Biodistribution of technetium-99m pertechnetate after Roux-en-Y gastric bypass (Capella technique) in rats[1]

Biodistribuição de tecnécio-99m pertecnetato após desvio gástrico em Y de Roux (técnica de Capella) em ratos

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ABSTRACT

Purpose: The biodistribution of sodium pertechnetate, the most used radiopharmaceutical in nuclear medicine, has not been studied in details after bariatric surgery. The objective was to investigate the effect of Roux-en-Y gastric bypass (RYGB) on biodistribution of sodium pertechnetate ($Na^{99m}Tc^-$) in organs and tissues of rats. **Methods:** Twelve rats were randomly divided into two groups of 6 animals each. The RYGB group rats were submitted to the Roux-en-Y gastric bypass and the control group rats were not operated. After 15 days, all rats were injected with 0.1mL of $Na^{99m}Tc^-$ via orbital plexus with average radioactivity of 0.66 MBq. After 30 minutes, liver, stomach, thyroid, heart, lung, kidney and femur samples were harvested, weighed and percentage of radioactivity per gram (%ATI/g) of each organ was determined by gama counter Wizard Perkin-Elmer. We applied the Student t test for statistical analysis, considering $p<0.05$ as significant. **Results:** Significant reduction in mean %ATI/g was observed in the liver, stomach and femur in the RYGB group animals, compared with the control group rats ($p<0.05$). In other organs no significant difference in %ATI/g was observed between the two groups. **Conclusion:** This work contributes to the knowledge that the bariatric surgery RYGB modifies the pattern of biodistribution of $Na^{99m}Tc^-$.

Key words: Biological Availability. Bariatric Surgery. Sodium Pertechnetate Tc 99m. Radiopharmaceuticals. Rats.

RESUMO

Objetivo: Avaliar o efeito da cirurgia de desvio gástrico em Y de Roux (BGYR) na biodistribuição do pertecnetato de sódio ($Na^{99m}Tc$) em órgãos e tecidos de ratos. **Métodos:** Doze ratos *Wistar* foram aleatoriamente distribuidos em dois grupos de seis animais cada. O grupo BGYR foi submetido a técnica cirúrgica do desvio gástrico em Y de Roux e o grupo controle não foi operado. No 15º dia de pós-operatório foi administrado 0,1 ml IV de $Na^{99m}Tc$ aos animais dos dois grupos, com atividade radioativa média de 0,66MBq. Após 30 minutos os ratos foram mortos e retirados fragmentos de fígado, estômago, tireóide, coração, pulmão, rim e fêmur. As amostras foram lavadas com solução salina 0,9% pesadas e submetidas ao Contador Gama 1470, Wizard™ Perkin-Elmer para se determinar o percentual de atividade radiotiva por grama (%ATI/g) de cada órgão. Empregou-se o teste t de *Student* para análise estatística, considerando $p<0,05$ como significante. **Resultados:** Redução significante na média de %ATI/g foi observada no fígado, estômago e fêmur nos animais submetidos a cirurgia de BGYR comparado com o grupo controle ($p<0,05$). Nos demais órgãos não houve diferença significante no %ATI/g entre os dois grupos. **Conclusão:** A cirurgia BGYR em ratos modificou a biodistribuição do $Na^{99m}Tc$ em alguns órgãos, podendo ter implicações clínicas na interpretação de exames cintilográficos.

Descritores: Disponibilidade Biológica. Cirurgia Bariátrica. Pertecnetato Tc 99m de Sódio. Compostos Radiofarmacêuticos. Ratos.

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Introduction

Obesity is rapidly increasing in the United States, with the prevalence of class 3 obesity approaching 8% in some populations[1,2]. Overall, in the past decades, the Brazilian population has experienced relatively rapid socioeconomic improvement, resulting in many lifestyle modifications that have promoted increased prevalence of obesity and associated diseases, such as diabetes and dyslipidemias[3]. Current treatment options for morbid obesity include pharmacologic agents, low-calorie diets, behavioral modification, exercise, and surgery. Dietary treatments produce an initial weight loss of less than 15% of the starting weight, and weight reductions generally decay to zero at 5 years[4]. The failure of most current approaches to control morbid obesity has led to the development of surgical procedures of the upper gastrointestinal tract designed to induce weight loss (bariatric surgery)[5].

The goal of bariatric surgery is to reduce caloric intake by either restricting the amount of calories an individual can take in (restrictive procedure) or reducing the amount of calories absorbed from the gastrointestinal tract (malabsorptive procedure). This can be accomplished in a number of ways. The most commonly described techniques are the Roux-en-Y gastric bypass (restrictive and malabsorptive), laparoscopic adjustable banding (restrictive only), and the bilio-pancreatic diversion with duodenal switch (malabsorptive and restrictive). Roux-en-Y gastric bypass (RYGB), is the predominant approach used in the United States[6], RYGB also creates a small stomach pouch to restrict food intake, but a portion of the jejunum is attached to the pouch to allow food to bypass the distal stomach, duodenum, and proximal jejunum. Bypassing this segment of the gastrointestinal tract might contribute to the clinical success of RYGB by altering the secretion of hormones that influence glucose regulation and the perception of both hunger and satiety[8]. Although the procedures can be successful, they can be associated with a number of complications. Unfortunately, these complications can sometimes be subtle and difficult to diagnose early. Since these patients have limited physiologic reserve, it is imperative that complications are identified early by image procedures and appropriately managed[9].

One of the most used diagnostic methods in identifying a great number of diseases and metabolic disorders is the use of radiopharmaceuticals, radioactive compounds used in diagnostic procedures as sources of radiation or tracers. Examination of gastric emptying, liver function, thyroid function, bone disorders, distant metastasis, etc, are used frequently in patients undergoing bariatric surgery[10]. Radiopharmaceuticals biodistribution may provide important information about its uptake to some target organs, but post-surgery data are scarce[11]. It is relevant to investigate technetium-99m pertechnetate biodistribution after RYGB, because it is highly secreted by gastric mucosa. After this operation, the stomach is mostly bypassed and alterations are expected to occur on biodistribution. Several drugs and surgery may interfere with the biological behavior of radiopharmaceuticals used in scintigraphic examinations and technetium-99m pertechnetate is used in more than 80% of scintigraphic examinations[12-14]. They may change the biological effects of the technetium-99m pertechnetate and their uptake to some organs. As a major surgery, RYGB may result in important anatomical and metabolic changing and unpredictable complications. So, scintigraphic studies may be needed in the postoperative period. If the technetium-99m pertechnetate biodistribution is changed in important organs and tissues due to bariatric surgery, scintigraphic examinations can generate false-positive or false negative images, leading to repetition of nuclear medicine procedures with unnecessary radiation exposure for patients.

The aim of this study is to analyze the effects of RYGB on biodistribution of technetium-99m pertechnetate in several organs and tissues of rats.

Methods

The use of laboratory animals followed the Council for International Organization of Medical Sciences Ethical Code for animal experimentation and the Brazilian guidelines for scientific use of animals (Law nº 11.794). The protocol was approved by the Ethical Committee of Research, UFRN. Rats were observed in individual polypropilene cages in room temperature of 24ºC, 45% relative humidity, 12-hour light/dark cycles, and they had free access to their diet and tap water. For preoperative procedures, rats were deprived of food for 16 to 18 hours and were anesthetized with a mixture of ketamine and xylazine (200 mg: 5 mg, 0. 8 ml/kg, intraperitoneally). For postoperative pain control, tenoxicam 1.5 mg/kg, was given to the rats postoperatively, once a day for 3 days.

Operative and laboratory procedures

Twelve Wistar rats (349.3 ±10.7 g) were equally divided into RYGB and control groups. The rat abdomens were shaved and prepared with 70% alcohol. A midline incision was made, and the stomach and distal esophagus were exposed. The stomach was divided 1 cm down of the esophagus and both gastric ends were oversewn using a running 6-0 polypropilene suture, and the suture lines were embrocated. The jejunum was divided 16 cm below the ligament of Treitz, creating a 16 cm biliary-pancreatic limb. A 4 to 5 mm end-to-side gastrojejunostomy was sewn using interrupted 6-0 polypropilene sutures on the anterior surface of the gastric fundus. The stump of proximal jejunum was closed with a running suture. A 7 to 8 mm side-to-side jejunojejunostomy was sewn 10 cm below the gastrojejunostomy. The procedure lasted approximately 30 minutes and the abdomen was closed in layers, using a running 4-0 nylon suture. Rats drank water and 10% glucose plus 2% saline solution starting 24 hours after the operation and for the first 3 days. This was followed by a solid diet (Labina-Purina). For the first three postoperative days, rats were hydrated with normal saline solution (20ml) injected subcutaneously to prevent dehydration. A surgical microscope with 10x magnification was used for the anastomosis. A single intramuscular dose of 75 mg/kg of ceftriaxone sodium was given as antimicrobial prophylaxis 30 minutes before the surgical procedures. The control group rats (n=6) were not operated.

The animals remained under observation for 15 days after surgery and were then injected with 0.1 ml of technetium-99m pertecnetate via the orbital plexus, corresponding to radioactive activity of 0.66 MBq. Thirty minutes after radiopharmaceutical administration, the animals were killed with an anesthesia overdose (thiopental sodium, intracardiac) and underwent surgery for removal of samples from the liver, kidney, heart, lung, thyroid, stomach and femur. The tissue samples were washed in 0.9% saline, weighed on a precision scale and their radioactivity was determined in an automatic gamma counter. The results were shown in counts per minute (CPM), corrected by disintegrations per minute (DPM). The efficiency of the gamma counter was 86%, as specified by the manufacturer. The specific activity of each sample was calculated by dividing its absolute count in DPM by its weight (DPM/g). The percentage of radioactivity of each sample (% ATI/g) was calculated by dividing its specific activity (DPM/g) by the total radioactivity of each animal. The total activity administered to each animal was calculated from the average of three patterns with the same volume injected.

The data were expressed as mean ± standard deviation. Statistical analysis for comparison between groups was performed by the Student t test, using a significance level of 0.05.

Results

All animals survived for the duration of the study. Table 1 summarizes the descriptive results of the percentage of radioactivity (% ATI) in organs of rats from groups RYGB and control. We applied the Student t test for independent samples. The significance level established for the test was 5%.

TABLE 1 - Percentage of radioactivity (% ATI/g) of each organ sample in animals submitted to Roux-en-Y gastric bypass and controls

Organs	*%ATI/g*		*P*
	RYGB	Control	
Liver	0.33 ± 0.05	0.56 ± 0.08	0.024
Kidney	0.58 ± 0.22	0.41 ± 0.07	0.119
Heart	0.21 ± 0.05	0.27 ± 0.07	0.128
Lung	0.53 ± 0.18	0.37 ± 0.14	0.098
Tyroid	2.91 ± 0.97	3.46 ± 1.67	0.506
Stomach	0.54 ± 0.32	2.99 ± 1.65	0.005
Femur	0.14 ± 0.03	0.22 ± 0.07	0.035

The values appear as mean± standard deviation. RYGB, Roux-en-Y gastric bypass

In the kidney and lung we observed an increased uptake of radioactivity on rats submitted to RYGB, comparing with controls, but the difference was statistically insignificant (p>0.05). However, in the RYGB rats a significantly decrease in the radioactive uptake (%ATI/g) occurred in the stomach, liver and femur, comparing with controls (p<0.05). When comparing the difference between the radioactive uptake of heart and thyroid from RYGB and control rats, there was a tendency for a further decrease in % ATI/g of RYGB animals, although this was not statistically significant (p>0.05).

Discussion

Obesity has become an epidemic condition and in the United States the percentage of obese adults increased from 15.3% in 1995 to 23.9% in 2005. Approximately 4.8% of patients are considered morbidly obese. Worldwide it is estimated that over 300 million people are obese[14]. Obesity results in an increased risk for serious diseases, including diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, degenerative arthritis, some forms of cancer and respiratory problems, and to generate socio-economic and psicossocial disturbs[15]. Thus, some weight loss therapies, such as diet and pharmaceutical systems complemented by physical exercises have been proposed. However, almost 95% of patients who have morbid obesity (BMI> 40kg/m^2) fail to achieve satisfactory weight loss[16]. Therefore, many efforts have been implemented to get good results with surgical techniques, and the bariatric operations have obtained good results at a significant weight loss for many years[17]. Despite the good results, bariatric surgery can cause anatomical and metabolic complications[18]. The diagnosis of these disturbs may require imaging examinations such as radiography and scintigraphy.

The technetium-99m is the most widely used radionuclide in nuclear medicine and research studies. It has a short half-life (6h), emits low radiation and small doses are needed for diagnostic procedures[19]. Changes in the biodistribution of technetium-99m pertecnetate in organs and tissues are well identified in several clinical studies. It has been used in vivo and in vitro, in the study of diseases, drugs, chemotherapy and plants that interfere with their distribution[20,21]. However, in the postoperative period of major surgical procedures, there are few studies that focus on the biodistribution of radiopharmaceuticals. To understand and explore the relationship between the RYGB and biodistribution of radiopharmaceuticals in organs and tissues, we used a reproducible and well characterized animal model. Scintigraphic examinations in the postoperative period are used to diagnose bleeding in gastrointestinal tract gastroesophageal reflux and the patency of anastomosis Diagnosis of metastases by cancer and postoperative changes in the kidneys, liver, lung, heart and other organs are made using scintigraphy with radiotracers and technetium-99m pertecnetate[19]. In this study, the RYGB did not affect the biodistribution of technetium-99m pertecnetate the heart, lung, kidney and thyroid.

The stomach is often examined in the postoperative of bariatric surgery, primarily for diagnosing the presence of fistulas, since the escape from the anastomosis may be early or late complication of this operation. A large case series of 63 patients with leaks after RYGBP reports that most were not detected by CT imaging and that most required surgery (63%), with morbidity of 53% and mortality of 10%[22]. In case of small fistulas, the rate of escape of contrast will be small, so that leaks may be overlooked by radiography. The morphofunctional radionuclide evaluation provides the efficiency of anastomosis of digestive tract, by showing the emptying time of the gastric remnant, excluding reflux and any radionuclide stagnation. Using scintigraphy, a small amount of diffused pertechnetate is absorbed by the gastric mucosa due to the high affinity for this radiopharmaceutical. It has been suggested that scintigraphy has high accuracy in diagnosis of complications in postoperative bariatric surgery[23]. In this study the uptake of pertechnetate was significantly decreased in the remnant functional stomach post RYGB, meaning that scintigraphic examination of this organ in the postoperative of bariatric surgery must be interpreted considering this finding.

Several different mechanisms may explain the observed changes in bone metabolism after bariatric surgery. Poor absorption of minerals and vitamins, including calcium and vitamin D has been documented[24]. A sustained deficiency of vitamin D in obese patients may result in metabolic and skeletal abnormalities, which may be detected before and after bariatric surgery. The increased turnover and reduced bone mineral density may occur as a physiological adaptation of weight loss and changes in the mechanics of the skeleton or as a result of pathophysiological responses to surgery[25]. All these metabolic changes, especially the increase in bone turnover may explain the decrease in biodistribution of technetium-99m pertecnetate in the femur of the animals submitted to RYGB as compared to the control group. In our study the uptake of technetium-99m pertecnetate by the liver of rats submitted to RYGB was significantly lower than in control rats, meaning that the liver function may be affected in operated animals. This results need to be treated with some caution. In fact, some authors demonstrated significant improvement in the levels of aminotransferases and gamma glutamyl transferase in the postoperative of obese patients submitted to RYGB[26], and others found postoperative values of aminotransferases transiently increased by fivefold to eightfold[27] The rat model for RYBG appears to be a reasonable model and will enable continued research involving metabolic changes, in order to validate our findings on biodistribution of radiopharmaceuticals. In conclusion, this work contributes to the knowledge that the bariatric surgery RYGB modifies the pattern of biodistribution of technetium-99m pertechnetate.

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