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Incidence of Adverse Events Related to Therapies with sodium iodine (^{131}I): Contribution to the Pharmacovigilance in Brazil

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Abstract Radiopharmaceuticals for therapeutic have been increasingly used for the treatment of various pathologies. Beta-emitting radionuclides stand out in this modality due to the physical characteristics of the emitted particle. Iodine-131 (^{131}I) is an example of a beta-emitting radionuclide, applied in the production of radiopharmaceuticals such as sodium iodine (^{131}I), which represents an excellent therapeutic modality in the treatment of differentiated thyroid carcinomas. As well as other therapeutic modalities, radionuclide therapy using radiopharmaceuticals can also cause adverse reactions. This study aimed to evaluate the incidence of possible adverse events related to therapy with sodium iodine (^{131}I), and evaluate the correlation with the administered activities, obtaining unprecedented pharmacovigilance data related to the use of therapeutic radiopharmaceuticals in Brazil. A retrospective analysis of medical records was carried out with electronic patients' data diagnosed with differentiated thyroid carcinoma and undergoing therapy with radioiodine. A total of 116 patients were recovered from January/2019 to April/2021 and 89 were included according to the inclusion criteria. Of the patients, 54.6% reported an adverse event after radioiodine therapy. The most frequent events were those related to the gastrointestinal tract and local irradiation, and it was possible to identify that there was an increased incidence of events in those patients who were treated with greater activities. Based on the results obtained, the present study demonstrated the presence of acute events related to therapy in the studied population and that the incidence of events was correlated with the activity prescribed.

Keywords: radioiodine therapy; differentiated thyroid carcinoma; adverse events.

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Incidência de Eventos Adversos Relacionados a Terapias com o iodeto de sódio (^{131}I): Contribuição para Farmacovigilância no Brasil

Resumo: Radiofármacos com finalidade terapêutica vêm sendo cada vez mais utilizados para tratamento de diversas patologias. Os radionuclídeos emissores beta destacam-se nessa modalidade devido às características físicas da partícula emitida. O iodo-131 (^{131}I) é um exemplo de radionuclídeo emissor beta, aplicado na produção de radiofármacos como o iodeto de sódio (^{131}I) que representa uma excelente modalidade terapêutica no tratamento de carcinomas diferenciados da tireoide. Assim como as demais modalidades empregadas na terapia do câncer, a terapia radionuclídea utlizando-se radiofármacos também pode provocar reações adversas. Esse estudo teve como objetivo avaliar a incidência de possíveis eventos adversos relacionados à terapia com o radiofármaco iodeto de sódio (^{131}I), bem como correlacionar os mesmos com as atividades administradas, obtendo dados inéditos de farmacovigilância relacionados ao uso de radiofármacos terapêuticos no Brasil. Foi realizada uma análise retrospectiva de prontuários eletrônicos de pacientes diagnosticados com carcinoma diferenciado da tireoide e submetidos à radioiodoterapia. Um total de 116 pacientes foram recuperados no período de janeiro/2019 à abril/2021 e 89 foram incluídos de acordo com os critérios de inclusão. Dos pacientes 54,6% relataram algum evento adverso após a radioiodoterapia. Os eventos mais frequentes foram aqueles relacionados ao trato gastrointestinal e irradiação local e foi possível identificar que há um aumento da incidência de eventos naqueles que foram tratados com atividades maiores. Com base nos resultados obtidos, o presente estudo demonstrou a presença de eventos agudos na população estudada, e que a incidência dos eventos apresenta correlação com a atividade prescrita.

Palavras-chave: radioiodoterapia; carcinoma diferenciado da tireoide; eventos adversos.

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1. INTRODUCTION

Radionuclides that emit beta particles (negatrons) are used in the composition of radiopharmaceuticals for therapeutic purposes in Nuclear Medicine. The most used are iodine-131 (^{131}I) and yttrium-90 (^{90}Y), however, other beta-emitters such as lutetium-177 (^{177}Lu) and rhenium-188 (^{188}Re) are increasingly being used for radionuclide therapy. Beta minus decay occurs when a nucleus with atomic number Z and mass A is transformed into a nuclide with atomic number Z+1 and mass A and results in the emission of a beta particle and an antineutrino[1].

Therapy of benign and malignant diseases of the thyroid with the radiopharmaceutical sodium iodide (^{131}I) emerged with the birth of Nuclear Medicine, in the 40s. Since then, this therapy has been performed on patients adult and pediatrics, and has contributed greatly to increasing life expectancy in all cases of differentiated thyroid cancer[2].

Differentiated Thyroid Carcinoma (DTC) is an endocrine neoplasm of with the highest prevalence in the world. DTC is understood as the malignant tumor of epithelial origin, with papillary carcinoma being the main representative of this category and, also include follicular carcinoma and of Hurthle cells [3].

The therapeutic modality of DTC varies according to the histological type of the tumor, staging and risk factors. These modalities include thyroidectomy, radioiodine therapy and external beam radiotherapy [4].

Radioiodine therapy, therapy using the radiopharmaceutical sodium iodide (^{131}I), has two purposes: radioablation, which aims to destroy remaining thyroid tissue after total thyroidectomy and therapeutic action, which in addition to destroying remaining tissue, it also eliminates locoregional and distant micrometastases [5].

Side effects of therapy with the radiopharmaceutical sodium iodide (^{131}I) can be acute or chronic. The most common adverse events reported after radioiodine therapy are bone marrow suppression, parosmia, anosmia, sialodenitis, nausea, vomiting, ovarian insufficiency, headache, among others. Local irradiation effects are also described as being very common and these include pain, discomfort and local edema in the head and neck region [6].

Despite the Institute of Energy and Nuclear Research at National Nuclear Energy Commission (IPEN-CNEN), producing the radiopharmaceutical sodium iodide (^{131}I) since the end of the 1950s, there are no controlled reports of adverse events from this radiopharmaceutical in Brazil.

The regulations for registration and Good Manufacturing Practices of Radiopharmaceuticals in Brazil is relatively recent, with the first Resolutions of the Collegiate Board of Directors (RDC) of ANVISA published in 2009[7], fact that made it difficult to verify the safety aspects of using this class of medicines, including pharmacovigilance reports. For the registration with ANVISA of the radiopharmaceutical sodium iodide (^{131}I) produced at IPEN-CNEN, efficacy and safety results from studies carried out in other countries were used, as there are few studies related to evaluating the safety of using radiopharmaceuticals in Brazil, hindering the collection of information for the Brazilian population.

Given this scenario, this work aimed to evaluate the incidence of adverse events associated with therapy using the radiopharmaceutical sodium iodide (^{131}I), applied in radionuclide therapy in Nuclear Medicine, as well as correlate them with the administered activity and also compared the events in the studied population with the events described in product leaflets.

2. MATERIALS AND METHODS

This is a descriptive, retrospective study that was carried out in the Nuclear Medicine service of a teaching hospital in the city of São José do Rio Preto/SP, Brazil.

After approval by the research ethics committee (5.490.569), medical records of patients undergoing radioiodine therapy were evaluated. The inclusion criteria for patients were over 18 years old with a diagnosis of differentiated thyroid carcinoma treated with radioiodine therapy. The exclusion criteria were the absence of information in the medical records of treated patients, with the main reason for absence being follow-up in other health centers.

The radiopharmaceutical sodium iodide (^{131}I), as solution or capsule for oral use, were administered to all patients in the present study with individualized and calibrated activities according to the nuclear doctor's prescription.

The activities were prescribed based on the staging of the disease according to the guideline of the Society of Nuclear Medicine and Molecular Imaging and the European Society of Nuclear Medicine [8].

The characterization of the therapy was carried out through analysis of the medical appointment before radioiodine therapy in the nuclear medicine service, in addition to using the anatomical pathology. The analysis of the reported events was carried out by consulting the information on the medical evolution of patients, hospitalized in a therapeutic room, and return medical appointment information after radioiodine therapy in the hospital endocrinology.

Table 1 shows the frequency of adverse events described in the product leaflets used for comparison.

Table 1 : Frequency of adverse events from radioiodine therapy

System/Organ	Adverse Event	Frequency
Immune system	Anaphylactic shock	Unknown
Malignant, benign and nonspecific neoplasms (polyps and cysts)	Leukemia	Unusual
	Solid tumors, Bladder cancer, Colon cancer, Stomach cancer, Lung cancer	Unknown
Hematological and Lymphatic Events	Erythropenia, Bone Marrow Depression	Very common
	Anaplastic anemia, Permanent bone marrow suppression	Unknown
Endocrine Events	Thyrotoxic crisis, Transient hyperthyroidism	Rare
	Thyroiditis, Hypoparathyroidism, Hypothyroidism, Hyperparathyroidism	Unknown
Nervous System Events	Parosmia, Anosmia	Very common
	Brain edema	Unknown
Eye-related events	Sicca syndrome	Very common
	Tear duct obstruction	Common
Respiratory, Thoracic and Mediastinal events	Dyspnea	Common
	Pulmonary fibrosis, Pneumonia, Vocal cord dysfunction, Oropharyngeal pain	Unknown
Gastrointestinal Events	Sialoadenitis, Ageusia, Dysgeusia, Nausea, Decreased appetite	Very common
	Vomiting	Common
	Gastritis, Dysphagia	Unknown
Hepatobiliary events	Unusual hepatobiliary function	Unknown
Renal and Urinary events	Radioactive cystitis	Unknown
Reproductive system events	Ovarian failure, Menstrual disorder	Very common

System/Organ	Adverse Event	Frequency
	Azoospermia, Oligoespermia, Decreased male fertility	Unknown
General events	Flu-like symptoms, Headache, Fatigue, Local pain	Very common
	Local edema	Common

Source : Product Leaflets IOD-IPEN-131, 2018 ; CAPSION 50-3700 MBq (I-131), 2018; Sodium Iodine I 131 Capsule USP, 2011.

3. RESULTS AND DISCUSSIONS

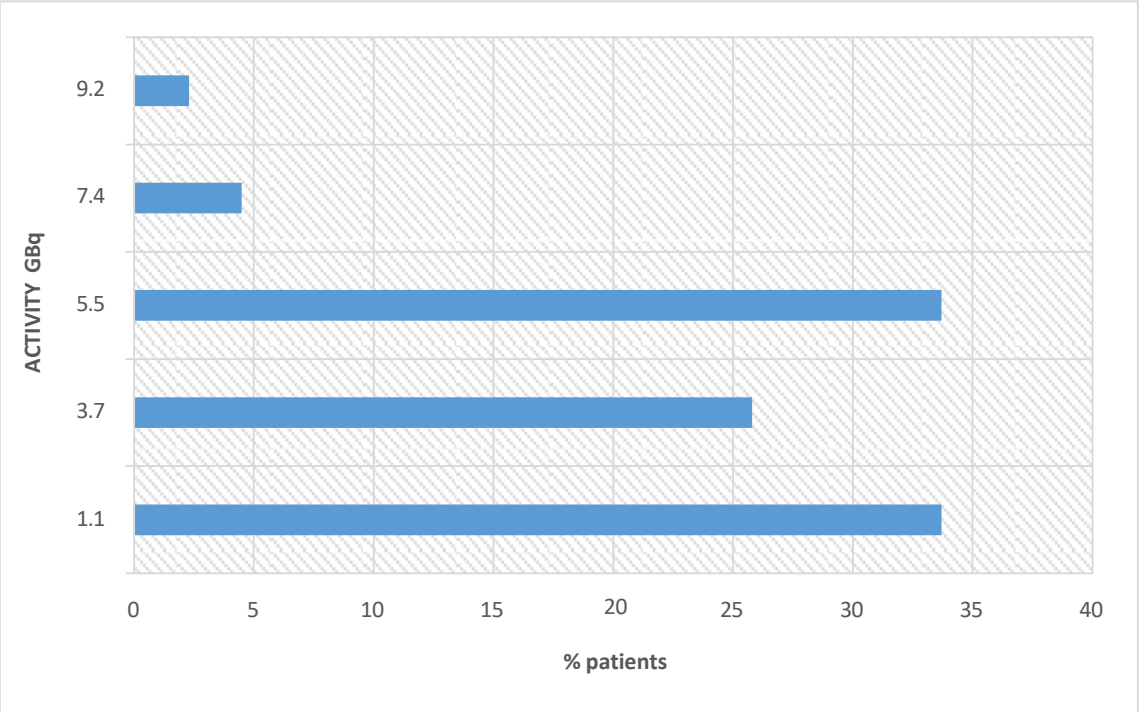
The medical records of patients treated with sodium iodide (^{131}I) from January/2019 to April/2021 were analyzed and 116 patients were recovered, of which 89 met the inclusion criteria, 73 (82 %) were female and 16 (18 %) were male.

Comparing the results obtained in this study and indices worldwide, differentiated thyroid carcinoma is the most common endocrine neoplasm in the world and affects about three times more women than men [9].

Analysis of the results revealed that the age of the patients ranged from 18 to 84 years old. The average age of patients in the survey carried out was 43 years old, a result that is at the lower limit of the average age range in which papillary carcinoma is diagnosed, which is between the mid-40 years old and early 50 years old [10].

The administered activity ranged from 1.11 GBq to 9.25 GBq as shown in figure 1.

Figure 1: Percentage distribution of managed activities



Source : Survey data, 2022.

Of the recovered patients, 54.6 % reported some adverse event after radioiodine therapy, 44.7 % being events related to the gastrointestinal tract, 36.2 % nausea, 4.2 % vomiting, and 4.2 % intestinal constipation.

Some studies have demonstrated that adverse events related to the gastrointestinal tract correlate with the administered activity. Previous studies demonstrated that there were no gastrointestinal tract symptoms with activities less than or equal to 1.1 GBq. Nausea from 1.5 GBq and vomiting in 1 % of patients with activities greater than 3.7 GBq [11;12].

In the present study, the results found followed the same pattern as the literature consulted, in which no patients treated with 1.1 GBq experience adverse events. Events related to gastrointestinal started to appear from 3.4 GBq activity.

A previous study, carried out in Iran, after investigating the gastrointestinal side effects of radioiodine, concluded that there is a significant correlation between administered activity and complaints and identified that the most prevalent event was nausea, in 26.4 % of patients [13].

In the present study, the most prevalent event was also nausea, being observed for greater activities (above 3.7 GBq), being characterized as very frequent [14;15;16]. As found in previous studies, the present study found a linear correlation between the increase in gastrointestinal adverse events and the increase in administered activity. In this study, Pearson´s correlation coefficient was approximately 0.70, indicating a strong positive correlation.

Regarding the effects related to local irradiation, 68 % reported some event of this nature, with 19.1 % experiencing local pain (thyroid region/surgical scar), 14.9 % local edema, 10.6 % pain in the head region and neck and 2.1 % vocal fold paralysis. Sialadenitis was reported by 12.8 % of patients.

The events related to local irradiation found in the present study are in accordance with those described in product leaflets [14;15;16]. Pain and local edema were frequent events in patients with activities greater than 3.7 GBq. A previous study demonstrated that neck pain was significantly more frequent among patients with a higher ablation dose[17].

According to the literature, radiation thyroiditis with mild, transient neck pain and edema is not uncommon (10-20 %). Symptoms of edema and discomfort are more frequent in patients with large thyroid tissue remnants [18].

One patient in our study presented with left-sided vocal fold paralysis who underwent total thyroidectomy and cervical lymph node dissection before performing RIT. It is believed that the paralysis was due to the surgical approach. Although rare, there are studies on the effects of radioiodine therapy on vocal quality and reports of vocal fold paralysis due to involvement of the laryngeal nerve after radioiodine therapy.

Menstrual irregularity was observed in 4.3 % of patients and 34 % reported general malaise after undergoing therapy: 6.4 % had hair loss and 2.1 % reported weight gain without changing their diet. Table 2 summarize the adverse events found in the present study.

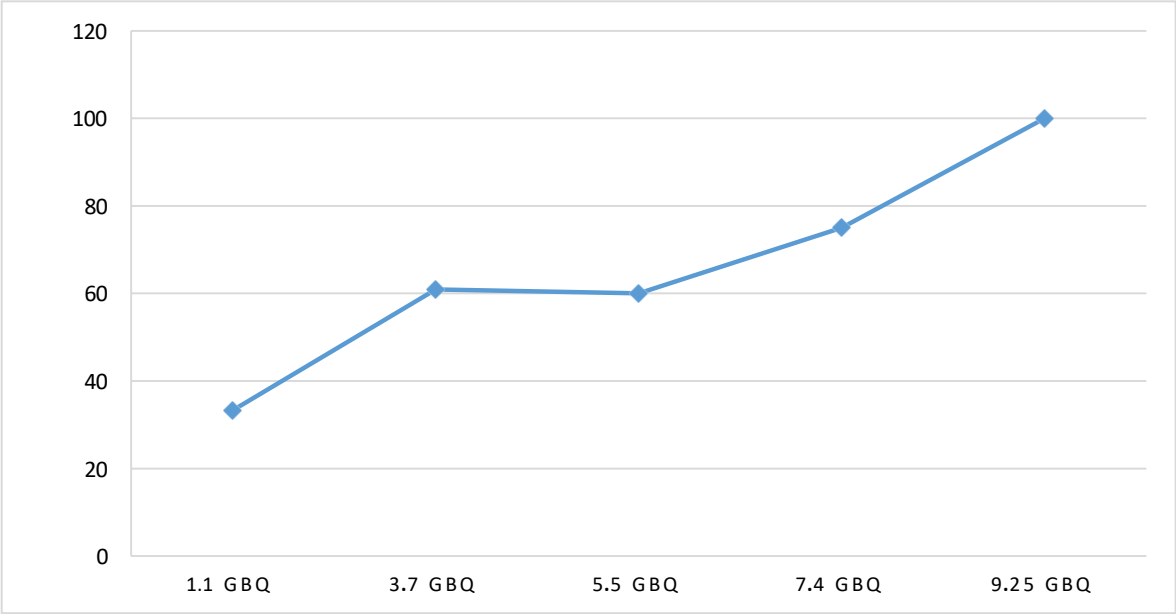
Table 2 : Adverse events reported by patients who underwent radioiodine therapy and percentage distribution.

	Reported adverse event	% Patients
Gastrointestinal tract	Nausea	36.2
	Vomiting	4.2
	Constipation	4.2
Local irradiation	Local pain	19.1
	Local edema	14.9
	Head and neck pain	10.6
	Vocal cord paralysis (Probably caused by surgery)	2.1
Salivary glands	Sialadenitis	12.8
Reproductive system	Menstrual irregularity	4.3
General events	General malaise	34.0
	Loss of hair	6.4
	Weight gain	2.1

Source : Survey data, 2022.

A higher prevalence of adverse events was observed in patients who underwent greater activities. All patients (100 %) treated with 9.25 GBq experienced one or more events and 75 % of patients treated with 7.4 GBq reported an event. The lowest prevalence of events was observed in patients treated with 1.11 GBq. Figure 2 shows the prevalence of adverse events (% patients) according to the activity administered.

Figure 2: Percentage of patients with adverse events X administered activities



Source : Survey data, 2022.

The most prevalent event was nausea, being observed for higher activities (above 3.7 GBq), and this finding is in accordance with what is described in the radiopharmaceutical product leaflets of sodium iodide (^{131}I), being characterized as very frequent [11;12;13]. Table 3 shows the relationship observed between event and administered activity.

Salivary gland dysfunction is the most common complication of radioiodine therapy for differentiated thyroid cancer[19]. In the present study, 12.8 % of patients presented sialadenitis. A previous study found that approximately a quarter of patients treated with 3.4 GBq or more were affected by ultrasound-confirmed chronic sialoadenitis and no lesions were detected in those patients who received activities less than or equal to 1.8 GBq, concluding that the main factor of risk for injury is the activity administered [20].

Table 3 : Relationship between reported adverse event and administered activity in patients who underwent Radioiodine therapy.

Activity (GBq)	Reported adverse event	% Patients
1.10	Local pain	3.3
	General malaise	20.0
	Local edema	3.3
	Menstrual irregularity	3.3
	Loss of hair	6.7
	Constipation	3.3
3.70	Local pain	8.7
	Local edema	13.0
	General malaise	26.0
	Nausea	21.7
	Head and neck pain	8.7
	Loss of hair	4.3
	Weight gain	4.3
	Constipation	4.3
5.55	Local pain	13.3
	Local edema	10.0
	General malaise	6.7
	Nausea	36.7
	Vomiting	3.3
	Head and neck pain	10.0
	Sialadenitis	10.0
7.40	Local pain	25.0
	Nausea	25.0
	Vomiting	25.0
	Vocal cord paralysis (Probably caused by surgery)	25.0
9.25	Local pain	100
	Nausea	100
	Sialadenitis	50.0
	Menstrual irregularity	50.0

Source : Survey data, 2022.

When observing the relationship between reported event and administered activity, it was found that those patients undergoing minor activities reported general malaise (20 %). Despite being an event described as adverse in product leaflets, it is believed that this event may be due to pre-treatment hormonal deprivation that results in hypothyroidism, as well as hair loss that is related to a symptom of this condition. It is then considered a secondary event and can be avoided by the administering of recombinant TSH (rhTSH).

Several studies have shown the advantages of using rhTSH in terms of preserving quality of life, lower radioiodine activity absorbed by abdominal organs and, a significant reduction in overall exposure to radiation in sensitive organs [8].

A study including 228 patients that compared individuals with hormone withdrawal and rhTSH use concluded that short-term hypothyroidism after L-T4 withdrawal is associated with a significant decline in quality of life that is offset by rhTSH[21].

This study was retrospective and only relied on information from patient records. Despite the small number of patients record analysed, it was possible to verify that some adverse events are reported more frequently in patients undergoing radioiodine therapy and are in accordance with the described in product leaflets and literature, for populations from other parts of the word, representing different ethnic groups.

Reports are collected by doctors and documented in the patient´s medical records following radioiodine therapy; however, there is no standardized format for these reports. We also recommend standardizing post-RIT interviews and that medical records contain more information about the initial diagnosis, stay and follow-up of the disease.

4. CONCLUSIONS

The present study demonstrated the presence of acute events related to radioiodine therapy in the evaluated sample, and that the incidence of events correlates with the administered activity.

Furthermore, it was verified that the frequency of reported events is in accordance with the frequency described in international product leaflets, corroborating the use of data from international literature or even product leaflets from international radioiodine manufacturers to compose the leaflet of radiopharmaceuticals produced in Brazil.

Despite the events reported in the literature, international product leaflets and the leaflet of radiopharmaceuticals sold in Brazil, therapy with sodium iodide (^{131}I) is considered a safe treatment and represents one of the most widespread and effective therapies for the treatment of differentiated thyroid carcinoma, and the adverse events found here do not outweigh the benefits of the treatment.

Based on the results of this study, it is recommended that patients treated with sodium iodide (^{131}I) and other radiopharmaceuticals for therapy be tracked more accurately to verify aspects of use and safety assessment at a national level.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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