Radiat Environ Biophys (2011) 50:579–584
DOI 10.1007/s00411-011-0380-y

ORIGINAL PAPER

# Mutagenicity of diagnostic and therapeutical doses of radiopharmaceutical iodine-131 in Wistar rats

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Received: 5 December 2010 / Accepted: 10 August 2011 / Published online: 25 August 2011


**Abstract** Iodine-131 ($^{131}$I) is a radioisotope used for the diagnosis and treatment of thyroidal disorders such as hyperthyroidism and cancer. During its decay, $^{131}$I emits beta particles and gamma rays; its physical half-life is 8 days, and it is accumulated preferentially in the thyroid tissue. This study aimed to evaluate the cytotoxicity and mutagenicity of diagnostic and therapeutic doses of $^{131}$I using bone marrow cells of rats treated in vivo in a test system with a single dose by gavage. Concentrations of 5, 25, 50 and 250 μCi in 1 ml of water were used, and after 24 h, the animals were killed. Also, a concentration of 25 μCi/ml of water was used, and the animals were killed after 5 days. The results showed that no concentration of $^{131}$I was cytotoxic and that all concentrations were mutagenic. As a result, there was no statistically significant difference detected by the $\chi^2$ test in the induction of chromosomal aberrations between the different doses. Thus, the present study demonstrated a significant increase in chromosomal aberration in bone marrow cells exposed to $^{131}$I regardless of the dose or the treatment time.

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## Introduction

There is an increased risk of cancer in individuals exposed to low levels of ionizing radiation for diagnosis or therapy. Radioactive iodine, mainly iodine-131 ($^{131}$I), is a major source of human exposure to ionizing radiation (Puerto et al. 2000). $^{131}$I is used in the diagnosis of thyroidal dysfunctions and for the treatment of hyperthyroidism and differentiated thyroid cancer (Thrall and Ziessman 2003). It emits beta particles ($\beta$) (E = 0.61 MeV) and gamma rays ($\gamma$) (E = 0.36 MeV) with a half-life of 8 days, but an organism can eliminate it quickly, via feces, urine and sweat (Turgut et al. 2006; Cardoso 2011). This radioisotope has clastogenic activity, and approximately 90% of its radiation effects are the result of $\beta$ radiation, which has a tissue penetration of 0.4 mm (Gutiérrez et al. 1997).

Radiation is known to affect cells directly or indirectly, interacting with genetic material and causing chromosomal aberrations or cell death (Joseph et al. 2009). Ionizing radiation, through interaction with the environment, causes the formation of oxidizing free radicals by radiolysis of water, which react with intracellular macromolecules and alter cellular metabolism. Ionizing radiation also acts directly on nuclear DNA and may result in single- or double-strand breaks (Calegaro 2007).

Studies conducted in several test systems with various doses of radioiodine, different than those tested here, showed high frequencies of chromosomal aberrations (Puerto et al. 2000; Silva et al. 2008) and micronuclei (Ballardin et al. 2002; Watanabe et al. 2004; Grawé et al. 2005; Joseph et al. 2009). The chromosomal damage induced by radioiodine exposure predisposes individuals to a future risk of developing cancer (Federico et al. 2008).

The objective of this study was to evaluate the cytotoxicity and mutagenicity of four concentrations of $^{131}$I

radioisotope, which is used for the diagnosis and therapy of various thyroidal injuries, through the chromosomal aberration test applied in the bone marrow cells of Wistar rats that were treated in vivo.

## Materials and methods

### Treatment solution

The radioisotope $^{131}$I was obtained from IPEN (Institute of Nuclear and Energy Research-SP/BR). The tested concentrations were calculated by the extrapolation of the body weight of Wistar rats and the concentrations used by humans for thyroidal disease diagnosis (5 μCi or 0.185 MBq), hyperthyroidism therapy (25 μCi or 0.925 MBq), thyroid nodules (50 μCi or 1.85 MBq) and thyroid cancer (250 μCi or 9.25 MBq) (Thrall and Ziessman 2003; Sisson et al. 2006).

### Wistar rats

Six Wistar rats, three males and three females for each group, were obtained from the Central Vivarium of the University of Maringá (UEM). Experiments were carried out using 35-day-old rats weighing approximately 100 g (bw). During the experimentation period, the animals were kept in the Mutagenesis/Radiation Laboratory of the Department of Cell Biology and Genetics/UEM under controlled temperature (±25°C), humidity (±50%) and with a photoperiod of 12 h light/dark according to the standards established by the Ethics Committee on Experimentation with Laboratory Animals/UEM (process number: PRO 027/2009).

In the experiment, two negative controls ($CO^-$) were used, one with 1 ml of water/100 g bw via gavage in a single dose and killing after 24 h and a second with daily dose for 5 days and killing after 24 h. A positive control ($CO^+$) was used with 1.5 mg of cyclophosphamide clastogenic drug/1 ml water/100 g bw intraperitoneally for 24 h to assess the responsiveness of the lineage.

Experiments were conducted with a single dose: with four concentrations of $^{131}$I (5, 25, 50 and 250 μCi) and killing after 24 h (1 day) and with a single concentration of $^{131}$I (25 μCi) and killing after 5 days (120 h). All concentrations were administered in 1 ml of water per 100 g of animal bw via gavage.

Measurements of the radiation exposure rates of each animal and the elimination of radiation via sweat, urine and feces through the measurement of the wood-wool bedding of each box were conducted after the treatments using a Geiger Muller counter, positioned 3 cm away from the object. The measurements started at 0 h and were repeated every 4 h for the first 12 h, resulting in the measurements at 0, 4, 8, 12 and 24 h for the 24 h treatment and 0, 4, 8, 12, 24, 48, 72, 96 and 120 h for the 5 day treatments. To check the radiation elimination rate of animals via sweat, urine and feces, the wood-wool bedding placed in each box was initially weighed (70 g) and changed whenever the radiation measurements were performed.

Food and water were changed daily, but the animals fasted for 2 h before and 2 h after the treatment, which is similar to humans under this kind of treatment. Water consumption was observed in all groups every 4 h for the first 12 h and every 24 h for the 5 day treatments.

### Chromosomal aberration test

The chromosomal aberration test was performed in order to obtain bone marrow cells of Wistar rats using the Ford and Hamerton method (1956) with some modifications. The mitotic cells were interrupted in metaphase with the intraperitoneal administration of 0.5 ml/100 g bw of colchicine (0.16%) 30 min before killing.

Analysis of the slides was performed using a light microscope to examine 100 metaphase stages per animal, totaling 600 for the control and treatment groups, and to search for the appearance of alterations such as gaps, breaks, fragments and other chromosomal aberrations. The results were expressed as a percentage of total aberrations, with and without gaps, and the number of aberrations per metaphase.

The mitotic index (MI) for the cytotoxicity evaluation was calculated from 5,000 cells by sex, totaling 10,000 cells per group. The MI calculation, as a percentage, was performed using the number of dividing cells divided by the total number of cells present in the field.

### Statistical analysis

The statistical calculation was performed using the $\chi^2$ test ($\alpha = 0.05$).

## Results

Table 1 presents the data for the average mitotic index and chromosomal aberrations of the treatment and control groups. According to the $\chi^2$ analysis, there were no differences when comparing the mitotic indexes. For each treatment performed, the percentage of total chromosomal abnormalities (including and excluding gaps) was statistically different when compared to their respective negative controls. For the animals treated for 24, the average values excluding gaps increased from 0.3 ± 0.5 (0 μCi) to 3.2 ± 3.4 (5 μCi), 2.8 ± 1.8 (25 μCi), 3.0 ± 0.9 (50 μCi),

**Table 1** Mean mitotic index (MI), total, types of alterations and altered metaphases obtained for Wistar rats treated with $^{131}$I for 24 h or 5 days and the different control groups

| Groups | MI Mean ± SD | Number of altered metaphases(%) | Total alterations (ū ± SD) | Total alterations without gaps (ū ± SD) | Total alterations/ Altered metaphases | Type of alteration | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Gap* | | Break | |
| | | | | | | ct | cr | ct | cr |
| $CO^+$ | 1.1 ± 0.3 | 91 (15.2) | 128 (21.3 ± 4.4) | 95 (15.8 ± 3.5) | 1.4 | 29 | 04 | 61 | 14 |
| *24 h* | | | | | | | | | |
| $CO^-$ | 1.4 ± 0.8 | 02 (0.3) | 02 (0.3 ± 0.5)[c] | 02 (0.3 ± 0.5)[c] | 1.0 | – | – | 02 | – |
| *Iodine-131* | | | | | | | | | |
| 5 μCi | 2.4 ± 0.8 | 15 (2.5) | 21 (3.5 ± 3.3)[ac] | 19 (3.2 ± 3.4)[ac] | 1.4 | 02 | – | 18 | 01 |
| 25 μCi | 2.2 ± 0.5 | 19 (3.2) | 26 (4.3 ± 2.8)[ac] | 17 (2.8 ± 1.8)[ac] | 1.3 | 08 | 01 | 13 | 04 |
| 50 μCi | 1.8 ± 0.4 | 19 (3.2) | 21 (3.5 ± 1.0)[ac] | 18 (3.0 ± 0.9)[ac] | 1.1 | 03 | – | 17 | 01 |
| 250 μCi | 2.0 ± 0.5 | 17 (2.8) | 21 (3.5 ± 1.8)[ac] | 20 (3.3 ± 1.8)[ac] | 1.2 | 01 | – | 18 | 02 |
| *5 days* | | | | | | | | | |
| $CO^-$ | 1.4 ± 0.2 | 02 (0.3) | 03 (0.5 ± 0.8)[c] | 01 (0.2 ± 0.4)[c] | 1.6 | – | 02 | 01 | – |
| *Iodine-131* | | | | | | | | | |
| 25 μCi | 1.6 ± 0.6 | 12 (2.0) | 13 (2.2 ± 1.1)[bc] | 13 (2.2 ± 1.2)[dc] | 1.1 | – | – | 12 | 01 |

Negative control ($CO^-$) with water; Positive control ($CO^+$) with cyclophosphamide

MI calculated from 10,000 cells/group, and 600 analyzed metaphases/group

*ct* = chromatid, *cr* = chromosome

[a] Statistically significant result, compared to the 24 h negative control ($p < 0.005$)

[b] Statistically significant result, compared to the 5 day negative control ($p < 0.02$)

[c] Statistically significant result, compared to the positive control ($p < 0.005$)

[d] Statistically significant result, compared to the 5 day negative control ($p < 0.005$)

and 3.3 ± 1.8 (250 μCi); also, 5 days after the treatment (at 25 μCi), the spontaneous frequency increased from 0.2 ± 0.4 to 2.2 ± 1.2.

On the other hand, there was no statistical difference regarding chromosomal alterations when comparing treatment with different concentrations of $^{131}$I for 24 h (5, 25, 50 and 250 μCi), and the chromosomal abnormality averages were similar among all four concentrations. Furthermore, the comparison between the two treatment times, 24 h (4.3) and after 5 days (2.2), with 25 μCi of $^{131}$I was also not statistically different.

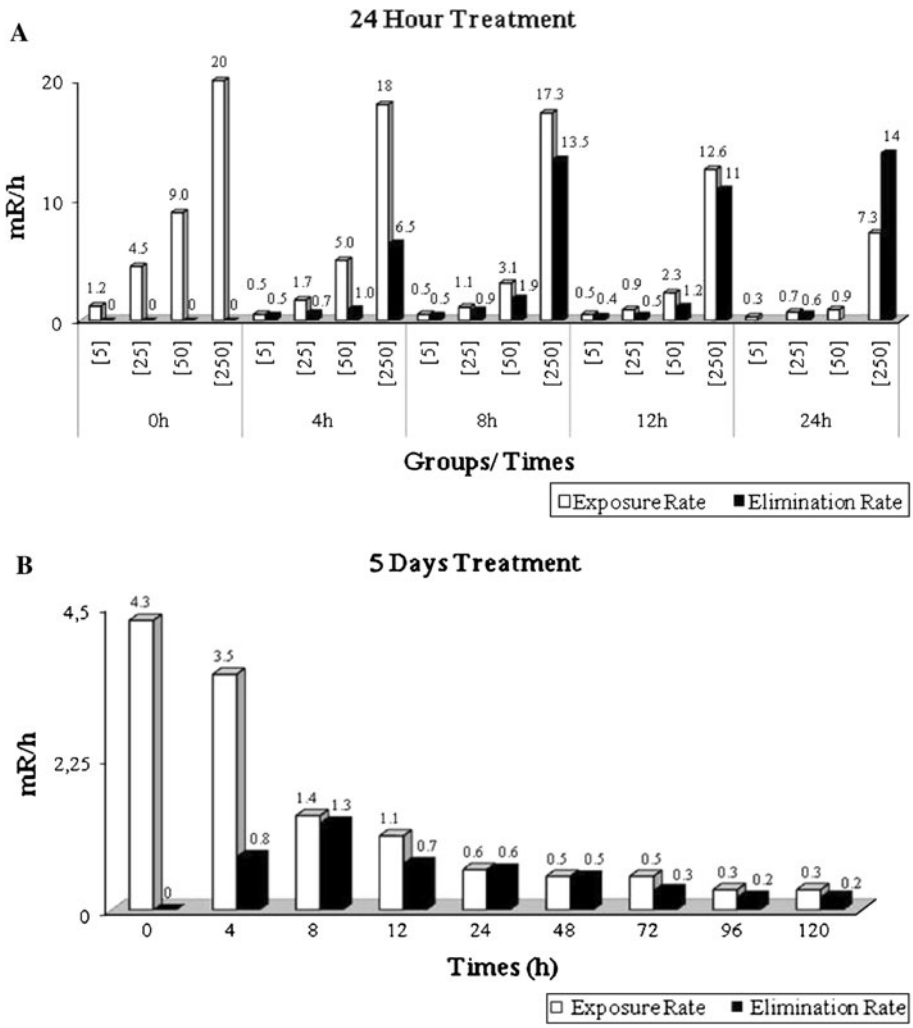
The data presented in Fig. 1a, b indicate that the rate of $^{131}$I radiation exposure at concentrations of 5, 25, 50 and 250 μCi was higher in the first 12 h (0, 4, 8 and 12 h) after treatment, with a gradual decrease over time. Moreover, the rate of radiation eliminated in the urine and feces (Fig. 1a, b) was higher at 8, 12 and 24 h after the treatments, indicating that with a decreasing rate of radiation exposure, there was an increase in the rate of radiation elimination in the urine and feces.

After 24 h, the administered $^{131}$I was reduced, via elimination through sweat, feces and urine, by the following amounts: 75% (5 μCi), 84% (25 μCi), 90% (50 μCi), 64% (250 μCi) (Fig. 1a) and 86% (25 μCi) (Fig. 1b), considering the initial exposure rate as 100% for all.

Figure 2 shows the water consumption of the animals from different treatment groups (both males and females) and shows that the groups treated with $^{131}$I (the group treated for 24 h exhibited a higher water consumption) were statistically different from the negative control group for the concentrations of 5 ($\chi^2 = 18.22$), 25 ($\chi^2 = 10$) and 250 μCi ($\chi^2 = 22.5$). The calculations for water consumption were based on the consumption of 80 ml of water in the negative control group, which was set at 100%. Water consumption increased in each group by the following amounts: 5 μCi, 33%; 25 μCi, 25%; 50 μCi, 15%; and 250 μCi, 37%. However, the water consumption for the group treated for 5 days with 131I was similar to the control group.

## Discussion

During the last decade, there has been an increasing emphasis on the mutagenic and carcinogenic effects of radiopharmaceuticals as a consequence of the increased use of ionizing radiation for diagnostic and therapeutic purposes. In



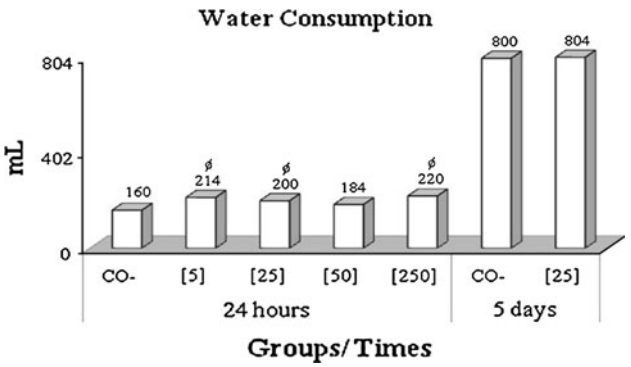




**Fig. 1** **a** Exposure rate and elimination of radiation in mR/h (milli Roentgen per hour) measured at different times in hours following treatment with $^{131}$I at concentrations of 5, 25, 50 and 250 μCi for 24 h. **b** Exposure and elimination of radiation after treatment with 25 μCi $^{131}$I for 5 days

**Fig. 2** Water consumption of the different groups treated with $^{131}$I at different concentrations for 24 h or 5 days and the negative control ($CO^-$). ¢ statistically significant result compared to the negative control at 24 h ($p < 0.005$)

this context, the radioisotope Iodine-131 is of particular interest because it is widely used in the diagnosis and treatment of individuals suffering from thyroidal disorders.

The results of this study indicate that $^{131}$I, at the concentrations tested (5, 25, 50 and 250 μCi), was not cytotoxic but was mutagenic to bone marrow cells of Wistar rats treated in vivo via gavage. The results of this study confirmed the genotoxic activity of this radiation as shown by several cytogenetic investigations performed in thyroid patients who received different doses of $^{131}$I (from 0.01 Ci to 0.85 Ci) (Gil et al. 2000a; Puerto et al. 2000; Ballardin et al. 2002; Watanabe et al. 2004; Joseph et al. 2009).

Irradiation generates oxygen-free radicals such as superoxide, hydrogen peroxide, hydroxyl radicals and their intermediaries, which in turn induce the lipid peroxidation of cellular membranes and structures. This process creates an imbalance between the generation of free radicals and their capture by cellular systems, which can cause severe damage to important cellular structures, including chromosomes. Furthermore, the increased production of superoxide radicals can induce the release of clastogenic factors in circulating plasma and the products of lipid peroxidation (4-hydroxynonenal aldehyde), inosine nucleotides and cytokines. These products can perpetuate and further increase chromosomal damage and may eventually exceed the DNA repair capacity (Ballardin et al. 2002).

Despite not being the most irradiated location, bone marrow is the critical target in determining the maximum dose of $^{131}$I to be administered due to its high radiosensitivity (Sapienza et al. 2005), which enables the use of the test system used here. In this study, the estimated radiation dose that the bone marrow of rats received from $^{131}$I was 0.001–0.003 cGy for the concentration of 5 μCi, 0.007–0.016 cGy for 25 μCi, 0.015–0.032 cGy for 50 μCi and 0.078–0.164 cGy for 250 μCi (calculated data, extrapolated from the work of Ballardin et al. (2002)). Even though these estimated doses were low, they may have been responsible for most of the observed chromosomal alterations, which were observed to be breaks (Table 1), and this result coincides with those given by Natarajan (2002).

Chromosomal aberrations observed in this study, as well as those found by Silva et al. (2008), may be partly a consequence of the combination of $^{131}$I accumulation in the thyroid gland, which acts as an internal source of irradiation, with the concomitant loss of selectivity of damaged bone marrow cells. One possible explanation for this phenomenon is the low penetration energy of $\beta$ particles, which may only affect a small number of cells but can deposit a fraction of the energy heterogeneously in the nuclei, thereby generating various types of damage in DNA. Moreover, in the case of thyroid cancer patients, who are commonly hypothyroid, $^{131}$I becomes concentrated into the remnant thyroid tissue and metastatic sites; hence, exposure of $^{131}$I may be higher and more genotoxic than originally expected (Gutiérrez et al. 1997).

However, some studies have demonstrated that patients who received $^{131}$I did not exhibit chromosomal damage from radiometabolic therapy (Gil et al. 2000b; Federico et al. 2008).

Despite the differences in the concentrations and in the nuclear medicine applications of the tested $^{131}$I doses (5, 25, 50 and 250 μCi) in acute treatment, they were statistically similar regarding the percentage of chromosomal abnormalities. These data corroborate with those of Barquinero et al. (1993), who also saw no correlation between the frequency of chromosome aberrations and the received ionizing radiation dose, and Puerto et al. (2000), who found no relationship between the amount of chromosomal abnormalities and the dose of $^{131}$I radioactivity administered or the age of patients.

The data from several investigations are contradictory regarding the increase (Gutiérrez et al. 1997, 1998; Gil et al. 2000a) or decrease (Watanabe et al. 1998; Puerto et al. 2000; Ballardin et al. 2002; Silva et al. 2008) of DNA damage induced by $^{131}$I concerning the time elapsed after exposure to radiation. In this study, the treatment with 25 μCi for 24 h and 5 days did not produce statistically different results. However, there was a 50% decrease in the total number of chromatid and chromosomal alterations after 5 days of treatment (13 alterations) compared to 24 h of treatment (26 alterations).

The study by Silva et al. (2008) also had a larger number of chromosomal aberrations in rat lymphocytes after 24 h of treatment with 0.30 mCi of $^{131}$I, with gradual decline after 7 and 30 days. Similar data were reported by Watanabe et al. (1998) using the micronucleus cell test with lymphocytes from 25 patients treated with 0.10 Ci of $^{131}$I, in which the micronuclei frequency significantly increased after therapy and decreased after 2 weeks before reaching the baseline. According to the authors, this effect may be caused by the short lifespan of lymphocytes (3–4 days) or by the rapid repair of cellular damage. According to Calegaro (2007), the body may react to the action of ionizing radiation, such as $^{131}$I, by the neutralization of oxygen radicals, activation of the repair of structural alterations in DNA, induction of apoptosis if there are signs of cellular inviability, and activation of immune responses that recognize the damaged cell as foreign by the alterations in the membrane.

These results corroborate with the present study, in which the damage occurred by exposure to a concentration of 25 μCi for 5 days may have been eliminated by DNA repair mechanisms, as shown by Plappert et al. (1995), or by the elimination of the damaged cells by a more rapid cell turn-over. Furthermore, analysis of the mitotic index (Table 1) shows that radiation increased the rate of cell division in the bone marrow cells of Wistar rats, possibly as a positive response to damage and as a way to quickly replace these cells.

According to Barrington et al. (2008), people may be exposed to radiation through contact with a patient who had received radioactive iodine to treat thyroid disorders. This exposure may occur because the patient will act as a source of gamma radiation and excrete the radioiodine through urine, feces, sweat and saliva. The peak of excretion in urine and saliva is between 24 and 48 h after administration, whereas in a normal organism with no pathology in the thyroid gland, 40–70% of ingested radiation is eliminated within 24 h (Reiners and Labmann 1999). These data were confirmed by measuring the woodwool bedding, which showed that 64–90% of the radiation was eliminated through sweat, feces and urine after 24 h. As evidenced in the data presented in Fig. 2, this process may be correlated with a higher consumption of water for the animals in groups treated with $^{131}$I.

Takahashi et al. (2000) found a significant increase in the retention of $^{131}$I in the thyroid and blood and a significant decrease in the urinary excretion in mice due to restriction of food and water for 4 or 24 h after administration of radiation. Despite the restriction of food and water for 2 h before and 2 h after administration of $^{131}$I,

this does not seem to have occurred in the present experiment because with all concentrations of $^{131}$I tested (5, 25, 50 and 250 μCi), animals had a high elimination rate of radiation through sweat, urine and feces, as measured in the wood-wool bedding.

Due to the high frequency of chromosomal aberrations induced in rats, $^{131}$I in humans should be used cautiously, preferably at low levels.

**Acknowledgments** The authors would like to thank the Coordination for the Improvement of Higher Level Personnel—CAPES and the Laboratory of Cytogenetics and Mutagenesis staff of the State University of Maringá—UEM.

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