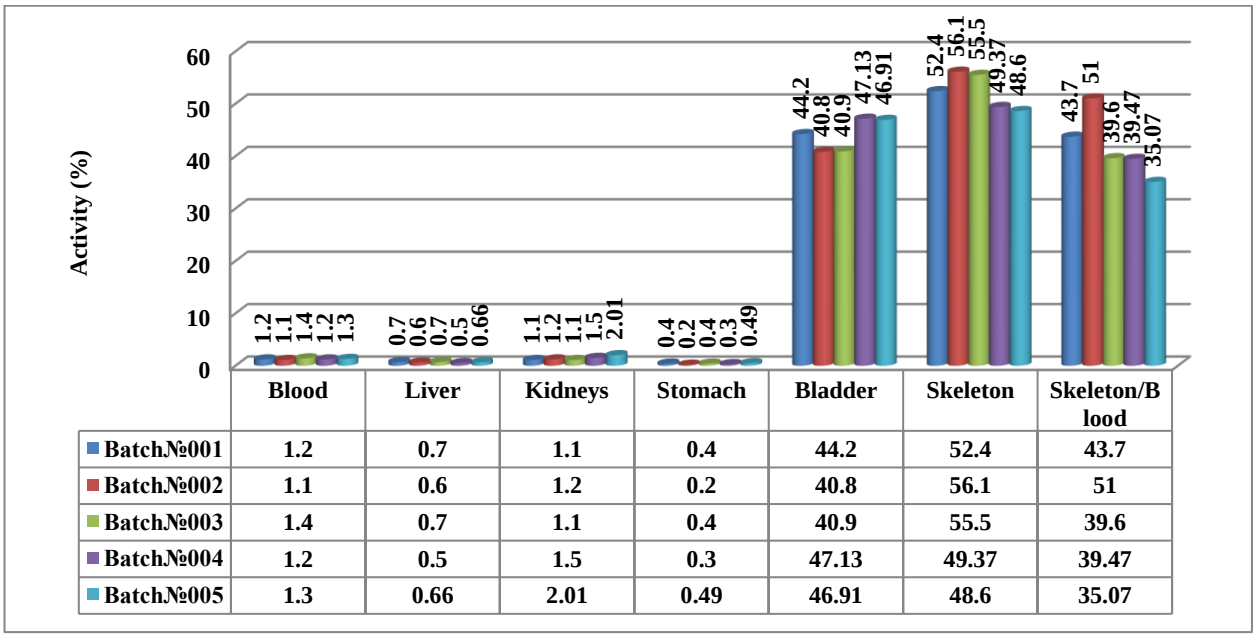
lesions, undergoes an early stage of intensified metabolic processes, which precedes the development of overt morphological changes detectable by radiography. Since MDP^{99m}Tc is intended for identifying metabolic processes in bones during various diseases, its pharmacokinetics were studied using the most accessible model of bone pathology — femoral fracture in rats. The obtained data are presented in Figure 2.

The obtained data show that the preparation from five batches exhibits pronounced osteotropism. When analyzing the accumulation in the area of the bone callus, the level of fixation of the drug is more than 1.3 times higher than the accumulation in normal bone tissue, averaging 52.4%. These results indicate that the optimal time for the study is 1 to 3 hours, although satisfactory skeletal visualization can still be achieved even 5 hours after administration.



	Blood	Liver	Kidneys	Stomach	Bladder	Skeleton	Skeleton/Blood
Batch№001	1.2	0.7	1.1	0.4	44.2	52.4	43.7
Batch№002	1.1	0.6	1.2	0.2	40.8	56.1	51
Batch№003	1.4	0.7	1.1	0.4	40.9	55.5	39.6
Batch№004	1.2	0.5	1.5	0.3	47.13	49.37	39.47
Batch№005	1.3	0.66	2.01	0.49	46.91	48.6	35.07

Figure 2. Histogram of MDP^{99m}Tc accumulation in the organs and tissues of female rats with femoral fracture (14 days post-fracture) at various time points after administration (activity, % of dose per organ)

Establishment of the Possible Expiry Date of the MDP^{99m}Tc Preparation.

To establish the potential expiration date of the MDP^{99m}Tc preparation, a study was conducted on its distribution in the animals' bodies based on the time elapsed since preparation. Different time intervals were examined: freshly prepared preparation, as well as preparations that were stored for 0.5, 1, 3, and 5 hours. The experiments allowed for the assessment of the stability and pharmacokinetic characteristics of the preparation over time after preparation. The data obtained during the study are presented in figure 3.

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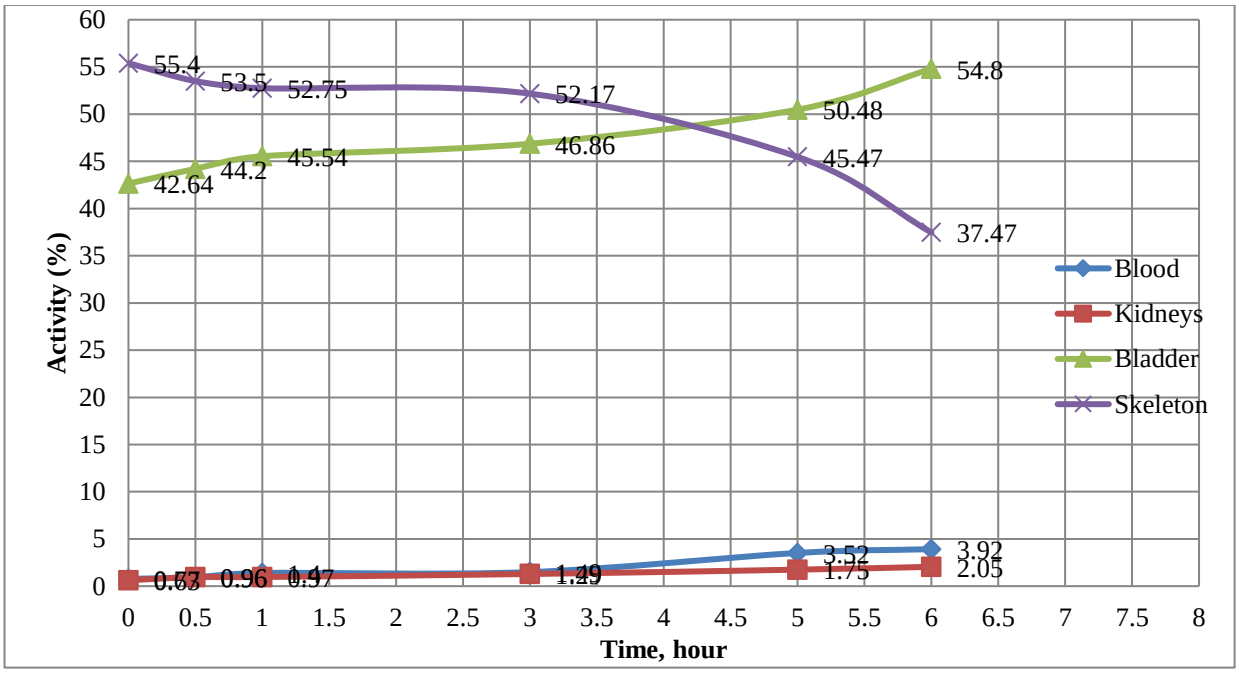

Figure 3. Accumulation of the MDP^{99m}Tc preparation in rat organs and tissues 1 hour after administration, depending on the storage time of the preparation.

The obtained data indicate that the MDP^{99m}Tc preparation retains its biological properties for up to 5 hours after preparation. The distribution of the drug in the animals' bodies and its pharmacokinetic characteristics do not undergo significant changes during this time period. The ratio of elimination to accumulation remains stable and satisfactory at all stages of the study, which suggests that the preparation maintains its effectiveness and predictable behavior in the body within the 5-hour window after preparation. These results confirm that the preparation can be used within this time frame without loss of quality and with expected diagnostic outcomes.

Determination of the shelf life of the MDP-Sn(II) Kit in lyophilized form for the preparation of the MDP^{99m}Tc radiopharmaceutical.

The shelf life of the MDP-Sn(II) kit in lyophilized form, used for the preparation of the MDP^{99m}Tc radiopharmaceutical, was studied over a 12-month storage period. During this period (at 3, 6, 9, and 12 months of storage), doses of the MDP^{99m}Tc preparation were prepared from the lyophilized powder. Following preparation, the distribution of the radiopharmaceutical in the organs and tissues of healthy rats was studied. The results of these experiments are presented in Table 1.

Table 1
Accumulation of MDP^{99m}Tc in the organs and tissues of rats 1 hour after administration, depending on the storage time of the lyophilized kit used to prepare the radiopharmaceutical

Batch Number	Storage Time	Accumulation of MDP^{99m}Tc Activity in Organs and Tissues of Rats as a Percentage of Total Activity,					Skeleton /Blood Ratio
		Blood	Liver	Kidneys	Bladder	Skeleton	
001	0 Freshly Prepared	1,2 ± 0,98	0,7 ± 0,32	1,1 ±0,19	53,5 ±6,80	42,6 ± 4,02	35,5
	3 Months	1,1 ±0,40	0,2 ± 0,05	0,8 ± 0,18	46,5 ± 8,03	44,1 ±0,61	40,0
	6 Months	1,6 ± 0,28	0,3 ± 0,15	1,0 ± 0,20	54,9 ± 4,55	48,1 ± 1,27	30,06
	9 Months	1,4 ± 0,41	0,4 ±0,15	1,2 ±0,05	46,7 ±0,17	47,8 ±3,16	34.14
	12 Months	2,1 ±0,86	0,5 ± 0,07	1,5 ±0,73	45,1 ±0,61	49,4 ± 6,72	23,52

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002	0 Freshly Prepared	1,7±1,30	0,6±0,13	1,6 ± 0,78	45,5± 5,78	45,1 ± 1,09	26,52
	3 Months	1,0 ±0,27	0,3 ± 0,06	1,1 ±0,67	44,3± 17,64	44,9 ±2,79	44,9
	6 Months	1,3±0,35	0,5 ± 0,08	1,6±0,81	38,20 ± 2,67	43,2 ±4,89	33,2
	9 Months	0,9 ± 0,55	0,3± 0,05	1,0 ± 0,46	42,9± 1,51	51,1 ±4,07	56,8
	12 Months	1,2±0,57	0,5 ±0,15	1,7 ± 0,25	49,7 ± 3,48	54,9 ± 7,46	45,7
003	0 Freshly Prepared	1,4 ± 0,40	0,7 ± 0,24	1,1 ±0,18	45,6 ±4,30	46,5 ± 0,41	33,2
	3 Months	1,4±0,48	0,5 ± 0,34	0,9 ± 0,32	42,0 ± 7,30	49,5 ± 1,07	35,35
	6 Months	1,5 ± 1,10	0,3 ± 0,04	1,4 ±0,65	40,6± 13,26	49,2 ±6,01	32,8
	9 Months	1,8 ±0,08	0,2 ± 0,03	0,8 ±0,12	46,3 ± 6,36	46,5 ± 11,57	25,8
	12 Months	1,6± 1,16	0,5 ± 0,03	1,2 ± 0,34	35,0 ± 7,50	53,3 ±0,06	33,31

As seen from the obtained data, when the MDP-Sn(II) lyophilized kit for the preparation of MDP^{99m}Tc is stored for 12 months, the distribution parameters of the drug in the body remained stable. One hour after intravenous administration, the accumulation of MDP^{99m}Tc in the skeleton for batches 001, 002, and 003 averaged 46.4%, 47.84%, and 49.0%, respectively. These data confirm the stability of the drug distribution in bone tissue even after prolonged storage of the lyophilizate.

Furthermore, the ratio of the concentration of the drug in the skeleton to that in the blood averaged 35.48 (ranging from 23.52 to 56.8), indicating the predominant accumulation of the substance in the bone tissue compared to the circulatory system. This confirms the drug's efficacy in its target area of action.

Thus, the results of the study confirm that the MDP-Sn(II) lyophilized kit maintains its efficacy and stability over 12 months of storage, making it suitable for preparing MDP^{99m}Tc with expected diagnostic results.

Study of the Pharmacokinetics of the MDP^{99m}Tc Radiopharmaceutical in Immature Animals.

To explore the potential characteristics of the MDP^{99m}Tc radiopharmaceutical and its applicability in pediatric medicine, we conducted a pharmacokinetic study on immature intact female rats. This investigation aimed to assess how the drug behaves in juvenile organisms and to evaluate the feasibility of using this radiopharmaceutical for pediatric diagnostic purposes. The pharmacokinetic data obtained, including distribution in various organs and tissues, clearance rates, and accumulation patterns, are presented in Table 2.

Table 2

Pharmacokinetics of the MDP^{99m}Tc drug in the organs and tissues of immature intact female rats after intravenous administration (activity, % dose/organ)

Organ	Time after administration, hours				
	0,5	1	3	5	24
Blood	1,15 ±0,40	1,2 ±0,52	0,97 ± 0,39	1,1 ±0,34	0,76 ±0,25
Liver	0,61 ±0,17	0,31 ±0,05	0,34 ±0,10	0,28 ± 0,04	0,32 ± 0,09
Kidneys	1,21 ±0,50	1,41 ±0,83	0,99 ± 0,44	0,91 ±0,08	0,74 ±0,38
Stomach	0,24 ± 0,08	0,19 ±0,05	0,70 ±0,95	0,65 ± 0,47	0,22 ± 0,08
Urinary Bladder	35,59 ±5,62	34,92± 1,09	37,29 ± 2,51	44,43 ± 1,51	67,51 ± 2,51
Skeleton	52,9 ±3,61	60,53 ± 4,64	59,2 ± 7,60	53,60 ±7,32	24,88 ± 2,39
Skeleton/Blood	46,0	50,44	61,03	48,72	32,2

As expected, the accumulation of the radiopharmaceutical (RP) in bone tissue in immature animals was higher than in adults. Already **30 minutes** after intravenous administration, active fixation of the radiopharmaceutical in bone tissue is observed, and the accumulation in the skeleton reaches **51.2%** of the administered dose. During the **1-3 hour** period after administration, the accumulation of the radiopharmaceutical in the skeleton reaches its maximum, amounting to about

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60% of the injected amount, after which it slightly decreases (to **52.9%** at **24 hours** post-administration). Meanwhile, the amount of the radiopharmaceutical in the blood decreases from **1.15%** (30 minutes after administration) to **0.76%** (24 hours post-administration). Almost all the radiopharmaceutical not incorporated into bone tissue is excreted in the urine, without accumulating in other organs and tissues.

Assessment of Pyrogenic Properties of the MDP^{99m}Tc Preparation.

A qualitative test for pyrogens was performed using dilutions of the preparation at 1:1, 1:10, and 1:100. According to regulatory requirements, the maximum allowable endotoxin concentration (MAC) for intravenously administered radiopharmaceuticals is 175/V EU/ml, where V is the maximum volume of the administered preparation. At a volume of 5 ml, the MAC is 35 EU/ml.

The permissible dilution factor for the Limulus Amebocyte Lysate (LAL) test is determined as the ratio of the MAC to the sensitivity of the reagent used, which in this case allows for a dilution of over 1000 times. During testing, gel formation was observed only in the 1:1 dilution, while no gel formation was noted at 1:10 and 1:100 dilutions. This indicates that the endotoxin content in the preparation is not less than 0.03 EU/ml and does not exceed 0.3 EU/ml, which is significantly below the allowable limit.

Based on the results obtained, it was concluded that the MDP^{99m}Tc preparation (all three tested batches) does not exhibit pyrogenic properties.

Sterility Testing of the MDP^{99m}Tc Preparation.

According to the results of the antimicrobial activity test, the preparation did not exhibit inhibitory effects on microbial growth under the test conditions. Visual monitoring for microbial growth was carried out daily over a 14-day period. No microbial growth was observed, indicating the sterility of the tested batches of the preparation.

Acute Toxicity Study.

An acute toxicity study of the MDP^{99m}Tc preparation was conducted in laboratory animals to assess potential toxic effects and determine the dose that may cause a lethal outcome (LD_{50}). The preparation was administered intravenously at a dose 70 times higher than the recommended diagnostic dose for humans, equivalent to µg/kg (calculated based on the active substance).

No mortality or pronounced signs of intoxication were observed following administration at the specified dose. In male animals, transient suppression was noted within the first hour post-injection, manifested as reduced activity, with no subsequent complications. Physiological parameters, including motor activity, appetite, skin condition, and response to stimuli, remained within normal limits throughout the observation period.

The data obtained indicate low acute toxicity and good tolerability of the MDP^{99m}Tc preparation.

Subchronic Toxicity Study.

To evaluate the effects of the preparation under subchronic administration, hematological parameters were assessed in laboratory animals. The results of the hematological analysis are presented in Table 3, which shows the main blood parameters in control group rats. These data serve as reference values for comparison with those of the test groups and are used to assess the potential impact of the preparation on hematopoiesis (Table 4).

Table 3.
Hematological Parameters of Rats in Control Groups

Parameter	Time, days					
	Before the test	Day 1	Day 3	Day 6	Day 10	Day 15
Hemoglobin g/dL	15,0 ±0,7	14,3 ±0,3	14,6 ±0,4	14,0 ±0,6	14,7 ±0,9	15,3 ±0,4
Erythrocytes million/µL	6,6 ± 0,4	6,2 ± 0,8	6,1 ± 0,2	6,3 ± 0,2	7,0 ±0,5	7,3 ± 1,2
Platelets thousand/µL	355,3 ±42,1	333,5 ± 32,5	310,6 ±42,6	308,6 ± 18,6	320,0 ±20,1	350,9 ±36,7
Leukocytes thousand/µL	9,5 ± 1,8	10,3 ± 1,3	9,6 ±3,1	8,7 ± 1,0	9,7 ± 1,3	11,7± 1,4

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Table 4.
Hematological Parameters of Rats in Experimental Groups

Parameter	MDP^{99m}Tc batch № 001					
	Before the test	Day 1	Day 3	Day 6	Day 10	Day 15
Hemoglobin, g/dL	15,0 ±0,7	13.3 ±0,7	13,5 ±0,9	13,7 ±0,2	14,2 ±0,5	13,7 ±0,2
Erythrocytes,	6,6 ± 0,4	5,6 ± 0,5	6,5 ±0,7	5,8 ± 0,4	6,3 ± 0,7	5,8 ±0,4
Platelets, thousand/µL	355,3 ±42,1	3 14,6± 14,4	301,5± 38,5	347,8 ± 17,9	307,8 ± 27,6	347,8 ± 17,9
Leukocytes,	9,5 ± 1,8	12,5 ± 1,1	10,8 ± 1,5	11,2 ±0,8	12,2 ±0,6	11,2 ±0,8
Parameter	MDP^{99m}Tc batch № **002**					
	Before the test	Day 1	Day 3	Day 6	Day 10	Day 15
Hemoglobin, g/dL	15,0 ±0,7	13,3 ±0,7	13,5 ±0,9	13,7 ±0,2	13,7 ±0,2	13,7 ±0,2
Erythrocytes,	*6,6* ± 0,4	5,6 ±0,5	6,5 ± 0,7	5,8 ± 0,4	5,8 ± 0,4	5,8 ± 0,4
Platelets, thousand/µL	355,3±42,1	314,6 ± 14,4	301,5 ±38,5	347,8 ± 17,9	347,8 ± 17,9	347,8 ± 17,9
Leukocytes,	9,5 ± 1,8	12,5 ± 1,1	10,8 ± 1,5	11,2 ±0,8	11,2 ±0,8	11,2 ±0,8
Parameter	MDP^{99m}Tc batch № **003**					
	Before the test	Day 1	Day 3	Day 6	Day 10	Day 15
Hemoglobin, g/dL	15,0 ±0,7	13,3 ±0,7	13,5 ±0,9	13,7 ±0,2	13,7 ±0,2	13,7 ±0,2
Erythrocytes,	*6,6* ± 0,4	5,6 ± 0,5	6,5 ± 0,7	5,8 ± 0,4	5,8 ±0,4	5,8 ±0,4
Platelets, thousand/µL	355,3±42,1	314,6 ± 14,4	301,5 ±38,5	347,8 ± 17,9	347,8 ± 17,9	347,8 ± 17,9
Leukocytes,	9,5 ± 1,8	12,5 ± 1.1	10,8 ± 1,5	11,2 ±0,8	1 1,2 ±0,8	11,2 ±0,8

The dynamics of the main hematological parameters showed that changes in these parameters in both the control and experimental groups of animals followed similar trends. This indicates the absence of any effect of the MDP^{99m}Tc drug on the hematopoietic system. All major parameters remained within the physiological norm during the observation period. No signs of toxic effects of the drug on the hematopoietic system were observed.
Considering the high lability of hematological parameters in rats under normal conditions and the absence of pathological forms of leukocytes in blood smears (such as lymphocytes with pyknotic nuclei, toxic granulation in neutrophils, or abnormal erythrocyte forms), it can be concluded that the MDP^{99m}Tc drug does not have a toxic effect on the rats' organisms.
Therefore, it can be concluded that MDP^{99m}Tc does not have any significant impact on the hematopoietic system of laboratory animals.

Biochemical Studies.

Biochemical blood parameters in animals (rats) are an important indicator of their physiological state under various experimental conditions. Tables 5 and 6 present the main biochemical blood parameters obtained as a result of the analysis.

Table 5
Biochemical Blood Parameters of Control Rats

Parameter	6 Day	15 Day
Total protein, g/L	63,75 ± 11,2	61,29 ± 1,10
Total bilirubin, µmol/L	22,67 ± 5,46	22,1 ± 5 , 1 0
Glucose, mmol/L	6,83 ± 1,07	7,04 ± 1,28
Creatinine, µmol/L	63,50 ±9,53	62,70± 10,10

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Table 6
Biochemical Blood Parameters of Experimental Rats

Parameter	MDP^{99m}Tc batch № 001		MDP^{99m}Tc batch № 002		MDP^{99m}Tc batch № 003	
	6 Day	15 Day	6 Day	15 Day	6 Day	15 Day
Total protein, g/L	66,53 ± 6,60	60,93 ± 6,59	55,66± 1,40	59,03 ± 1,37	60,93 ± 6,59	55,16 ± 1,40
Total bilirubin, μmol/L	22,95 ± 3,60	22,10 ±2,40	22,95 ± 1,20	24,65 ± 3,59	22,10 ±2,40	22,95 ± 1,20
Glucose, mmol/L	8,71 ±0,12	9,22 ±0,37	9,22 ± 0,37	8,88 ±0,37	9,22 ±0,37	9,22 ± 0,37
Creatinine, μmol/L	66,70±10,80	50,00±10,00	55,30±11,06	65,40±13,10	50,00±10,00	55,30 ±11,06

During the biochemical analysis of the serum of animals receiving the test drug, it was found that the values of key biochemical parameters in the experimental group were not significantly different from those in the control group. Statistical processing of the results showed no significant differences ($p > 0.05$), indicating the maintenance of normal functional conditions of the liver, kidneys, and other organs involved in metabolism and detoxification.
Thus, the obtained results confirm the biochemical neutrality of the drug when applied at the tested dose and regimen. This, combined with other data, suggests a favorable safety profile for the drug.

Study of Body Weight Dynamics.

The study of body weight dynamics in animals is an important component of preclinical safety and tolerability assessment of the test substance. Changes in body weight can serve as informative indicators of the overall health status, reflecting processes such as metabolic shifts, the response to drug administration, adaptive mechanisms, and potential toxic effects. As part of the preclinical study, the changes in body weight of experimental animals were evaluated throughout the observation period. Body weight was recorded at regular intervals, which allowed for the identification of characteristic trends and potential deviations from the norm. A comparative analysis of the data between the control and experimental groups enables the assessment of statistically significant differences and the determination of the potential impact of the test drug on the overall physiological status of the animals. The results of the body weight dynamics measurements are presented in Table 7.

Table 7
Body Weight Dynamics of Experimental and Control Animals

	Body weight of animals (g)		
	Before the test	6 Day	15 Day
Control Animals	163,3 ± 12,3	166,0 ±7,2	184,0 ±9,0
MDP^{99m}Tc batch № 001/ **Experimental Animals**	165,0 ±7,3	171,3± 11,2	182,5 ±8,5
MDP^{99m}Tc batch № 002/ **Experimental Animals**	165,0 ±7,3	169,4 ±8,3	179,7 ±7,5
MDP^{99m}Tc batch № 003/ **Experimental Animals**	165,0 ±7,3	173,7 ±9,2	180,0 ±6,9

Weighing of control and experimental rats showed an increase in body weight in animals from all groups, with a difference of 12% for the control group and approximately 10% for the experimental groups by the end of the experiment. The weight gain in the experimental groups was not significantly different from that observed in the control group.

IV. CONCLUSION

The pharmacokinetics study of the radiopharmaceutical MDP^{99m}Tc in the organs and tissues of female rats after intravenous administration showed that the physiological distribution of the test radiopharmaceutical exhibits pronounced osteotropism. One hour after intravenous injection, up to 52.4% of the drug localizes in the skeleton.
According to the differential accumulation coefficients (bone pathology/normal, skeleton/blood), the drug enables the possibility of performing osteoscintigraphy. This fact confirms the functional suitability of the drug as a radiopharmaceutical for diagnosing pathological processes in bone tissue associated with osteoblastic activity.

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The optimal time for conducting the investigation aimed at visualizing the skeleton should be considered 1–3 hours after intravenous injection.

The MDP-Sn(II) kit in the form of a lyophilized powder for preparing MDP^{99m}Tc does not alter its biological properties during 1 year of storage, while the prepared drug retains its stability for up to 5 hours post-preparation.

Throughout the observation period, the overall condition, behavior, weight changes, as well as hematological and biochemical parameters of the experimental animals did not differ from those of the control group. The fluctuations in hematological and biochemical indicators remained within the physiological norm for white non-pedigree rats. The MDP^{99m}Tc preparation tested was sterile and apyrogenic. The obtained results confirm the safety of the drug.

The conducted studies allow recommending the lyophilized kit for the preparation of MDP^{99m}Tc for clinical trials.

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