Evaluation of contrast media submitted to ionizing radiation*

Avaliação de meios de contraste submetidos à radiação ionizante

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Abstract **OBJECTIVE: The purpose of the present study was to investigate the influence of ionizing radiation from x-rays and gamma rays on the molecular structure stability of several radiologic contrast media employed in diagnostic imaging by means of ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy. MATERIALS AND METHODS: Eight different types of iodinated contrast media (three ionic and five non-ionic) were exposed to x-rays and gamma rays irradiation. Subsequently, the ^{1}H and $^{13}C\{^{1}H\}$ nuclear magnetic resonance spectra of these contrast media were collected. RESULTS: The ^{1}H and $^{13}C\{^{1}H\}$ nuclear magnetic resonance spectra of both ionic and non-ionic contrast media irradiated by x-rays or gamma rays demonstrated the absence of any alteration of the contrast media chemical composition. CONCLUSION: There is no problem in keeping contrast media inside examination rooms or close to radiological equipment. It is important to mention that, during the tests, the samples were directly irradiated, while in a radiology examination room, the irradiation is not direct and, therefore, radiation levels in these cases are much lower than those employed in the present study.**

Keywords: Imaging diagnosis; Contrast media; Ionizing radiation; Nuclear magnetic resonance spectroscopy; X-rays; Gamma rays.

Resumo **OBJETIVO: O presente estudo consistiu em investigar a influência da radiação ionizante por raios X e raios gama sobre a estabilidade molecular de diversos meios de contraste radiológicos utilizados em exames de diagnóstico por imagem, por meio da espectroscopia de ressonância magnética nuclear de ^{1}H e ^{13}C. MATERIAIS E MÉTODOS: Oito diferentes meios de contraste iodados (três iônicos e cinco não iônicos) foram expostos à radiação por raios X e raios gama. Em seguida, espectros de ressonância magnética nuclear de ^{1}H e $^{13}C\{^{1}H\}$ foram coletados. RESULTADOS: Os espectros de ressonância magnética nuclear de $^{13}C\{^{1}H\}$ de ambos os meios de contraste iônicos e não iônicos irradiados por raios X ou raios gama mostraram que não houve alterações na composição química desses contrastes. CONCLUSÃO: Não há problemas em armazenar as amostras nas salas, ou próximo aos equipamentos em que são realizados os exames. Enfatiza-se que a radiação recebida pelas amostras durante os ensaios foi direta, enquanto em uma sala de exames de radiodiagnóstico a radiação é indireta e, portanto, os níveis de radiações nestes casos são bastante inferiores àqueles empregados neste estudo.**

Unitermos: Diagnóstico por imagem; Meios de contraste; Radiação ionizante; Espectroscopia de ressonância magnética nuclear; Raios X; Raios gama.

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INTRODUCTION

Radiologic contrast media are compounds which are introduced into the organism by different vias, in order to increase in the definition of radiographic images due to the contrast improvement caused by such compounds, allowing acquisition of high-definition images and as consequence higher accuracy in diagnostic imaging[1,2]. The use of compounds to improve the quality of radiologic images dates more than half a century[3]. Since then, adverse reactions resulting from the oral or intravenous administration of a foreign substance to the human body have been reported as such compounds are not always harmless, and may alter the blood circulation causing unexpected reactions[4,5]. Taking this fact into account, several precautions must be taken with patients as well as in the preparation and storage of contrast media[6,7].

All iodinated contrast media currently in use are derived from 2,4,6-triiodobenzoic acid (Figure 1). They are classified ac-

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cording to their physicochemical characteristics, including chemical structure, osmolarity, viscosity, number of iodine atoms in the structure, biological properties, ionization capacity in solution, hydrosolubility, lipophilicity and toxicity [6]. Ionic contrast media are those capable of dissociating into cations and anions in aqueous solutions, while the non-ionic ones do not dissociate (Figure 1), but interact with water molecules by means of intermolecular interactions[5]. Special care in the storage and asepsis of contrast media is essential, including storage away from light, as they are photosensitive, and away from the incidence of x-rays due to the possibility of ionizing radiations causing molecular degradation, thus changing the molecular structure of the contrast media and, as a consequence, its contrast properties on the radiological images. Additionally, it is important to store them under temperatures between 15 and 25°C, as in lower temperatures could occurs the crystallization of the contrast media, checking storage time and not using vials after they have been opened for more than 24 hours, due to the risk of contamination by microorganisms[8].

The present study investigates the influence of from x-rays and gamma rays ionizing radiations on the molecular structure stability of several commercial contrast media widely employed in radiologic imaging diagnosis by radiography and computed tomography by means of ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. The aim of the work consisted in checking possible changes on the molecular structure of the contrast media due to the incidence of ionizing radiations, once they would alters the physicochemical and biological properties, as well as their toxicity, in order to corroborate with the reported data in the literature[8].

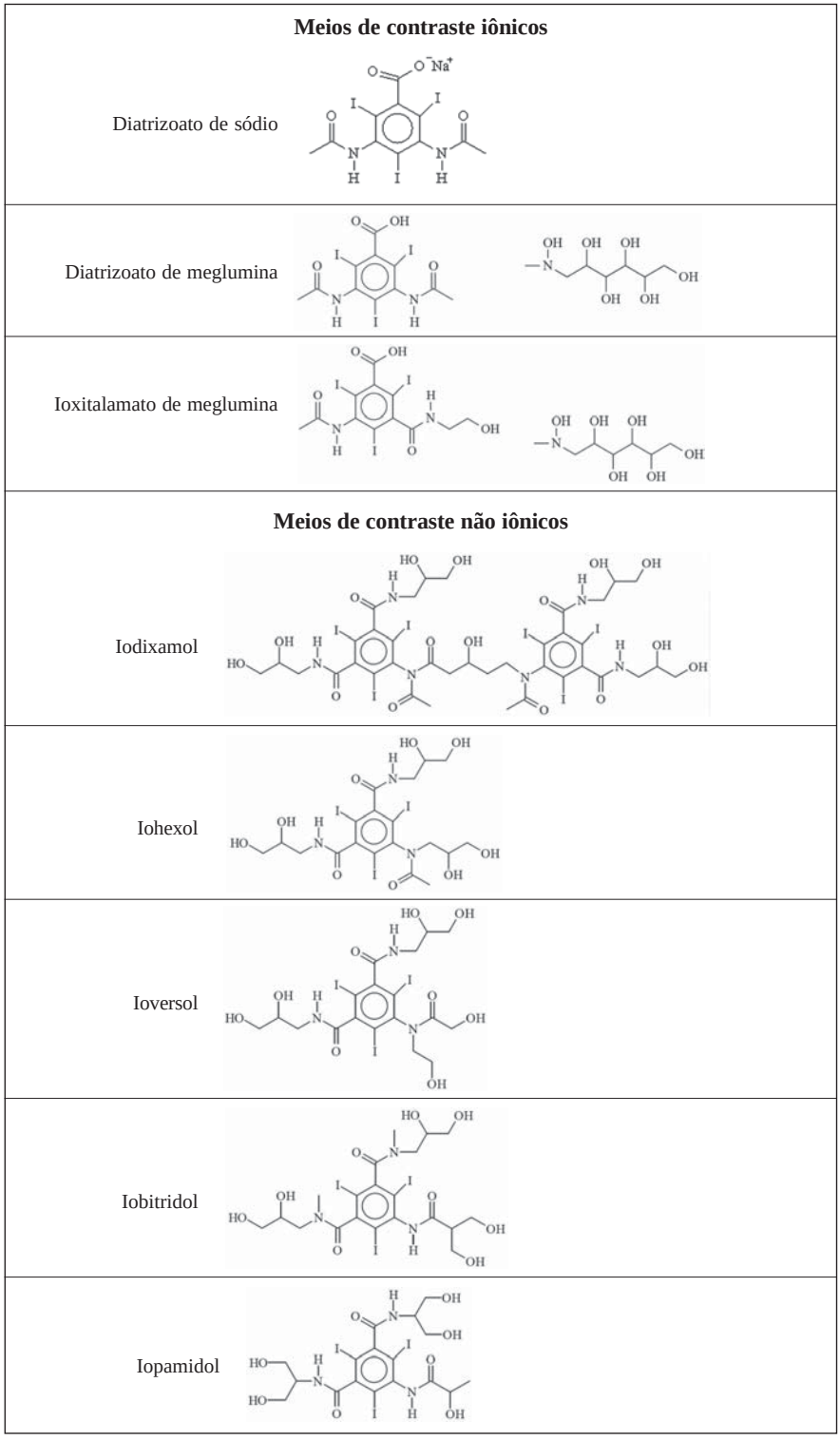

Figure 1. Molecular structures of the evaluated iodinated contrast media.

MATERIALS AND METHODS

Samples

Eight different iodinated contrast media, three ionic and five non-ionic (Figure 1) were obtained from four manufacturers available in Brazil. The contrast media, with respective manufacturers were as follow: Iopamiron 300 and Pielograf 76% (Bayer Schering Pharma; Berlin, Germany), Ominipaque and Visipaque (Farmasa; São Paulo, Brazil), Henetix and Telebrix (Guerbet; Paris, France), Optiray 320 and Optiray 350 (Mallinckrodt; Saint Louis, USA). Eight aliquots were taken of each contrast medium, of which four were submitted to x-rays radiation exposition, two to gammas ray radiation exposition and two were kept as control, without any radiation exposure. In order to irradiate the contrast media,

aliquots of 1.7 mL of each medium were transferred in to microcentrifuge tubes, identified by letters in order to make impossible to the instrument operator to known the samples origin. The sample preparation was performed in the Chemistry Laboratory of the Universidade Tecnológica Federal do Paraná (UTFPR), according to asepsis procedure for each open and aspirated vial[9].

X-rays irradiation

The samples irradiation by x-rays was performed in the Radiotherapy Department of Hospital Erasto Gaertner in the city of Curitiba, PR, Brazil, on a Radcal 9010 radiation monitor and a 10X5-6 Radcal ionization chamber (Radcal Corp.; Monrovia USA), with a sensitive volume of 6 cm^3 calibrated to the radiodiagnosis energy level, thus determining the exact radiation that the samples were being exposed. The source of radiation utilized was an x-ray tube from a RMX 625 R radiotherapy simulator (Raytheon Medical Systems; Melrose Park, USA), with inherent filtration equivalent to 0.5 mm of aluminum. The samples were exposed to different doses of x-rays radiation, ranging from 9.85 to 10200 mR (Table 1), at a distance of 50 cm from the source, and voltage of 90 kV[10].

Gamma rays irradiation

The irradiation of the samples by gamma rays was performed using a mean energy of 1.25 MeV, from a cobalt-60 source installed in a Theratron 780 C teletherapy unit (MDS Nordion; Ontario, Canada) with a 0.5 cm bolus of gel over the samples. The source-surface distance was 50 cm and the performance at such distance was 5 Gy/min. The samples were exposed to two radiation doses: 0.1 and 10 Gy [10]. In both the cases the samples were irradiated in an 8 × 8 cm^2 field.

NMR Analysis

The ^1H and $^{13}C\{^1H\}$ NMR spectra were acquired on an Avance 400 (Bruker; Karlsruhe, Germany) NMR spectrometer operating at 9.4 Tesla, installed in the NMR Laboratory of Universidade Federal do Paraná (UFPR), observing the ^1H and ^{13}C nuclei at 400.13 and 100.62 MHz, respectively, in D_2O (deuterated water) at room temperature of approximately 295 K in a 5 mm direct detection multinuclear probe. For this, aliquots of 0.2 ml of each contrast medium were filtered in cotton directly into 5 mm NMR tubes, with the help of Pasteur pipettes, follow by 0.4 ml of D_2O containing (3-trimethylsilyl)-2,2',3,3'-tetradeuteropropionic acid, sodium salt (TMSP-d_4 – internal reference)[11]. The ^1H NMR spectra were acquired with the *zg* pulse sequence by accumulating four averages, 64 K points (1 K = 1024) and spectral window of ~13 ppm [11,12]. In some samples it was necessary the pre-saturation of the water signal, using the *zgpr* pulse sequence. On their turn, the $^{13}C\{^1H\}$ NMR spectra were acquired with the *zgpg30* pulse sequence, accumulating 1024 averages, 32 K points and spectral window of ~255 ppm. Both the ^1H and $^{13}C\{^1H\}$ NMR spectra were processed with aid of TopSpin software (Bruker; Karlsruhe, Germany) by applying exponential multiplications of the free induction decay (FID) by factors of 0.3 and 3.0 Hz for the construction of ^1H and ^{13}C NMR spectra with 64 K and 32 K points, respectively. All NMR chemical shifts are giving in ppm related to the internal standard signal from TMSP-d_4 at 0.0 ppm[11].

Table 1 X-rays radiation doses to which the samples were exposed.

mAs	Current at filament (mA)	Focus	Radiation doses (mR)
1.70	50	Fine	9.85
10	200	Gross	95.4
100	200	Gross	945
1200	200	Gross	10200

RESULTS

In order to evaluating the effected of the application of ionizing radiations on contrast media utilized in radiology, $^{13}C\{^1H\}$ and ^1H NMR spectra were acquired from the samples after being exposed to ionizing radiations from by x-rays or gamma rays. In a similar way, NMR spectra were obtained from samples of the same contrast media without exposition to ionizing radiations, used as references for comparison with those irradiated.

Figure 2 and 3 show the $^{13}C\{^1H\}$ and ^1H NMR spectra comparison, respectively of a ionic contrast medium sample that was exposed to different x-rays radiation doses, while Figures 4 and 5 show the $^{13}C\{^1H\}$ and ^1H NMR spectra comparison, respectively of ionic contrast medium sample that was submitted to different gamma ray radiation doses.

Figures 6 and 7 present the $^{13}C\{^1H\}$ and ^1H NMR spectra comparison, respectively, of a non-ionic contrast medium sample submitted to different x-rays radiation doses, while Figure 8 shows the ^1H NMR spectra comparison of non-ionic contrast medium sample submitted to different gamma ray radiation doses.

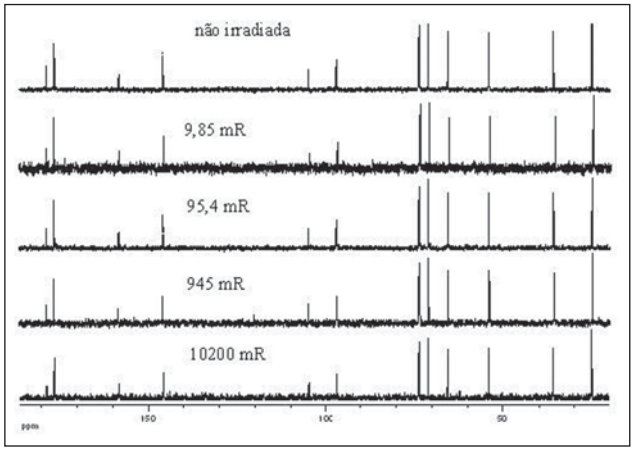

Figure 2. $^{13}C\{^1H\}$ NMR spectra comparison (expansion of the region from 20 to 186 ppm) of an ionic contrast medium exposed to different x-rays radiation doses.

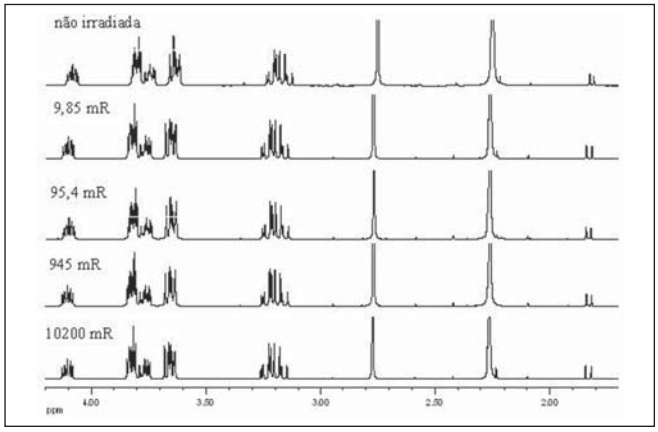

Figure 3. ^{1}H NMR spectra comparison (expansion of the region from 1.5 to 4.2 ppm) of an ionic contrast medium exposed to different x-rays radiation doses.

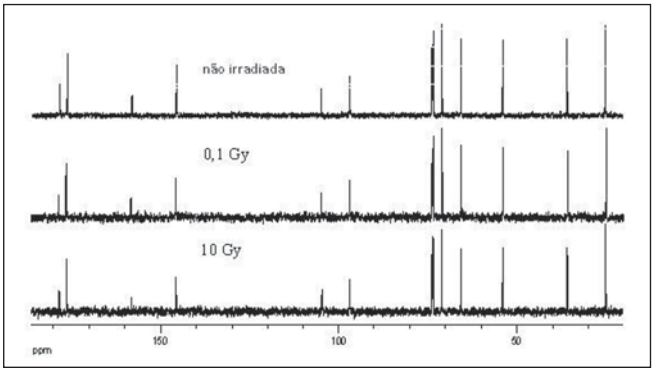

Figure 4. ^{13}C{^{1}H} NMR spectra comparison (expansion of the region from 20 to 186 ppm) of an ionic contrast medium exposed to different gamma rays radiation doses.

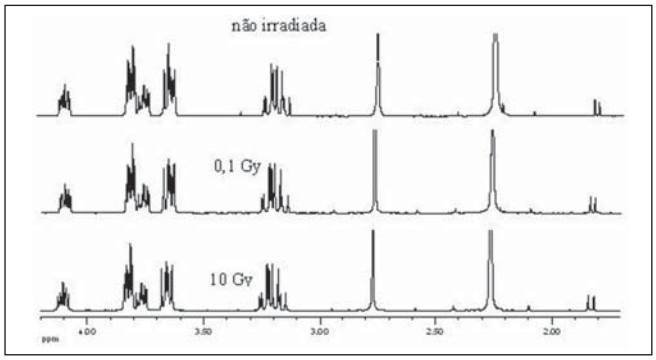

Figure 5. ^{1}H NMR spectra comparison (expansion of the region from 1.7 to 4.2 ppm) of an ionic contrast medium exposed to different gamma rays radiation doses.

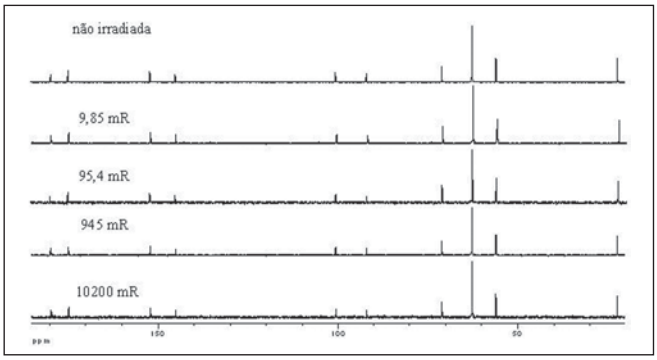

Figure 6. ^{13}C{^{1}H} NMR spectra comparison (expansion of the region from 20 to 185 ppm) of a non-ionic contrast medium exposed to different x-rays radiation doses.

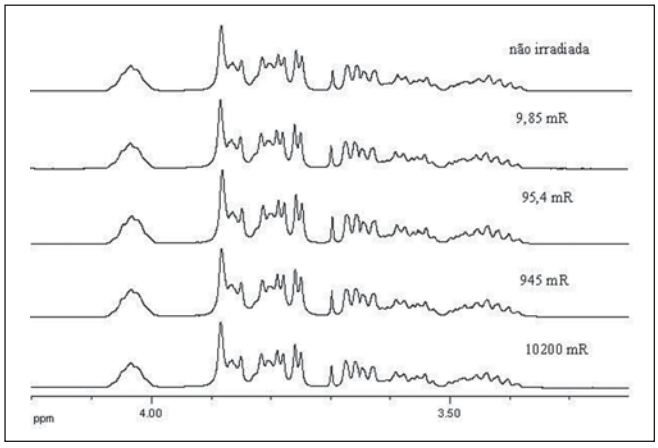

Figure 7. ^{1}H NMR spectra comparison (expansion of the region from 3.2 to 4.2 ppm) of a non-ionic contrast medium exposed to different x-rays radiation doses.

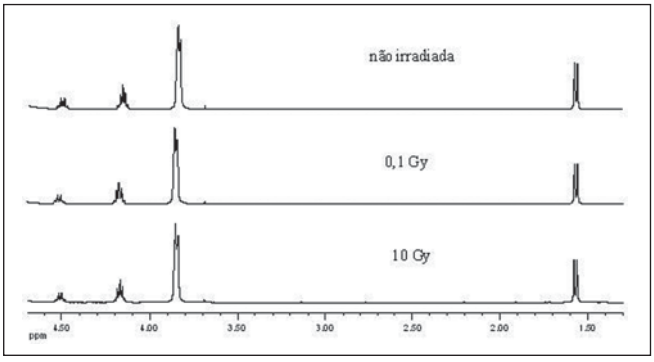

Figure 8. ^{1}H NMR spectra comparison (expansion of the region from 1.3 to 4.7 ppm) of a non-ionic contrast medium exposed to different gamma rays radiation doses.

DISCUSSION

The ^{13}C{^{1}H} NMR spectra in both ionic and non-ionic contrast media irradiated by x-rays or gamma rays showed that at the energy levels utilized any changes in the molecular structures of the investigated contrast media occurs, as observed on Figures 2, 4 and 6 for a determined contrast medium. In the same way, the ^{1}H NMR spectra, which has higher sensitivity than those from ^{13}C{^{1}H}[11], also showed no changes on the chemical structure of the investigated contrast media, as shown on Figures 3, 5, 7 and 8. In other words, there

was no degradation of the analyzed contrast media, as there were no evidences of new signals in the NMR spectra, which would be an indicative of formation of new compounds, as a consequence of decomposition of the contrast media. This becomes evident when the NMR spectra of the control samples which were not submitted to any radiation were compared with those from samples submitted to irradiation, either by x-rays or gamma rays. In other words, as all samples presented the same spectral profile at the ^{1}H and $^{13}C\{^{1}H\}$ NMR analysis (Figures 2 to 8). Therefore, the molecular structure of the investigated contrast media is not affected when exposed to irradiation with x-rays or gamma rays, and then there is no problem in storing them in the equipment room or close to the equipment in which the examinations are performed. Emphasis is given to the fact that the radiation received by the samples during the trials was direct, while in an actual study the radiation would be indirect and, therefore, the levels of radiation in such cases would be different from those utilized in the present study.

In spite of the fact that some contrast media manufacturers recommend avoiding their storage in the presence of disperse ionizing radiations, the present study did not detect any influence of ionizing radiations from x-rays or gamma rays on the molecular structure of the evaluated iodinated contrast media in the described conditions. Probably, this observation from manufacturers refers as a general precaution in the sense of preserving and manipulating only the necessary quantities of contrast media for the day's examination needs, while greater quantities might, in some cases, be stored in the examination room being unnecessarily exposed and becoming a constant practice in diagnostic imaging centers.

CONCLUSION

The investigations demonstrated that the ionizing radiation utilized in radiology diagnostic imaging by radiography and computed tomography do not cause any changes in the molecular structures (degradation) of the currently utilized contrast media, independently of exposure levels from x-rays or gamma rays radiation in which the contrast media were submitted, and thus allowing the clinical use of such contrast media.

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