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Biodistribution of the Radiopharmaceutical Sodium Pertechnetate after Biliopancreatic Bypass with a Duodenal Switch

Irami Araújo-Filho, Amália Cínthia Meneses Rêgo, José Brandão-Neto, Arthur Villarim-Neto, Eryvaldo Sócrates Tabosa Egito, Ítalo Medeiros Azevedo and Aldo Cunha Medeiros*
Programa de Pós-Graduação em Ciências da Saúde; Universidade Federal do Rio Grande do Norte; aldo@ufrnet.br; Rua Cordeiro de Faria, s/n; 59010-180; Natal - RN - Brasil

ABSTRACT

Study with the purpose to examine the effects of duodenal switch (DS), regularly performed in morbidly obese patients, on biodistribution of sodium pertechnetate in several organs of rats. There was no early or late mortality in either rats groups. The values of percent radioactivity per gram of tissue (%ATI/g), showed no significant difference in liver, stomach, small bowel, duodenum, kidney, heart, bladder, bone and brain, when compared the DS rats with sham and controls rats. A postoperative significant increase ($p<0.05$) in mean %ATI/g levels was observed in spleen, pancreas and muscle in group DS rats, as compared to group S and C rats. In the lung there was an increase and in thyroid a decrease in mean %ATI/g of DS rats, when compared to sham rats ($p<0.05$). In conclusion, the biliopancreatic diversion with duodenal switch in rats modified the biodistribution of sodium pertechnetate in thyroid, lung, pancreas, spleen and muscle.

Key words: Bariatric surgery, duodenal switch, sodium pertechnetate, biodistribution

INTRODUCTION

Worldwide, it is estimated that more than 300 million people are obese (Haslam & James, 2005). Obesity, particularly abdominal obesity, is associated with increased risks of hypertension, diabetes, hyperlipidemia, sleep apnea, coronary heart disease, and stroke (Li et al., 2005). The accumulating evidence identifying obesity-related mortality and comorbidities is an important factor that has led to increased numbers of patients seeking treatment through bariatric surgery. This is a surgical procedure that reduces caloric intake by modifying the anatomy of the gastrointestinal tract and provides effective treatment for many patients with morbid obesity. Bariatric operations are classified as either restrictive or malabsorptive. Restrictive procedures limit intake by creating a small gastric reservoir with a narrow outlet to delay emptying. Malabsorptive procedures bypass varying portions of the small intestine where nutrient absorption occurs (DeMaria & Jamal., 2005). The biliopancreatic diversion with duodenal switch (DS) is a hybrid operation involving both components of weight loss surgery. In the DS, a lateral gastrectomy provides a restricted gastric volume, while excess fat absorption is limited by shortening the functioning length of the intestine. This involves diversion of the biliopancreatic secretions by partitioning the

* Author for correspondence

bowel into two limbs – an alimentary channel, and the biliopancreatic (afferent) limb. These two limbs of small bowel are reconnected to form the common channel (Hess, 1998; Marceau et al., 1998). DS produces a sustained weight loss, with low side effects and without any increase in the perioperative morbidity and mortality rate, comparing to other bariatric operations (Biron et al., 2004; Rabkin., 2004; Anthone et al., 2003).

There are numerous complications that may arise following any of the bariatric surgical procedures that require understanding and delineation of the specific anatomy of the operation performed. These complications may include nutrient deficiencies or gastrointestinal pathology. Anastomotic leak and stricture commonly occurs (Schauer et al., 2000; DeMaria et al., 2002). The most frequently reported complication of gastric band placement is prolapse of stomach superiorly through the band producing obstruction at the band (O'Brien et al., 1999). Radiographs and scintigraphies may show an air fluid level in the gastric pouch, malposition, angulation of the band bands, problems with gastric emptying, and gastric obstruction (O'Brien et al., 2005).

The radiopharmaceuticals are frequently used in diagnostic procedures (Bingener-Casey et al., 2002, Carter & Kotlyarov, 2005). Examinations of gastric emptying, patency of anastomoses, enterogastric reflux, hepatic and thyroid diseases, osteoporosis and metastasis, frequently are carried after bariatric surgery (Kitabaiashi et al., 2002; Fonseca et al., 2000; Badiali et al., 2001; Obradovic et al., 2000). Several works have studied the relationship between chemotherapy, phytotherapy and other drugs with the biodistribution of sodium pertechnetate (Braga et al., 2000; Oliveira et al., 2002; Gomes et al., 1998; Ripoll-Hamer et al, 1995; Simões et al., 1997; Feliciano et al., 2002, Abreu et al., 2006., Santos et al., 1995). With regard to potential consequences of bariatric surgery in the biodistribution of radiopharmaceuticals, little or no study was published until now.

As DS is a restrictive and malabsorptive operation, of raised anatomical and metabolic repercussion, postoperative evaluation of patients through scintigraphy can be necessary. If the biodistribution of sodium pertechnetate to organs and tissues is modified as a result of bariatric surgery, scintigraphic examinations can be false-positive or false-negative, resulting in repetition of examinations with unnecessary exposition of patient to ionizing radiations. The purpose of this study was to examine the effects of DS, similar to that performed in morbidly obese patients, on biodistribution of sodium pertechnetate in several organs and tissues of rats.

MATERIAL AND METHODS

Male Wistar rats (12 weeks of age and weighing 328g ± 33g) were obtained from Center of Experimental Surgery-UFRN, Brazil. Animals were housed in polypropilene cages for 1 week to acclimatize them to the study laboratory: 12-h light/dark cycle, room temperature of 25°C, and 50% relative humidity. Rats were allowed free access to water and standard rat chow (Labina, Purina®). The study was approved by the Institutional Animal Care Committee of the University Hospital-UFRN, Brazil, and the international guidelines for the care and use of laboratory animals were followed throughout the study.

Rats were randomly divided into three groups: duodenal switch group (DS), control group (C), and sham-operated group (S). After 12 h of food deprivation, rats were anesthetized with a ketamine and xylazine mixture (200 mg: 5 mg, 0.1 ml/100 g, IM), the abdomen was shaved and prepared, and the operations were performed with aseptic technique. All the surgical procedures were performed by the same investigator, a well trained and experienced surgeon in animal surgery and three previous series of experiments were performed in sequence to develop the DS model. A single intramuscular dose of 75 mg/kg of ceftriaxone sodium (Roche, SP, Brazil) was given as antimicrobial prophylaxis 30 minutes before the surgical procedures.

In the DS rats (n=7) the surgery was performed via an upper 3 cm midline incision. A sleeve 75% longitudinal gastrectomy was performed leaving a tabularized stomach. (Figure. 1). The duodenum was divided about 1 cm beyond the pylorus. The stump of duodenum was closed with running sutures. The small bowel was divided at its midpoint, and the distal end (alimentary limb) was anastomosed to the proximal duodenum. The proximal end of the divided small bowel, now the distal end of the iliopancreatic limb, was anastomosed to the ileum 5 cm from the ileocecal valve to create a 10cm common channel. (Figure

1). The anastomosis were hand sewn using interrupted polypropilene 6-0 sutures (Prolene® - Ethicon), using a surgical microscope (DFV-M900, São Paulo, Brazil). The hydration was done with normal saline (10ml) injected subcutaneously into the back of the rats for the first 2 postoperative days. Postoperatively pain was treated with tenoxicam (Roche Pharm., Brazil); 0.5 mg/kg was given to the rats once a day for 3 days. Rats were allowed to drink and eat 24 h after surgery. Liquid diet (Nestogeno, Nestlé, Brazil, 1 cal/g) was provided for the first 2 days, followed by ground Purina Labina chow. The sham rats (n=7) were submited to a laparotomy and soft malipulation of stomach, duodenum and small bowel. The control rats (n=7) were not operated. Body weight, using a digital scale (Filizola®, São Paulo, Brazil), and operative complications were evaluated daily for 10 days.

On the 10th day all the animals were anaesthetized again, and injected with 0.1 mL of $Na^{99m}TcO_4$ in the orbital plexus, corresponding to activity of 0.66 MBq. After 30 minutes, the animals were killed by lethal dose of anesthetic. Samples of the liver, spleen, stomach, small intestine, duodenum, pancreas, kidney, heart, lung, thyroid, bladder, muscle, bone (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 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.

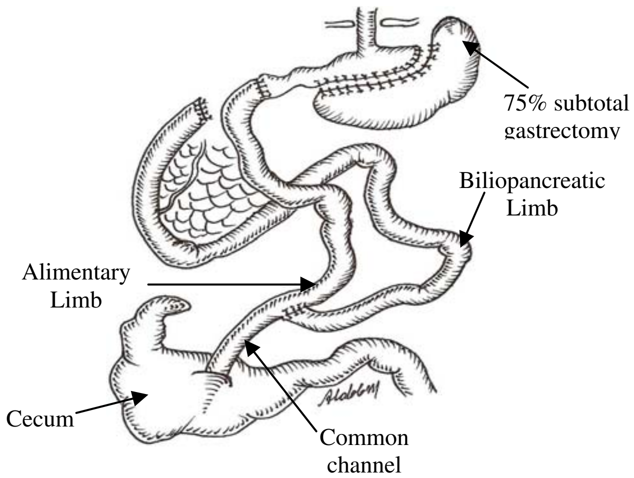

Figure 1 - The biliopancreatic diversion with duodenal switch operation

Data are expressed as mean ± standard deviation. Statistical analysis was performed using one-way analysis of variance and the Tukey test as appropriate. *p*<0.05 were considered to be statistically significant.

RESULTS

There was no early or late mortality in either rat groups. The values of all sodium pertechnetate biodistributions, expressed as percent radioactivity per gram of tissue (%ATI/g), are shown in Table 1. There was no significant difference in %ATI/g in liver, stomach, small bowel, duodenum, kidney, heart, bladder, bone and brain, when compared the DS rats with S and C rats. A postoperative significant ($p<0.05$) increase in mean %ATI/g levels was observed in spleen, pancreas and muscle in DS rats, as compared to S and C rats. Looking at each group separately, in the lung there was a significant ($p>0.05$) increase and in thyroid a decrease in mean %ATI/g of DS rats, when compared to sham rats.

Table 1 - Results of the percentage of radioactivity/g of organs and tissues (%ATI/g).

Organs	%ATI/g			
	Switch	**C**	***Sham***	$P^{(1)}$
Liver	0.42 ± 0.103	0.35 ± 0.069	0.35 ± 0.097	0.256
Spleen$^{(2)}$	0.26 ± 0.079^{ab}	0.18 ± 0.028^{a}	0.17 ± 0.045^{b}	0.016
Stomach	3.39 ± 1.321	2.98 ± 1.507	4.23 ± 0.941	0.205
Small bowel	0.19 ± 0.052	0.19 ± 0.052	0.26 ± 0.109	0.209
Duodenum	0.65 ± 0.541	0.44 ± 0.088	0.61 ± 0.484	0.633
Pancreas$^{(2)}$	0.27 ± 0.089^{ab}	0.14 ± 0.045^{a}	0.15 ± 0.078^{b}	0.006
Kidney	0.53 ± 0.157	0.42 ± 0.075	0.36 ± 0.174	0.115
Heart	0.28 ± 0.131	0.27 ± 0.061	0.16 ± 0.079	0.050
Lung$^{(2)}$	0.44 ± 0.075^{a}	0.39 ± 0.143	0.28 ± 0.075^{a}	0.030
Thyroid$^{(2)}$	1.48 ± 2.070^{a}	3.60 ± 1.578	4.44 ± 1.143^{a}	0.010
Bladder	0.30 ± 0.115	0.33 ± 0.094	0.32 ± 0.173	0.929
Muscle$^{(2)}$	0.09 ± 0.028^{ab}	0.06 ± 0.018^{a}	0.05 ± 0.026^{b}	0.008
Bone	0.14 ± 0.032	0.14 ± 0.032	0.14 ± 0.050	0.958
Brain	0.03 ± 0.033	0.01 ± 0.003	0.01 ± 0.007	0.244

Mean ± standard deviation·

1. P-value.
2. Groups identified by the same letter differ significantly. P<0.05 using the Tukey test.

Preoperative and postoperative data of weight loss of DS rats are summarized in Figure 2. Before treatments, there were no significant differences between the groups in terms of weight. The operative time for the sham operation was equivalent to that of DS. Postoperatively in group DS there was a significant decrease in body weight during the 10 days of observation attributed to the effects of operation (p<0.05). Body weight in the C and S groups gradually increased by day 10, when the rats were euthanized (Figure 2). So, the differences in the mean weight of DS rats at the end of the 10 days were significant, when compared to C and sham rats (p<0.05).
Body weight decreased significantly (p<0.05) in the duodenal switch group when compared with the sham and control groups. No difference was observed between sham and control rats.
In day 1 (operative day) no difference was observed among all the rat weights, meaning that the groups were uniform.

DISCUSSION

Obesity has become an epidemic condition and in the United States, the percentage of adults who are obese increased from 15.3% in 1995 to 23.9% in 2005. Approximately 4.8% are considered to be extremely or morbidly obese. Worldwide, it is estimated that more than 300 million people are obese (Ogden et al., 2006; Haslam & James, 2005).
Obesity results in a major risk for serious diseases, including diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, degenerative arthritis, certain forms of cancer and respiratory problems and may result in socioeconomic and psychosocial impairment (Ali et al., 2006). Therefore many weight-lowering therapies, such as dietary and pharmaceutical regimens completed with physical exercise, have been proposed. However, almost 95% of morbidly obese (BMI ≥40 kg/m^2) patients fail to achieve acceptable long-term weight loss with any form of non-operative treatment Ali et al., 2006). Hence, great efforts have been made to achieve better results using surgery. The bariatric operations have proved very successful and cost effective in achieving marked and maintained weight loss. In spite of good results, bariatric surgery may cause anatomic and metabolic complications (DeMaria et al., 2002). The diagnostic of these side effects may require image exams such as radiography and scintigraphy.
To understand and explore the relationship between bariatric surgery and biodistribution of radiopharmaceuticals to organs and tissues, a well-characterized and reproducible animal model was used. To achieve this purpose, this is a report of the experience with a biliopancreatic diversion with duodenal switch rat model.

Technetium-99m (99mTc) is the most used radioisotope in nuclear medicine as well as in basic research. It has a low mean life (6 h), low radiation and a low doses is needed for diagnostic procedures (Braga et al., 2006). It has been used in vivo and in vitro under the form of sodium pertechnetate, in the study of diseases, drugs, chemotherapics and phytoterpics that interfere in its biodistribution (Oliveira et al, 2002; Amorim et al., 2003). Red blood cells and leukocytes labeled with 99mTc have been used in the study of drugs, and in the evaluation of the mononuclear system (Palestro et al., 2006).

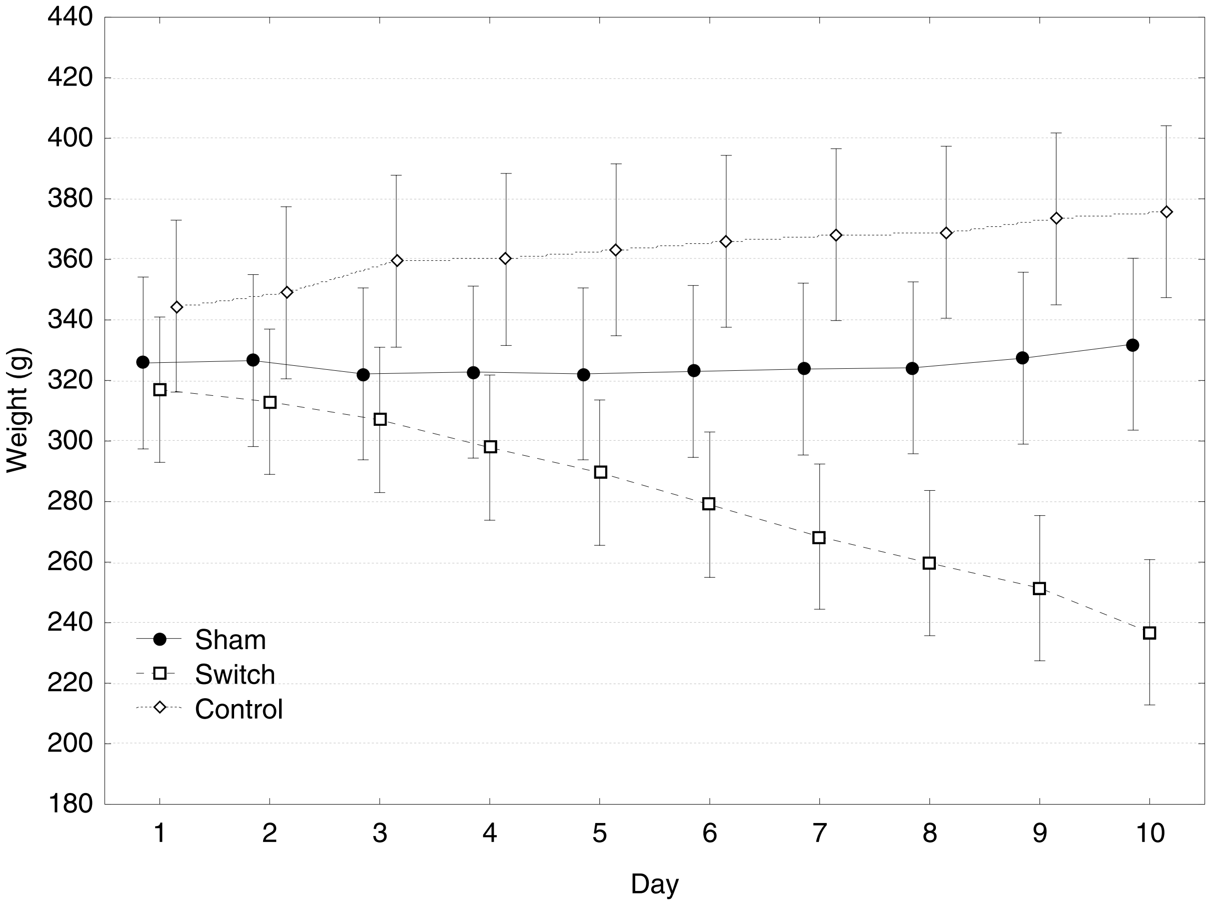

Figure 2 - Effect of duodenal switch, sham and control on body weight in rats during the observation period

Postoperative scintigraphic exams are accomplished to diagnose digestive bleeding (Bingener-Casey et al., 2002), gastroesofageal reflux (Adachi et al., 1999), as well as anastomoses patency (Blachar, 2004). Diagnosis of cancer metastasis (Leen., 1999), and postoperative chances in kidney, liver, lung, heart and other organs are done using scintigraphy with radiotracers and pertechnetate (Aktas et al., 2005; Chalela, 1999).

In the present work the DS did not affect the biodistribution of sodium pertechnetate in liver, stomach, small bowel, duodenum, kidney, heart, bladder, bone and brain. The stomach is commonly examined in the postoperative of bariatric surgery to diagnose mainly leaks, because leakage from the reservoir or the connecting tube is a late complication of bariatric surgery. In small leaks the escape rate of a radio-contrast agent may be low, and hence these leaks may be overlooked on radiography. By contrast, using scintigraphy, the slowly diffusing pertechnetate is re-absorbed by peritoneal blood vessels and subsequently absorbed into the gastric mucosa, because of high gastric affinity for pertechnetate. This fact may explain because, in this study, biodistribution of pertechnetate was not affected in stomach. It has been suggested a higher accuracy of scintigraphy as compared with radiography in the assessment of leakage in bariatric surgery. (Van DenBossche et al., 2002). The liver, small bowel, duodenum, kidney, heart, bladder, bone and brain have a few affinity for pertechnetate and we did not find alteration in biodistribution of this radiopharmaceutical in them. So, if a scintigraphy is to be done to study anyone after bariatric surgery, false results certainly are not expected.

The biodistribution of pertechnetate showed elevated in spleen and this organ may be the target of future scintigraphies. Splenectomy during exploratory laparotomy after bariatric surgery significantly increases morbidity and mortality. Peters et al, (1990) related that six of 200 patients having primary or revisional vertical banded gastroplasty for morbid obesity or failure of previous bariatric surgery had splenic injury. Eventual scintigraphy in these patients should be interpreted with caution.

Obese patients often complain of dyspnea despite not having demonstrable lung disease It has been hypothesized that increased chest wall mass along with increased abdominal size imparts a restrictive ventilatory defect, which then imposes an increased work of breathing (Sahebjani, 1996). The bariatric procedures are performed in morbidly obese patients who tend to have reduced chest wall compliance, reduced lung volume, less functional residual capacity, and increased physiologic intrapulmonary shunt during mechanical ventilation (Damia et al., 1988). Therefore, morbidly obese patients may be at risk for intraoperative and postoperative complications, which may be diagnosed by scintigraphy. Together, pulmonary emboli, anastomotic leaks, and respiratory failure account for 80 percent of all deaths in the first 30 days following bariatric surgery (Virji & Murr, 2006). As in this study the biodistribution of pertechnetate was higher in lungs of operated rats then in controls, the interpretation of eventual lung exams (Giordano et al., 1997) in patients has to be with caution.

In the past five years, several confirmed cases of pancreatic disorders occurred in persons who had undergone bariatric surgery (Service et al., 2005). Some patients presented with repeated episodes of symptoms of profound postprandial neuroglycopenia associated with endogenous hyperinsulinemic hypoglycemia and demonstration of diffuse beta-cell hypertrophy and hyperplasia in resected pancreatic tissue. A plausible explanation, with broader implications, is that bariatric surgery results in long-term stimulation of beta-cell growth and activity by gut hormones (glucagon-like peptide 1) that are perturbed as a result of the altered gastrointestinal transit. These metabolic disorders may explain the high radioactivity observed in pancreas of DS operated rats (D'Alessio & Vahl, 2004). Moreover, at least in rodents, GLP-1 triggers beta-cell neogenesis and proliferation while inhibiting apoptosis (Brubaker & Drucker, 2004).

In this study the %ATI/g in thyroid was decreased in DS rats compared to sham rats. Paradoxically, a great percentage of obese patients have hypothyroidism, that is improved after bariatric surgery (Raftopoulos et al., 2004). The reduction in the %ATI/g in thyroid can be related to the postoperative energy deficiency, knowing that half of the small bowel is defunccionalyzed and the stomach is highly reduced. Steps et al had attributed this phenomenon to a reduction of the transport of sodium pertechnetate to the thyroid gland, as happen with iodine in malnourished patients (Passos et al., 2000; Passos et al., 2002). Further studies are necessary to explain these findings.

Bariatric surgery has become the treatment of choice for morbid obesity and it greatly changes the body composition for years following surgery. The lean body mass (muscle) is significantly reduced in the postoperative period (Tanner et al., 2002). In this study we found a paradoxical relationship between weight loss, muscle loss, and increased muscle %ATI/g. So that, questions remain with regard to the physiological mechanisms and pathophysiological consequences of duodenal switch, and biodistribution of radiopharmaceuticals is one of them. It has been related that the polyneuropathy and miopathy after bariatric surgery are resultant of the deficiency of B12 vitamin, tiamin and vitamin D respectively (Koffman et al., 2006). The highly significant muscular uptake of sodium pertechnetate in DS rats may be a consequence of muscle inflammation for vitamin D deficit (Plotnikoff & Quigley, 2003).

In conclusion, the data of this study permits the conclusion that the biliopancreatic diversion with duodenal switch in rats modified the biodistribution of sodium pertechnetate in tireóide, lung, pancreas, spleen and muscle.

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RESUMO

Estudo objetivando examinar efeitos do procedimento cirúrgico switch duodenal (SD) na biodistribuição do pertecnetato de sódio em vários órgãos de ratos. Não ocorreu mortalidade precoce e tardia nos animais operados. Os valores do percentual de radioatividade/grama de tecido (%ATI/g) mostraram nenhuma diferença significativa no fígado, estômago, intestino, duodeno, rim, coração, bexiga, osso e cérebro, comparando-se o grupo SD com sham e controle. Aumento significativo (p<0,05) na média de %ATI/g foi observado no baço, pâncreas e músculo (grupo SD), comparado com os grupos sham e controle. No pulmão houve aumento e na tireóide diminuição no %ATI/g nos ratos SD, comparados com os sham e controles (p>0,05). Em conclusão, a cirurgia denominada derivação biliopancreática com switch duodenal em ratos modificou a biodistribuição de pertecnetato de sódio na tireóide, pulmão, pâncreas, baço e músculo, podendo significar que a interpretação de exames cintilográficos nesses órgãos deve ser feita com cautela .

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