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Physicochemical Analysis According to Radiation Dose of Iodinated Contrast Agent

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Abstract

The purpose of this study was to determine whether a high energy radiation dose used for radiation therapy might be one of environmental factors affecting physical and chemical changes of a contrast agent by identifying components of the contrast agent and analyzing its chemical structure.

Chemical structures of standard samples were analyzed using NMR Spectroscopy for Iopamidol preparation P contrast agent and Ioversol preparation O contrast agent. As one of environmental factors, radiation dose was 200 cGy (6 MV, 10 MV) and 300 cGy (6 MV, 10 MV) in the photon beam of an LINAC device. In an electron beam, 200 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV, 20 MeV) and 300 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV, 20 MeV) were irradiated. 1H-NMR spectra were obtained for stimulated sample through NMR analysis. Chemical shift value was compared with a standard.

With changes of radiation dose, physicochemical change was not observed for the Ioversol preparation O contrast agent. In the electron beam of the Iopamidol preparation P contrast agent, a singlet peak was clearly seen in all contrast agents irradiated at a dose of 300 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV) in the 2.5 ppm region. A quartet peak in the 3.6 ppm region was also clearly seen for the contrast agent irradiated at a dose of 300 cGy (20 MeV). There was no physical or chemical change depending on the radiation dose of the photon beam.

In ^{1}H-NMR analysis, the Iopamidol preparation P contrast agent showed a physicochemical change in the electron beam, but not in the photon beam. Thus, it can be concluded that Ioversol preparation O contrast agent has better physicochemical safety in than Iopamidol preparation P contrast agent.

Keywords: Non-ionic monomer Contrast Agent, Iopamidol, Ioversol, Radiation Dose, Electron, NMR Spectroscopy

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Introduction

In the medical field in the late 20th century, clinical applications of contrast agents have increased due to remarkable developments in the field of Computed Tomography (CT), Magnetic Resonance Image (MRI), angiography, interventional procedures, and ultrasound. Contrast agents have evolved into important medical products in the diagnosis of diseases (Dawson P., *et al.*, 1999).

In general, there are two types of contrast agents: negative contrast agents and positive contrast agents. Negative contrast agents appear blacker than surrounding organs by using air, oxygen, and so on. They are materials with good permeability. Positive contrast agents appear whiter than surrounding organs by using barium and iodine that are chemical components with high X-ray absorption rates. Positive contrast agents are further classified into water-soluble contrast agents and lipid-soluble contrast agents based on their water solubilities. Water-soluble contrast agents are classified into ionic and nonionic contrast agents.

Ionic contrast agents were mainly used in the past. They can cause hypersensitivity reactions. In addition, they cause high osmotic pressure that can lead to endothelial damage, disturbance of Blood-Brain Barrier (BBB), thrombosis, thrombophlebitis, and heart disorders. Thus, nonionic contrast agents are widely used nowadays because they exhibit high contrast effects with reduction of various side effects and pain known to be caused by ionic contrast agents with high osmotic pressure because nonionic contrast agents have low osmotic pressure. Nonionic contrast agents used in medical institutions include Iopamidol, Iopromide, Iohexol, Iobitridol, Ioversol, and Iomeprol. Most of them rely on imports (Lim K.Y., *et al.*, 2003), of which Iopamidol and Ioversol rank the 1st and 2nd in market share among major contrast agent items based on a 2016 report by the Korea Health Insurance Review and Assessment Service. As such, the use of a contrast agent is increasing in frequency due to its high accuracy for diagnosis purposes (HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE. 2016).

Contrast agents for blood vessels may cause adverse drug reactions. Thus, the risk of using them should be recognized. Drug side effects caused by contrast agents can be fatal depending on the situation (Kim Y.S., *et al.*, 2004; William H.B., *et al.*, 1991). According to an analysis on drug safety by the Korea Pharmaceutical Safety Management Agency in 2011, the mortality rate caused by contrast agents was about 1 in 100,000, which was very low. However, contrast agent-related mortality rate varies from about 1/75,000 to about 1/1,200,000 depending on the type of contrast agent, reporter, and reporting period (Korea Institute of Drug Safety & Risk Management. 2011-19).

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Side effects caused by contrast agents can generally be classified into hypersensitivity reactions, chemical toxicity and specific constitution reactions, and physical and chemical structures. Evaluating the physical and chemical structure of a contrast agent is very important. There is a need to understand chemical structures and compositions of a contrast agent. Therefore, the objective of this study was to analyze physical and chemical changes according to radiation dose as one of environmental factors using an NMR Spectrometer for contrast agents used in medical institutions. Results of this study could contribute to consumer safety by preparing improvement measures for problems encountered when using contrast agents.

Materials and Methods

Literature about physicochemical analysis of iodine preparation contrast agent according to radiation dose as one of environmental factors was reviewed and various radiation doses were selected. According to radiation dose, samples were obtained and subjected to analysis using the NMR Spectrometer. Changes in chemical shift value were compared to those of standard samples.

Research Materials

Iopamidol preparation P contrast agent and Ioversol preparation O contrast agent are nonionic water-soluble contrast agents most frequently used as vascular contrast agents in medical institutions. Thus, they were selected for analysis in the present study. P contrast agent is Korea's first high-purity X-ray contrast agent synthesized and commercialized. Iopamidol preparation contrast agent is the most widely used one in Korea, with a market share of more than 17% (Dailymedi. 2017). The molecular formula of Iopamidol preparation is $C_{17}H_{22}I_3N_3O_8$ in Fig. 1. The main ingredient of Iopamidol preparation contrast agent is Iopamidol 510 mg per 1 ml, which accounts for 51% of its total ingredients. Regarding additives, Tromethamine as a buffering agent and Disodium EDTA as a neutralizing agent are added in a small amount. Other additives include hydrochloric acid and sodium hydroxide acting as pH regulators and 49% water for injection (DONGKOOK LIFE SCIENCE. 2019).

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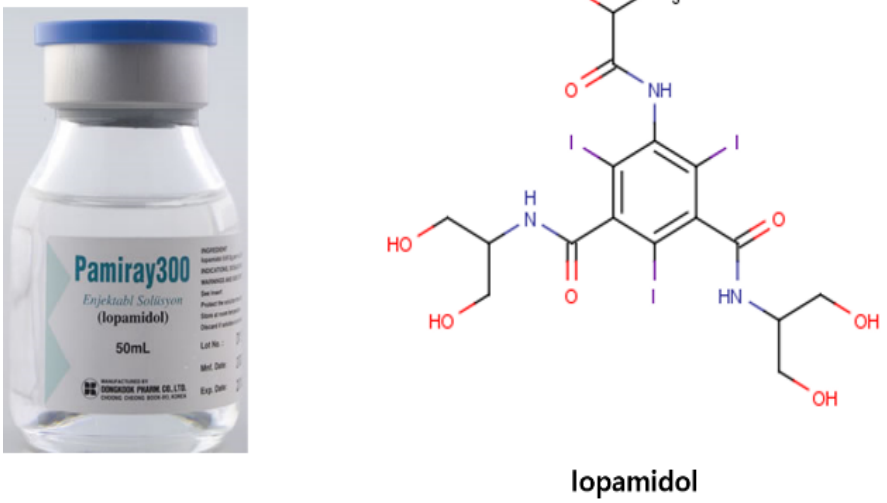

Figure 1: Chemical structure of iopamidol

The Ioversol preparation O contrast agent has a molecular formula of $C_{18}H^{24}I_3N_3O_9$ in Fig. 2. Its main component is Ioversol 678 mg per 1 ㎖, which accounts for 68% of its total components. Regarding additives, Tromethamine as a buffering agent and Disodium EDTA as a neutralizer are added in a small amount. Other additives include hydrochloric acid and sodium hydroxide acting as pH regulators and 32% water for injection (Ministry of Food and Drug Safety. 2017).

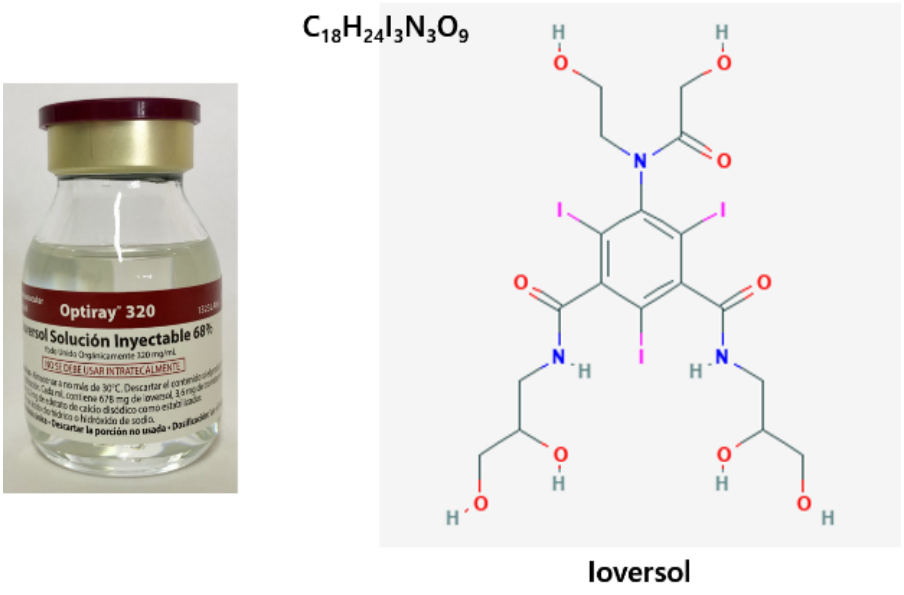

Figure 2: Chemical structure of ioversol

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Experiment Equipment

The equipment used for physical and chemical analysis according to environmental factors of the iodinated contrast agent was a 500 MHz Nuclear Magnetic Resonance Spectrometer of Bruker Avance (Germany) owned by Korea Basic Science Institute (KBSI).

Research Methods

For Iopamidol preparation P contrast agent and Ioversol preparation O contrast agent, solution was extracted. The solution that went through a pretreatment process of dilution using D_2O as solvent was filled into an NMR tube made of special glass and then inserted into a ^{1}H-NMR spectrometer to obtain spectra. After that, the structure of the material was derived from NMR spectrum data of the standard sample contrast agent. Elements of the material were estimated and analyzed based on chemical shift values.

Regarding radiation doses, 200 cGy (6 MV, 10 MV) and 300 cGy (6 MV, 10 MV) were irradiated in photon beam for Iopamidol preparation P contrast agent and Ioversol preparation O contrast agent using a Varian's LINAC device commonly used for cancer treatment in medical institutions. In the electron beam, 200 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV, 20 MeV) and 300 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV, 20 MeV) were irradiated. The dose rate of the LINAC device was set to be 600 cGy/min. The irradiation field was set to be 10×10 cm and the SSD was set to be 100 cm.

Results

^{1}H-NMR analysis of standard samples by contrast agent types

Analysis of iopamidol formulation P contrast agent

As a result of ^{1}H-NMR spectrum analysis of a standard sample of Iopamidol preparation P contrast agent, a resonance of a singlet peak was found in the 1.14 ppm region, indicating that its molecular structure had a HO element. The resonance of the quartet peak appeared in the 1.47 ppm region, indicating the presence of CH_3 element in the molecular structure. The resonance of a singlet peak appeared in the 3.65 ppm region, indicating an OH (HO) element in the molecular structure. The resonance of a triplet peak appeared in the 3.79 ppm region. The resonance of the quartet peak appeared in the 4.08 ppm region and the resonance of the triplet peak was found in the 4.41 ppm region in Fig. 3.

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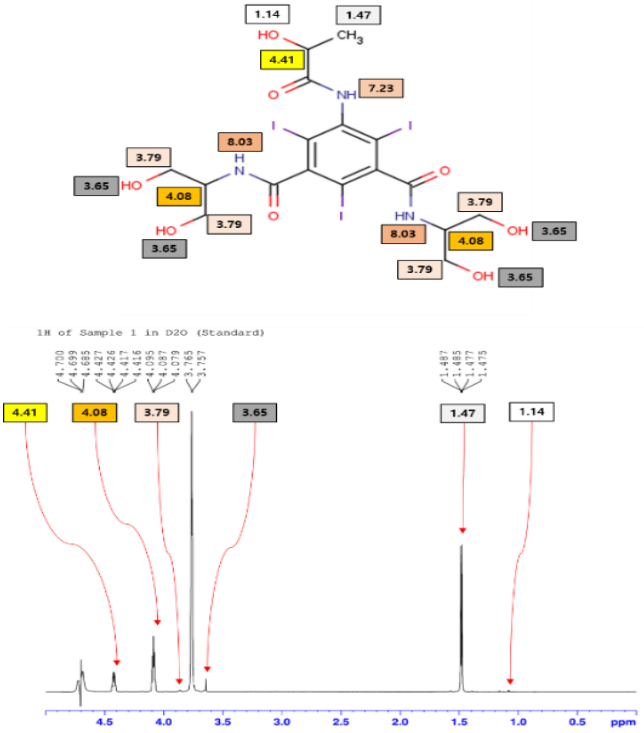

Figure 3: ^{1}H-NMR analysis of standard samples of iopamidol formulation P contrast agent

Analysis of ioversol formulation P contrast agent

As a result of ^{1}H-NMR spectrum analysis of the standard sample of Ioversol preparation O contrast agent, it was difficult to observe its components because the resonance of multiplets peak was distributed in the 3.35 ppm region. Although the resonance of multiplets peak was distributed in the 3.50~3.52 ppm region, amine group and carboxyl group appeared complex in the molecular structure. The resonance of the quartet peak appeared in the 3.58 ppm region, indicating the presence of an OH element in the molecular structure. The resonance of a singlet peak appeared in the 3.65 ppm region, indicating the presence of an OH (HO) element in the molecular structure. The resonance of the doublet peak was found in the 3.81 ppm area. The resonance of the quartet peak was found in the 3.93 ppm area and the resonance of the singlet peak was found in the 4.57 ppm area in Fig. 4.

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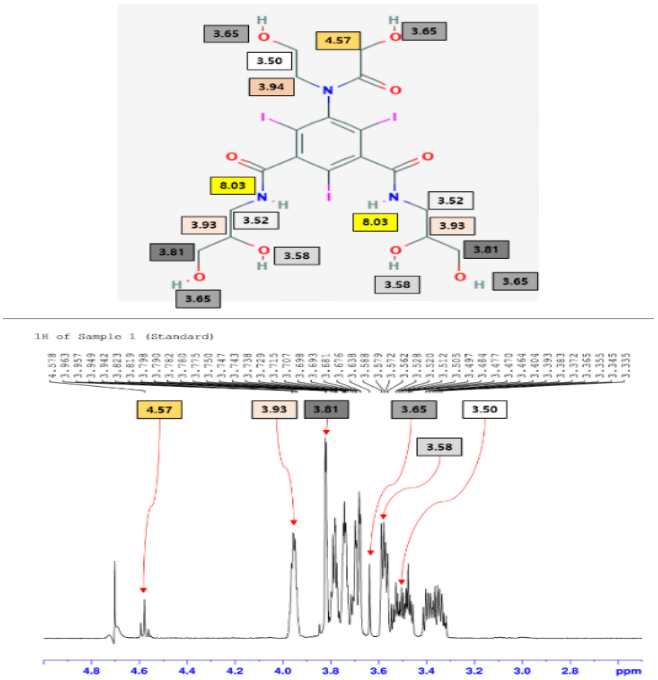

Figure 4: ^{1}H-NMR analysis of standard samples of ioversol formulation O contrast agent

^{1}H-NMR analysis of radiation dose

Analysis according to dose 200 cGy

As a result of comparing and analyzing ^{1}H-NMR spectra of standard samples of Iopamidol preparation P contrast agent and Iopamidol preparation P contrast agent irradiated according to the change of radiation dose, at a radiation dose of 200 cGy (6 MV, 10 MV) photon beam, the peak resonance of physicochemical change did not appear. In addition, the contrast agent irradiated with a radiation dose of 200 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV, 20 MeV) in the electron beam did not show a peak resonance of physicochemical change.

As a result of comparing and analyzing ^{1}H-NMR spectra of standard samples of the Ioversol preparation O contrast agent and the Ioversol preparation O contrast agent irradiated according to the change of radiation dose, at a radiation dose of 200 cGy (6 MV, 10 MV) photon beam, the peak resonance of physiochemical change did not appear. The peak resonance of physical and chemical changes did not appear in the contrast agent irradiated with a radiation dose of 200 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV, 20 MeV) in the electron beam.

Analysis according to dose 300 cGy

As a result of comparing and analyzing ^{1}H-NMR spectra of standard samples of Iopamidol preparation P contrast agent and Iopamidol preparation P contrast agent irradiated according to radiation dose, at a radiation dose of 300 cGy (6 MV, 10 MV) of the photon beam, the peak resonance of physiochemical change did not appear. For the contrast agent irradiated with a

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radiation dose of 300 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV) in an electron beam, regardless of the energy, in the 2.5 ppm region, the resonance of the singlet peak, which was not present in the standard sample, was clearly observed. It did not have neighboring protons in Fig. 5.

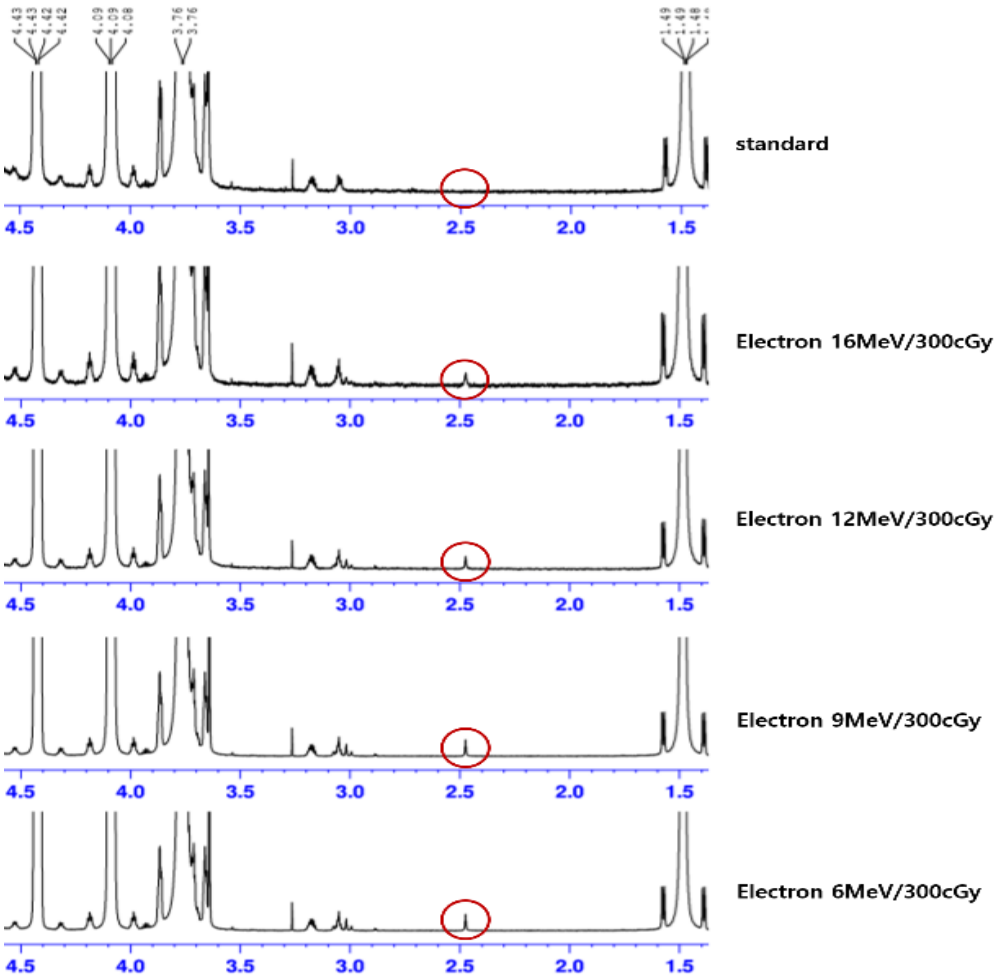

Figure 5: ^{1}H-NMR spectrum of iopamidol formulation P contrast agent according to electron beam energy and dose 300 cGy

In the 3.6 ppm region, the peak of the standard sample had a resonance of a singlet peak. A resonance of the quartet peak appeared in the contrast agent irradiated with a radiation dose of 300 cGy (20 MeV), which had three neighboring protons in Fig. 6.

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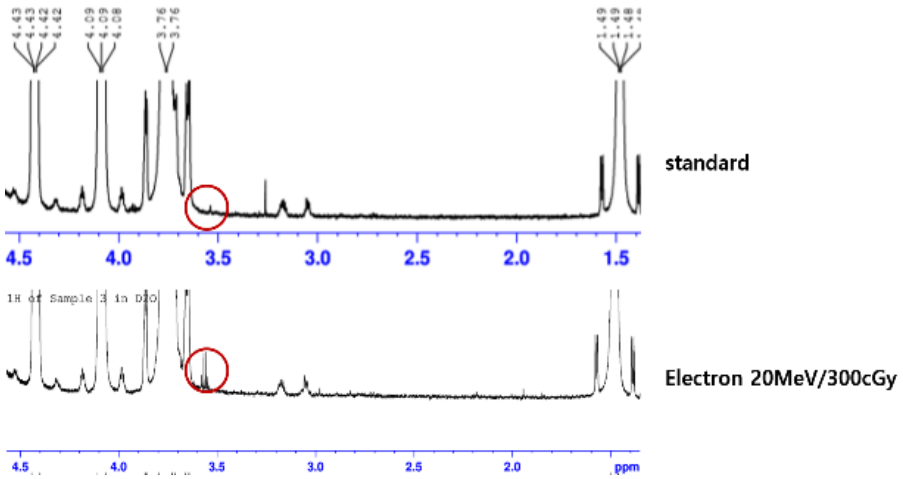

Figure 6: ^{1}H-NMR spectrum of iopamidol formulation P contrast agent according to electron energy 20 MeV and dose 300 cGy

As a result of comparing and analyzing ^{1}H-NMR spectra of standard samples of the Ioversol preparation O contrast agent and the Ioversol preparation O contrast agent irradiated according to radiation dose, at a radiation dose of 300 cGy (6 MV, 10 MV) of the photon beam, the peak resonance of physiochemical change did not appear. The peak resonance of physiochemical change did not appear in the contrast agent irradiated with a radiation dose of 300 cGy (6 MeV, 9 MeV, 12 MeV, 16 MeV, 20 MeV) in the electron beam either.

Discussion

It has been estimated that the prevalence of side effects is 3~8 times higher in those using ionic contrast agents than that in the general population (Wieten D.M., *et al.*, 1973). The incidence rate of side effects of ionic contrast agents is 17~35% when repeatedly administered. However, when a nonionic contrast agent is used, the incidence rate of side effects can be reduced to 5% (Siegle R., *et al.*, 1991). As a result of this, medical institutions mostly use a nonionic contrast agent as a vascular contrast agent. Although nonionic contrast agents have a very low likelihood of causing adverse reactions, residual risks are always present (Katayama H., *et al.*, 1990).

The mechanism of side effects caused by the use of a vascular contrast agent can be classified into chemical toxicity and specific constitutive reactions to the contrast agent. Side effects related to chemical toxicity are those that cause side effects to organs in proportion to the dose of the administered contrast agent. However, no discussion has been made on the effect of physical and chemical changes of a contrast agent on the human body due to environmental factors.

When the active ingredient of iodine preparation contrast agent is exposed to light such as X-

ray and high energy irradiation, the contrast agent substance is decomposed (Bettmann M.A. 1996). To avoid decomposition, some products are supplied in colored containers. However, this method does not protect products from decomposition by X-rays (Oldroyd S.D., *et al.*, 1995; Krause W., *et al.*, 1994). In addition, in the process of radiotherapy using high energy, CT or angiography is performed. Radiotherapy is sometimes performed while the contrast agent is not completely discharged from the body. In this study, as a result of studying physicochemical changes of the contrast agent by selecting the energy and dose mainly used in the radiation treatment process, it was found that some contrast agents had an effect on the electron beam. Therefore, it is necessary to analyze physical and chemical changes of the contrast agent according to various environmental factors. Based on results of this study, guidelines for safety evaluation of iodinated contrast agents and storage management methods should be further reinforced and established.

Conclusion

With a change of radiation dose as one environmental factor, Ioversol preparation O contrast agent showed no peak of physicochemical change at any energy or dose. Iopamidol preparation P contrast agent did not show any physical or chemical change in the photon beam. However, in the electron beam, there was a physical change in the 2.5 ppm region with a chemical change in the 3.6 ppm region. As a result of this study, it was found that high-dose electron beam irradiation caused a change in physical and chemical properties as a result of the formation of foreign substances due to dissociation from chemical bonds under the influence of dose rather than energy. Therefore, contrast agents must be stored in a shaded area as they might deteriorate from potential penetration of a high-dose radiation energy.

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References

1. Bettmann, M.A., 1996. Xenetix – a milestone in diagnostic imaging: concluding comment s. *Acta Radiol*, 37(S92).
2. Dawson, P., David O., and Ronald G., 1999. Textbook Contrast agent. *British Library*, 1-14. ISBN:1 899066 31 4
3. Dailymedi, 2017. Newspaper of Republic of Korea, viewed 23 March 2017,

http://www.dailymedi.com/detail.php?number=816967

4. DONGKOOK LIFE SCIENCE, 2019. URL of DONGKOOK LIFE SCIENCE, http://www.dkls.co.kr/product/list.php?type=medicine
5. HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE, 2016. URL of HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE of Republic of Korea, http://www.hira.or.kr/co/search.do?searchWord=%EC%A3%BC%EC%9A%94+%EC%A1%B0%EC%98%81%EC%A0%9C+%ED%92%88%EB%AA%A9
6. Kim, Y.S., Song, S.W., Ku, Y.M., Song, H.H., Yoon, S.A., Song, H.C et al., 2004. Clinical Characteristics and risk factors of contrast dye nephrotoxicity in patients performing arteriography. *The Korean Journal of Nephrology,* 23(2), pp.248-55.
7. Korea Institute of Drug Safety & Risk Management, 2011-19. Agency of Republic of Korea, https://www.drugsafe.or.kr/iwt/ds/ko/bbs/EgovBbs.do?bbsId=BBSMSTR_000000000001
8. Katayama, H., Yamaguchi, K., and Kozuka, T., 1990. Adverse reactions to ionic and non-ionic contrast agent. *Radiography*. 175, pp.621-3.
9. Krause, W., Miklautz, H., Kollenkirchen, U., and Heimann, G., 1994. Physico-chemical parameters of X-ray contrast agent. *Invest Radiol,* 29, pp.72-80.
10. Lim, K.Y., Goo, J.M., Kim, S.H. and Kim, J.H. 2003. Clinical efficacy of pamiray as a nonionic intravenous contrast material for abdominal CT. *Journal of the Korean Radiological Society,* 49(3), pp.197-201.
11. Ministry of Food and Drug Safety, 2017. Agency of Republic of Korea, https://nedrug.mfds.go.kr/searchDrug?sort=&sortOrder=false&searchYn=true&page=1&searchDisearch=detail&itemName=%EC%9D%B4%EC%98%A4%EB%B2%84%EC%86%94&entpName=&ingrName1=&ingrName2=&ingrName3=&itemSeq=&stdrCodeName=&atcCodeName=&inindutyClassCo=&sClassNo=&narcoticKindCode=&etcOtcCode=&makeMaterialGb=&searchCosea=AND&eeDocData=&searchConUd=AND&udDocData=&searchConNb=AND&nbDocData=&startPermitDate=&endPermitDate=
12. Oldroyd, S.D., Haylor, J.L., and Morcos, S.K., 1995. The acute effect of Ioversol on kidney function: role of endothelin. *Eur J Radiol,* 19, pp.91-5.
13. Siegle, R., Halvosen, R., and Dillon, J., 1991. The use of iohexol in patients with previous reactions to ionic contrast material. *Invest Radiol,* 26, pp.411-6.
14. William, H.B., and Dennis, P.S., 1991. Acute reactions to intravascular contrast agent:

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 1, 2021, Pages. 1642 - 1653
Received 15 December 2020; Accepted 05 January 2021.

types, risk factors, recognition, and specific treatment. *AJR*, pp.157-1153.

15. Wieten, D.M., Hirsch, F.D., and Hartman, G.W. 1973. Acute reaction to urographic contrast medium. Incidence, clinical characteristics and relationships to hypersensitivity states. *Am J Roentgenol*, 119, pp.832-40.