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Changes in Chemical Structure of Iopamidol Contrast Agents According to Radiation and Environmental Conditions

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Abstract

Background: To prevent contrast agent's side effects, it is important to provide accurate information about the contrast agent and fulfill the duty of explaining the medication, experience of side effects, and medical history. However, the incidence of safety accidents associated with contrast agents is continuously increasing. Therefore, the objective of this study was to prepare an improvement plan for problems derived by analyzing changes in chemical structure of contrast medium according to radiation and external environment.

Method: The chemical structure of the standard sample was analyzed using Nuclear Magnetic Resonance Spectroscopy (NMR) in P contrast agent of Iopamidol preparations used in Korean medical institutions. Samples were obtained by irradiation under 3Gy and 5Gy conditions according to the Photon 10MV, Electron 20MeV condition and the radiation dose according to the radiation and environmental conditions. Contrast agent samples after opening and sealed but expired samples were also obtained. These samples were analyzed and chemical shift values in the ^{1}H-NMR spectrum using NMR analysis were compared.

Findings: ^{1}H-NMR analysis results of P contrast medium irradiated with Photon 10MV and 5Gy and sealed but expired P contrast medium samples showed no change in chemical shift. However, there were changes in chemical shift value in P standard sample, showing triple peaks in 1.1-1.2ppm range. In addition, the sample irradiated by Electron 20MeV and 3Gy showed double peaks. The sample irradiated by Electron 20MeV and 3Gy condition showed a single peak in the 3.0-3.5ppm region, demonstrating a change in chemical shift value. In the 1.0-1.4ppm region, P contrast medium standard samples showed triple peaks and opened contrast medium samples showed double peaks in the middle peak among the triplet, demonstrating changes in chemical shift value.

Improvements: Changes in chemical structure of contrast agent were observed in contrast medium after electron irradiation and in contrast medium after opening. In this regard, guidelines for the administration of contrast medium should be prepared as soon as possible so that consumers could have accurate information and their right of choice.

Keywords: *Contrast Agent, Iopamidol, Chemical Structure, Radiation, NMR, Chemical Shift*

Introduction

X-ray was discovered by a German physicist, Professor Roentgen, in 1895. It has revolutionized medical imaging. Internal structures of the human body can be revealed depending on relative densities of adjacent tissues. By energy absorbing or transmitting X-rays, medical image could be convert into a black and white ratio. However, for some biological tissues, it is difficult to use X-ray absorption to distinguish between absorption and the neighboring tissue. In the case of barium sulfate and vascular and biliary. To overcome this problem, in the early days, clinical application of iodinated benzoate was started by filling the tube or body cavity with a substance of sufficient density for X-ray absorption[1-2].

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The iodinated material not only provides contours of the invisible tissue in traditional X-rays, but also provides physiological data as it penetrates into the tissue where disease is expected and exits through blood vessels. In addition, various iodide microparticles have been developed to show the outline of the reticular endothelial tissue in a very limited range. Such substances were developed in the early 19th century to nicely complement the existing X-ray technology[3-4].

Contrast agent technology has advanced dramatically since then. The development of non-ionic contrast agents has removed charges, reduced osmotic pressure, and reduced overall toxicity tremendously[5].

With these remarkable advances in CT, MRI, and ultrasound, the clinical application of contrast agents has completely changed the existing concept, enabling the clarification of difference in density of adjacent tissues that could not be distinguished by X-rays in the past. Most importantly, new possibilities for tissue growth have been developed. By changing the magnetic moment or reaction state of the tissue, it plays an important role in magnetic resonance and ultrasound imaging. Expression of target tissues by this concept and selective enhancement have provided the basis for more exciting developments in the evolution of contrast agents[6].

However, the occurrence of safety accidents ranging from mild side effects such as rash after injection of contrast agent to death in serious cases due to increase in contrast agent use continues to increase. Recently, harm cases of contrast agents received by the Consumer Injury Surveillance System (CISS) have been steadily received and side effects related to contrast agents have increased more than eight times over five years from 1,688 cases in 2009 to 14,572 cases in 2014. In order to prevent contrast agent's side effects, it is important to provide accurate information about the contrast agent drug and fulfill the duty of explaining the medication, experience of side effects, and medical history[7-8].

Thus, the objective of this study was to grasp safety status of contrast agents used by hospitals and prepare improvement measures for problems derived by analyzing chemical structure changes according to the change of external environment. Results of this study will help us secure consumer safety.

Method

The most useful method for determining the structure of matter is the study of spectroscopy. Among many spectroscopy methods known to date, the best is the NMR spectroscopy method which can analyze even a small amount of sample. This method has recently been extended to all fields dealing with materials, not only in the structure of chemicals, but also in fields of metabonomics for quantitative analysis, drug development, and drug design. P contrast agents of Iopamidol formulations were also analyzed using NMR to identify chemical structural changes.

1. Research Materials

The water-soluble iodine contrast agent has a basic structure of tri-iodinated benzene, in which three iodine atoms are bonded to positions 2, 4, and 6 of the benzene ring[9-10].

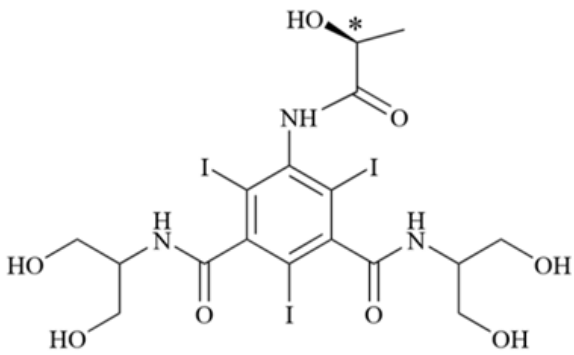
Since tri-iodinated benzene itself is not soluble in water, water-soluble iodine contrast agent is made by combining substituents with side chains (R1, R2, R3) corresponding to positions other than iodine bonds to provide water solubility[11-12]. Therefore, the difference between various iodine contrast agent is the difference in the structure of the substitution material. By changing this structure, the water-soluble iodine contrast agent is improved[13].

Non-ionic monomers that are widely used at present have many (5-6EA) -OH bonds on three side chains, including a carboxyl group. Hydroxyl groups have a very high affinity for water, making the entire compound water-soluble. Since non-ionic monomers are not ions, dissociation does not occur in aqueous solution or blood. They exist in one molecule. Therefore, low osmotic pressure can greatly reduce the risk of side effects. In addition, the number of iodine in non-ionic monomeric contrast medium determines the contrast of radiographic images[14-16].

Non-ionic monomer contrast agents currently used by hospitals mainly have six types: Iopamidol, Iopromide, Iohexol, Iobitridol, Ioversol, Iomeprol[Table 1]. Among which, P contrast agent of Iopamidol formulation accounts for more than 60% of the Korean medical market. P contrast agent features Iopamidol formulation with the lowest viscosity among the first contrast agents developed in Korea. It has a molecular formula of $C_{17}H_{22}I_3N_3O_8$[Figure 1]. As an additive, a mixture of tromethamine, sodium calcium edetate, hydrochloric acid, and water for injection shows effect for peripheral vein and cerebral artery angiography[17].

Table 1. Types of Non-ionic Monomer Contrast Agent

Formulation	Product Name
Iopamidol	Iopmiro, Pamiray
Iopromide	Ultravist
Iohexol	Omnipaque, Omnipure, Iobrix, iMAX, Hexosure, Ashexol, Bonorex, Everay
Iobitridol	Xenetix
Ioversol	Optiray, Tomoray
Iomeprol	Imeron



IOPAMIDOL

Figure 1. Chemical Structure of P Contrast Agent (Iopamidol)

2. Experiment Equipment

NMR spectra enable structural analysis of compounds based on locations of resonance peaks. For most organic compounds, analysis with ^{1}H and ^{13}C is commonly used. The principle of NMR can usually be described in three steps: 1) alignment of magnetic nuclear rotation in the applied constant magnetic field; 2) perturbation caused by the oscillating magnetic field in which the alignment of the nuclear spindle is weak, which is generally called high frequency pulse; and 3) the NMR signal is detected after RF or pulse with the voltage that is induced in the detection coil by preceding surrounding nuclear spin.

The distribution of electrons in the molecule changes the resonance frequency. Thus, even the same kind of nucleus might have different NMR resonance frequencies. In NMR, instead of directly indicating the resonance frequency, the difference from the resonance frequency of the reference material is converted into a chemical shift and displayed. In addition, spectral peaks can be cracked through spin-spin coupling with other nuclei with the same molecular spin.

In ^{1}H-NMR, the resonance signal is recorded by how much it is shifted from resonance signals of 12 equivalent hydrogens among TMS (Tetra Methyl Silane). In ^{13}C-NMR spectrum, the resonance signal is recorded by how far it is from resonance signals of four equivalent carbons among TMS. The position of the resonance peak is called a chemical shift expressed as δ in ppm (part per million) (Equation 1).

------- (Equation 1)

The chemical shift value of ^{1}H appears over the range of 0-10ppm. ^{13}C chemical shift value is distributed over the range of 0-220ppm, wider than ^{1}H [18].

3. Research Methods

This study aims to understand changes in safety and environment of the contrast medium for P contrast agent which has the highest share among the 6 non-ionic monomer contrast agents used in Korean hospitals by analyzing its chemical composition using NMR in accordance with changes of radiation dose, radiation energy, and time.

First, NMR was used to accurately identify the chemical structure of the standard sample of P contrast medium. Next, the P contrast agent stimulated by a change in radiation energy, dose, or time under the following conditions was collected:

(1) Radiation energy: Photon 10MV, Electron 20MeV;

(2) Radiation dose: 3Gy, 5Gy;

(3) Changes in time were analyzed for sealed and expired P contrast media;

(4) External exposure: analysis after opening.

The structure of the material was derived from data of chemical structure analysis using NMR. Elements of material structure were estimated and analyzed by using chemical shift values.

Result

1. ^{1}H-NMR analysis of standard samples of P contrast agent

Analysis of the standard sample of P contrast agent was well shown in the ^{1}H-NMR spectrum. Broad peaks appeared in the 8.968ppm region of the ^{1}H-NMR spectrum. Double lines appeared around 4.5ppm. Single lines appear in 4.159ppm and 3.849ppm regions. The triplet that appeared around 3.6ppm was tromethamine. The doublet that appeared around 1.5ppm and the triplet that appeared around 1.2ppm were impurities. The highest peak in the 4.8ppm region was predicted to be water[Figure 2].

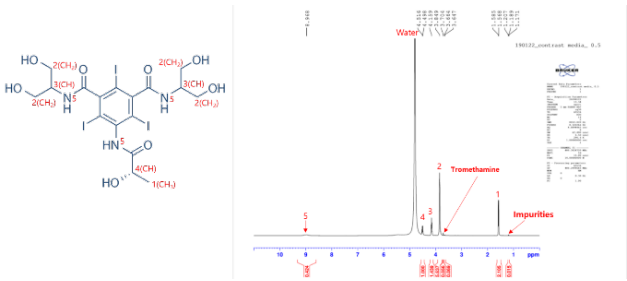


Figure 2. ^{1}H-NMR analysis of standard samples of P contrast agent

2. ^{1}H-NMR comparison analysis of specimens irradiated with standard P contrast agent and photon 10MV at 5Gy

According to ^{1}H-NMR analysis, the standard sample of P contrast medium and the P contrast medium irradiated by photon 10MV and 5Gy showed no change in chemical shift.

3. ^{1}H-NMR comparison analysis of specimens irradiated with standard P contrast agent and electron beam 20MeV at 3Gy

Analysis of ^{1}H-NMR analysis for the reference sample of P contrast medium and P contrast medium irradiated by electron 20MeV at 5Gy showed that the P reference sample had peaks in triplet at 1.1-1.2ppm region, but had double line peaks in the condition of electron beam energy 20MeV and dose 3Gy, demonstrating a change in chemical shift value[Figure 3]. In the 3.0-3.5ppm region, the P standard sample did not show a peak. However, it showed a single line peak in the condition of electron beam energy of 20MeV at 3Gy, providing evidence that the chemical shift value was changed[Figure 4].

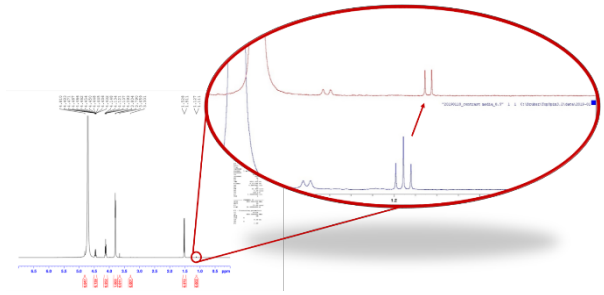


Figure 3. ^{1}H-NMR comparison analysis of specimens irradiated with standard P contrast agent and electron beam 20MeV at 3Gy (1.1-1.2ppm area)

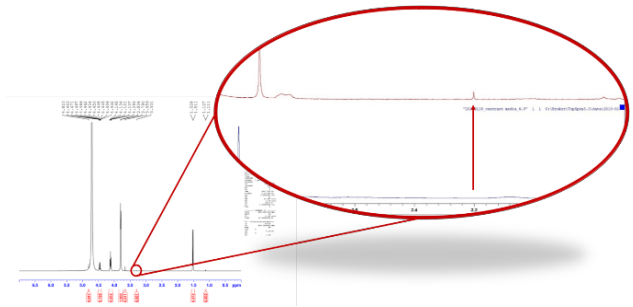


Figure 4. ^{1}H-NMR comparison analysis of specimens irradiated with standard P contrast agent and electron beam 20MeV at 3Gy (3.0-3.5ppm Area)

4. ^{1}H-NMR comparison analysis of standard P contrast agent and after fixed period of time sealed P contrast agent

^{1}H-NMR analysis of the standard sample of P contrast agent and the sealed but expired P contrast agent showed no change in chemical shift value.

5. ^{1}H-NMR comparison analysis of P contrast agent standard samples and after opening

According to ^{1}H-NMR analysis of P standard sample and opened P contrast medium sample, the P standard sample clearly showed triple peaks in the 1.0-1.4ppm region. The opened contrast medium sample showed double peaks in the middle among the triplet, demonstrating changes in chemical shift value[Figure 5].

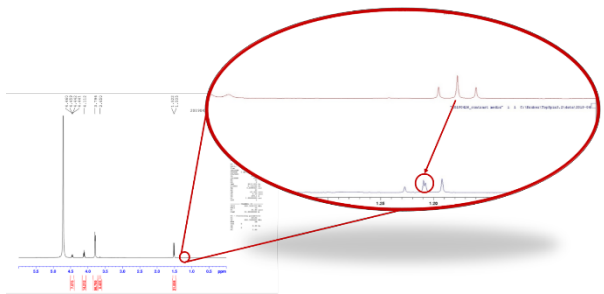


Figure 5. ^{1}H-NMR comparison analysis of P contrast agent standard samples and after opening

Conclusion

In this study, chemical structure change was analyzed by NMR for P contrast agent of Iopamidol preparation among non-ionic monomer contrast agents according to changes in radiation dose, radiation energy, and time. As a result, ^{1}H-NMR analysis of P contrast medium irradiated with photon 10MV at 5Gy and sealed but expired P contrast medium showed no change in chemical shift. However, there was a change in chemical shift value in contrast agent after irradiated electron beam and in opened contrast agent sample. In this regard, government guidelines for the administration of contrast medium should be prepared as soon as possible. Accurate information on the contrast agent should be provided to consumers for their right of choice.

Ethical Clearance: Not required

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Conflict of Interest: Nil

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