Biodistribution of the radiophamarceutical sodium pertechnetate ($Na^{99m}TcO_4$) after massive small bowel resection in rats[1]

Biodistribuição do radiofármaco pertecnetato de sódio ($Na^{99m}TcO_4$) em ratos submetidos a ressecção extensa de intestino delgado

Dâmaso de Araújo Chacon[2], Irami Araújo-Filho[2], Arthur Villarim-Neto[2], Amália Cínthia Meneses Rêgo[3], Ítalo Medeiros Azevedo[4], Mário Bernardo-Filho[5], José Brandão-Neto[6], Aldo Cunha Medeiros[6]

1. Research performed at Nucleus for Experimental Surgery, Federal University of Rio Grande do Norte (UFRN), Brazil.
2. Fellow PhD degree, Postgraduate Program in Health Sciences, UFRN, Brazil.
3. Graduate Student, Scientific Initiation Program, UFRN, Brazil.
4. Statistician, Department of Surgery, UFRN, Brazil.
5. PhD, Chairman, Biophysics and Biometry Department, UERJ, Brazil
6. PhD, Full Professor, Postgraduate Program in Health Sciences, UFRN, Brazil.

ABSTRACT

Purpose: To evaluate the biodistribution of sodium pertecnetate ($Na^{99m}TcO_4$) in organs and tissues, the morphometry of remnant intestinal mucosa and ponderal evolution in rats subjected to massive resection of the small intestine. **Methods**: Twenty-one Wistar rats were randomly divided into three groups of 7 animals each. The short bowel (SB) group was subjected to massive resection of the small intestine; the control group (C) rats were not operated on, and soft intestinal handling was performed in sham rats. The animals were weighed weekly. On the 30th postoperative day, 0.1 mL of $Na^{99m}TcO_4$, with mean activity of 0.66 MBq was injected intravenously into the orbital plexus. After 30 minutes, the rats were killed with an overdose of anesthetic, and fragments of the liver, spleen, pancreas, stomach, duodenum, small intestine, thyroid, lung, heart, kidney, bladder, muscle, femur and brain were harvested. The biopsies were washed with 0.9% NaCl.,The radioactivity was counted using Gama Counter Wizard™ 1470, PerkinElmer. The percentage of radioactivity per gram of tissue (%ATI/g) was calculated. Biopsies of the remaining jejunum were analysed by HE staining to obtain mucosal thickness. Analysis of variance (ANOVA) and the Tukey test for multiple comparisons were used, considering $p<0.05$ as significant. **Results**: There were no significant differences in %ATI/g of the $Na^{99m}TcO_4$ in the organs of the groups studied ($p>0.05$). An increase in the weight of the SB rats was observed after the second postoperative week. The jejunal mucosal thickness of the SB rats was significantly greater than that of C and sham rats ($p<0.05$). **Conclusion**: In rats with experimentally-produced short bowel syndrome, an adaptive response by the intestinal mucosa reduced weight loss. The biodistribution of $Na^{99m}TcO_4$ was not affected by massive intestinal resection, suggesting that short bowel syndrome is not the cause of misleading interpretation, if an examination using this radiopharmaceutical is indicated.

Key words: Short Bowel Syndrome. Sodium Pertechnetate Tc 99m. Pharmacokinetics. Rat

RESUMO

Objetivo: Avaliar em modelo animal com ressecção extensa do intestino delgado a biodistribuição de pertecnetato de sódio ($Na^{99m}TcO_4$) em órgãos e tecidos, a evolução ponderal e a morfometria da mucosa do intestino delgado remanescente. **Métodos**: Vinte e um ratos *Wistar* foram aleatoriamente divididos em três grupos de sete animais cada. O grupo intestino curto (IC) foi submetido a ressecção extensa do intestino delgado, o grupo controle (C) não foi operado e o grupo *sham* foi submetido a leve manipulação cirúrgica das alças intestinais.Todos foram pesados semanalmente. No 30º dia pós-operatório foi administrado 0,l mL de $Na^{99m}TcO_4$ aos animais dos três grupos, IV no plexo orbital, com atividade radioativa média de 0,66MBq. Após 30 minutos os ratos foram mortos e retirados fragmentos do fígado, baço, pâncreas, estomago, duodeno, intestino delgado, tireóide, pulmão, coração, rim, bexiga, músculo, fêmur, e cérebro. As amostras foram lavadas com solução de NaCl 0,9%.A radioatividade foi contada peloContador Gama 1470, Wizard™ Perkin-Elmer e calculado o percentual de atividade radioativa por grama (%ATI/g) de cada órgão. Biópsias do jejuno foram submetidas a análise da espessura da mucosa (coloração HE). Utilizou-se avaliação estatística paramétrica (ANOVA) e teste de Tukey, considerando $p<0,05$ como significante. **Resultados**: Não houve diferenças significantes da %ATI/g nos órgãos dos grupos estudados ($p>0,05$). Verificou-se acentuada redução inicial de peso, em seguida um aumento do peso dos animais tratados a partir da segunda semana de observação e aumento da espessura da mucosa jejunal do grupo IC, comparado com os demais. **Conclusão**: Em ratos com síndrome do intestino curto, uma adaptação na espessura da mucosa contribuiu para reversão na perda de peso inicial e para que a biodistribuição do $Na^{99m}TcO_4$ não fosse afetada pela ressecção extensa do intestino, sugerindo que o intestino curto não é causa de interpretações duvidosas, quando exame cintilográfico com este radiofármaco estiver indicado.

Descritores: Síndrome do Intestino Curto. Pertecnetato Tc99m de Sódio. Farmacocinética. Ratos.

Introduction

Radioisotopes are used in nuclear medicine for diagnostic and therapeutic purposes. The labelling capacity of these isotopes for the plasmatic proteins is well known, and their bioavailability and pharmacokinetics can be modified by drugs and diseases[1,2]. Among the most useful artificial radioisotopes, technetium-99m, in the chemical form of sodium pertechnetate ($Na^{99m}Tc0_4$), is the most important. Its use in nuclear medicine is due to the emission of gamma energy of 140 KeV, enabling it to take advantage of the scintillation detectors and obtain enhanced image quality; this is known as scintigraphy[3]. It has a short life, is low cost, and is obtained from a molybdenum/technetium generator ($^{99}Mo/^{99m}Tc$).[3] It is easily distributed through the vascular fluid, interstitial space with uptake by the salivary glands, thyroid, stomach, intestines and other organs[3]. It is rapidly eliminated by the urine and when incorporated to specific substances, produces organ images of different densities and functions[4]. Experimental studies carried out with the labelling of red blood cells with ^{99m}Tc identified important biological effects, in addtion to alterations in the labelling process[5,7]. Gomes et al carried out a study with mitomicin-C that described alterations in the labelling of red blood cells[6]. The literature reports that several natural drugs reduce the efficiency of labelling red blood cells with ^{99m}Tc[7]. An experimental study with Vincristin, used in oncology protocols, showed an interaction of this drug with ^{99m}Tc in several organs[8]. However, there are no reports of research studying the biodistribution of radiopharmaceuticals after surgical procedures. In the present study, we used an experimental model of massive resection of the small intestine, characterizing the short bowel syndrome, which results in unsuitable water and nutrient absorption, causing malnutrition[9,10]. In spite of the short bowel syndrome, the intestine can be adapted through physiologic, cellular and moleculares mechanisms[9]. In some patients, dilation and lengthening of the remnant small intestine occur as a phenomenon of functional adaptation. Surgical techniques have been reported that attempt to lengthen this intestinal segment. Such procedures are complex and frequently ineffective, and call for assessments of their efficacy[11]. Recently, new therapeutic methods, such as isolated small intestine transplantation or combined with liver transplantation, have been an alternative for cases of hepatic failure due to total parenteral nutrition in the treatment of short bowel syndrome[12]. Given the antiabsorptive effect of the operation, with great repercussions on the metabolism, radioisotope images may be necessary in the postoperative, in order to control the series of pathological conditions resulting from short bowel syndrome. Scintigraphy can be used in the postoperative of intestinal resections to assess the morphology and metabolism of several organs. Under these conditions, it becomes relevant to study the biodistritubion of $Na^{99m}Tc0_4$ in specific organs and tissues. Therefore, the present paper aims to study, in an animal model of massive resection of the small intestine, the biodistribution of $Na^{99m}TcO_4$ in several organs by means of radiation counting in organs and tissues in the postoperative period. We also evaluated the ponderal evolution of the animals after the operation, as well as the mucosal morphometry of the remnant small intestine.

Methods

Twenty-one Wistar rats, age around 180 days, weighing 265g±31g were used. They were supplied by the animal colony of the Nucleus for Experimental Surgery of the Federal University of the Rio Grande do Norte, Brazil. All the animals were weighed and observed in individual cages with water and food (Labina ® Purina) *ad libitum* and acclimated in the laboratory for 7 days. They were maintained under temperature control (21ºC), air humidity (60 – 70 %) and lighting (12/12 hours light/dark cycle) and handled in accordance with the Animal Experimentation Code of Ethics (Council for International Organizations of Medical Sciences) and the rules of the Brazilian College of Animal Experimentation. They were randomly divided into three groups: the experimental group rats, denominated short bowel, (SB, n=7) were subjected to massive resection of the small intestine (90%); control group rats were not operated on (C, n=7) and the third group underwent a simulated operation, called sham (n=7). Rats were fasted overnight before surgery, and anesthetized with sodium pentobarbital (20mg/kg intraperitoneal) and ketamine (20mg/kg intramuscular); they were operated on under sterile conditions. A 3 cm midline laparotomy was performed and intestinal transections were done 5 cm above the ileocecal junction and 5 cm from the duodenojejunal transition. With the aid of a surgical microscope (DF Vasconcelos, São Paulo, Brazil), interrupted sutures of 6-0 prolene (Ethicon®, Brazil) were used for bowel anastomosis. The animals typically have a small bowel length of 100 cm, and accordingly, residual length was 5 cm of jejunum and 5 cm of ileum (10 cm), corresponding to 90% of resection. After surgery, the abdomen was closed with interrupted sutures of 4-0 nylon suture (Ethicon®). The animals were allowed water immediately after surgery and food on the second postoperative day. The sham rats were subjected to a 3 cm medium laparotomy and mild manipulation of the small bowel. The rats were weighed weekly with a digital scale (Filizola® São Paulo, Brazil) and observed for 30 days. On the 30th day all the animals were anaesthetized again, and injected with 0.lmL of $Na^{99m}TcO_4$ in the venous orbital plexus, corresponding to radioactive activity of 0.66MBq. After 30 minutes, the animals were killed by lethal dose of anesthetic. Samples of the liver, spleen, pancreas, stomach, duodenum, small intestine, thyroid, lung, heart, kidney, bladder, muscle, femur and brain were harvested. The samples were washed in 0.9% NaCl , weighed on a high-precision digital scale (Bel-Mark 160-II Itália®) and subjected to radioactivity detection using a 1470 Wizard™

Gamma Counter- Perkin-Elmer, with automatic correction of radiation decline. The percentage of radioactive activity/g (%ATI/g) of each organ was calculated by dividing the activity/g of the tissue by the total activity administered to each animal. Samples with 2cm of jejunum were harvested 2 cm below the anastomosis. After washed in 0.9% saline, the excised tissues were fixed in 10 % buffered formalin for 48 h, dehydrated and embedded in paraffin. Sections cut at 5μm thickness were stained with hematoxilyn and eosin and morphology was assessed by an observer, who was unaware of the tissue origin. For the morphometric study of intestinal mucosa, Media Cybernetics – LP, USA, Image Pro-Plus software was used with an Olimpus BX-50 microscope fitted with a digital (Samsung®) video camera. The video camera transferred the image from the microscope to the computer screen. The measurement of the mucosal thickness was delimited with a computer mouse from the apex of the villus to the *muscularis mucosae* and was expressed in microns (μm). The analysis was made under 40x magnification using specimens in which the *villi* and the crypts were perpendicular to the *muscularis mucosae*. For the analysis of the different data related to postsurgical weight loss, to the measurements of total mucosal thickness, and to the biodistribution of sodium pertechnetate of the different groups, parametric variance (ANOVA) was used. For the multiple comparisons, the Tukey test was used. A significance level of 5% ($p<0.05$) was established.

Results

All the animals survived the surgical procedures. Table 1 shows the results of the differences in %ATI/g among groups SB, C and sham. We observed an increase in the biodistribution of $Na^{99m}TcO_4$ in the thyroid and duodenum of SB rats, when compared to control rats. However, since the standard deviation was high, there was no significant difference ($p>0.05$). In the stomach, an apparent tendency for reduced biodistribution of the %ATI/g occurred in the SB rats, compared to sham rats, but without statistical significance ($p>0.05$). In several organs the percentages of radioactive activity (%ATI/g) had very similar values among the groups, without significant differences (Table

TABLE 1 – Biodistribution of $Na^{99m}TcO_4$ in the organs of the respective groups

Organs	*%ATI/g*			ANOVA (1)
	SB	C	Sham	
Liver	0.35 ± 0.089	0.36 ± 0.079	0.39 ± 0.113	0.794400
Spleen	0.22 ± 0.090	0.18 ± 0.031	0.19 ± 0.044	0.565470
Estomach	2.58 ± 0.730	2.72 ± 0.614	4.11 ± 1.793	0.116180
Small bowel	0.28 ± 0.107	0.20 ± 0.052	0.28 ± 0.130	0.690700
Duodenum	1.73 ± 1.814	0.41 ± 0.062	1.13 ± 1.719	0.378723
Pancreas	0.16 ± 0.063	0.14 ± 0.055	0.18 ± 0.125	0.811183
Kidney	0.41 ± 0.086	0.42 ± 0.082	0.36 ± 0.187	0.738872
Heart	0.17 ± 0.075	0.27 ± 0.057	0.17 ± 0.084	0.076831
Lung	0.35 ± 0.105	0.38 ± 0.125	0.31 ± 0.058	0.581337
Thyroid	5.35 ± 1.979	3.71 ± 1.256	3.80 ± 1.058	0.187603
Bladder	0.39 ± 0.114	0.33 ± 0.109	0.27 ± 0.139	0.309546
Muscle	0.07 ± 0.028	0.06 ± 0.019	0.05 ± 0.035	0.570391
Femur	0.16 ± 0.055	0.14 ± 0.036	0.15 ± 0.050	0.760950
Brain	0.02 ± 0.013	0.01 ± 0.003	0.03 ± 0.027	0.482193

Mean ± Standard deviation

(1) P- from analysis of variance (ANOVA).

The results of the test did not show statistically significant differences ($p>0.05$), for all the variables. %ATI/g, percent radioactivity per gram of tissue.

TABLE 2 – Jejunal mucosa thickness of rats and their respective groups.

Variable	Groups			ANOVA (1)
	SB	C	Sham	
Mucosal thickness in μm(2)	334.34 ± 25.9^{ab}	194.40 ± 39.0^{a}	194.22 ± 33.2^{b}	0.0000

Values expressed in Mean ± Standard deviation

(1) p-value of analysis of variance (ANOVA).

(2) Groups identified with the same letter differ significantly at a level of 5% (Tukey test).

SB = Short bowel; C = control.

1). The weight of SB rats decreased during the first and second weeks of survival and, after that, their weight gradually increased until the 30th postoperative day, when it was nearly the same as the C and SHAM rats, which continually increased their weight over time (Figure 1). The differences in the mean weight of SB rats at the end of the second week were significant, when compared to C and SHAM rats ($p<0.05$). The presence of an increase in intestinal mucosa thickness was detected in all IC rats, when compared to C and SHAM rats until the end of the observation period, as seen in Table 2 ($p<0.05$) and Figure 2.

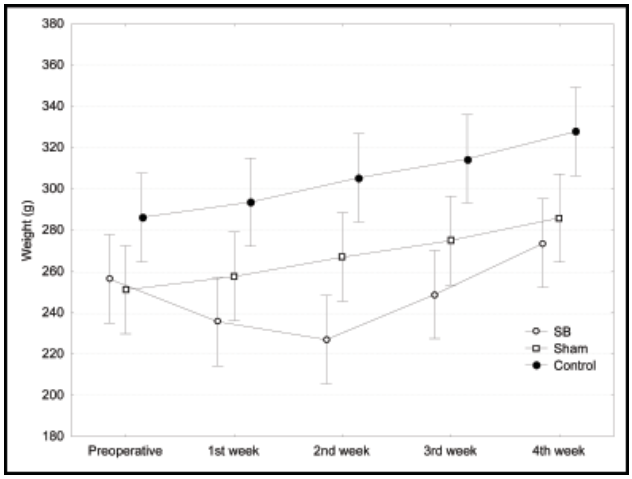

FIGURE 1 – Mean weight of rats in each group and postoperative period; SB, short bowel.

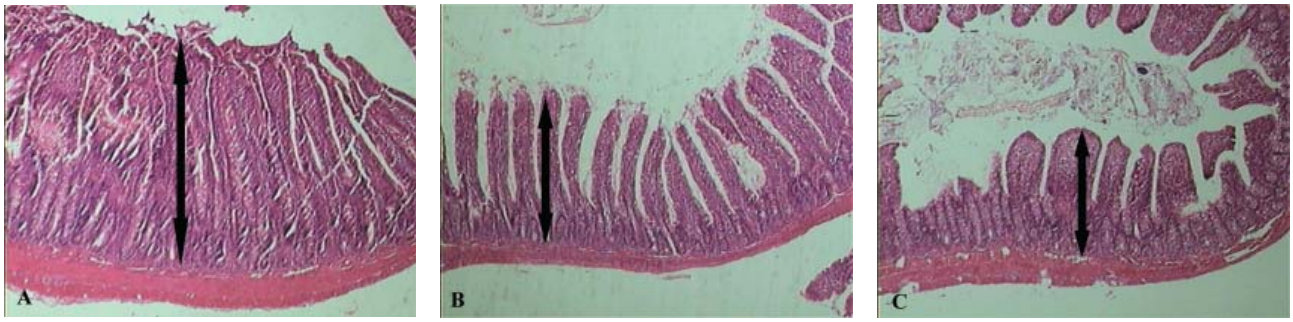

FIGURE 2 – Small intestine morphology and mucosal cell proliferation on day 30 in short bowel (A) control (B) and sham (C) animals. Massive intestinal resection (A) induced significant increases in total mucosal thickness (arrows), when compared to control and sham animals (B, C) (see Table 2; $p<0.05$). HE, 40x

Discussion

The alterations in the biodistribution of $Na^{99m}TcO_4$ in organs and tissues are very well identified in several studies that used no experimental surgical models [1,,6,,8,13,14]. However, in the postoperative of major surgical procedures, there are no reports concerning the biodistribution of radiopharmaceuticals. The present experimental model of the short bowel syndrome in rats submitted to massive resection of the small intestine was used to determine the biodistribution profile of $Na^{99m}TcO4$ in several organs and tissues. Intestinal failure is characterized by malnutrition and/or dehydration as a result of the inadequate digestion and absorption of nutrients. The most common cause of intestinal failure is short bowel syndrome, which occurs when the functional small bowel mass is reduced below the level necessary for adequate nutrient and water absorption. This condition frequently results from a massive resection of the small bowel. Following resection, the intestine is capable of adaptating in response to enteral nutrients as well as other trophic stimulation. Rodents are commonly used in well-characterized models to assess the process of intestinal adaptation[16]. Following small bowel resection in the rat, the remnant intestinal mucosa undergoes compensatory alterations in an attempt to restore normal absorptive capacity. Morphologic and functional changes include increases in mucosal length, enterocyte proliferation, as well as increased electrolyte, glucose and amino acid uptake[16,17]. In humans, the alterations of intestinal absorption due to massive resection of the small intestine usually cause significant weight loss[15]. However, in rodents, there is a rapid adaptation of the intestinal mucous membrane, which minimizes weight loss[16]. These mechanisms of intestinal adaptation take place at physiologic, cellular and molecular levels and they do not correspond to what occurs in the human intestine [17]. Nutrients, electrolytes, hormones, cytokines and other elements take part in the process, which involves mainly the intestinal mucous membrane. The process begins with apoptosis and continues with an increase in epithelial cells, vilosities and mucosal crypts, and a consequent remodeling of their architecture. Functionally, this allows for increased substance transport through the intestinal mucosa[17]. In the present study a significant decrease was observed in the weights of rats submitted to massive intestinal resection, in the immediate postoperative period, and weight recovery beginning at the end of the second week. These data coincide with a classic study on the subject, where morphological and functional

adaptations of the jejunum were observed between the first and second postoperative weeks[18]. This phenomenon was also shown in the morphometry of the jejunal mucous membrane of the animals subjected to massive resection of the present study. Therefore, the mucous membrane hyperplasia observed in the jejunal mucosa of the SB rats of the present experiment, likely contributed to the rapid weight recovery of the animals, starting from the second postoperative week. Welters et al (2002) verified that intestinal function recovery begins with the hyperplasia of the intestinal mucosa and that absorptive function depends on the maturity of the enterocytes, a fundamental factor for nutrient metabolism[19]. The precocious postoperative recovery of the animals, represented by weight and morphology of the intestinal mucosa recovery, and the healthy behavior of the SB rats, comparable to the controls, certainly contributed to the absence of significant clinical alterations and malnutrition. Consequently, there was no negative effect on the biodistribution of $Na^{99m}TcO_4$ in the vital organs. In an experimental study using malnutrition-inducing diets, Passos et al[20] (2000) showed that malnutrition affected the biodistribution of $Na^{99m}TcO_4$ in different organs such as the thyroid, brain, stomach and heart. In their study, the intestine was not surgically manipulated. Studies in animals have been investigating substances that regulate the absorptive function of the intestine[21]. These mechanisms are mediated by multiple factors, including enteral or parenteral nutrition, hormones and growth factors[22]. Recently, studies on the use of the human growth hormone (GH), the epidermal growth factor (EGF) and the glucagons-like peptide-2 (GLP-2), produced in the L-cells of the small intestine, have confirmed them as agents that increase intestinal adaptation after massive resection[23]. The study suggests that, whereas GLP-2 is important in controlling adaptation, there are spatial or regional systems in place that use varying pathways. The significant increase in nutrient-stimulated GLP-2 secretion suggests that GLP-2 is involved not only in the initiation, but also in maintaining the ongoing adaptive process. The increases in mucosal proliferation that are temporally associated with a maintained GLP-2 release, suggest that GLP-2 is important in initiating and maintaining the small intestine's adaptive response to resection[24]. Curtis et al (1984) studied rats submitted to massive resection of the small intestine using marker $^{51m}Cr^{l3m}C$ and protein, and observed the animals for one week. They concluded that the rats had no alteration in absorption and digestion time when compared to the treated group and the control; this demonstrated the fast physiological adaptation of the animals[25]. A growing number of tissue factors are being investigated for having great potential in promoting intestinal adaptation in animals and humans with short bowel syndrome, in the hope of obtaining effective therapies for the syndrome in the future[23,26]. In summary, massive intestinal resection in the current study did not interfere significantly with the biodistribution of the radiopharmaceutical $Na^{99m}TcO_4$ in the organs studied. Certainly the mucosal hyperplasia of the remnant intestine was a preponderant factor for the quick weight loss reversal of the animals, and consequent preservation of their healthy metabolism. The present study does not allow us to comment on the mechanisms by which intestinal resection results in the stimulation of trophic effects and mucosal adaptation, allowing normal biodistribution of $Na^{99m}TcO_4$ in rats. Identifying factors that may enhance the process of intestinal adaptation is an exciting area of research with important potential clinical applications. This area will require further studies.

Conclusion

In rats with experimentally-induced short bowel syndrome, an adaptive response by the intestinal mucosa reduced weight loss. The biodistribution of $Na^{99m}TcO_4$ was not affected by massive intestinal resection, suggesting that short bowel syndrome could not be the cause of misleading image interpretation when an examination with this radiopharmaceutical is indicated.

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Correspondence:
Dâmaso de Araújo Chacon
Rua Almte. Nelson Fernandes, 797/1200
59022-600 Natal - RN Brazil
damasochacon@uol.com.br

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