

—Report on Experiments and Clinical Cases—

Interaction Between Iopamidol and Gadopentetate Dimeglumine: An in-vitro Experimental Study of Direct Mixing

Hiromitsu Hayashi, Minoru Machida, Kazuhiro Furukawa and Tatsuo Kumazaki

Department of Radiology, Nippon Medical School

Abstract

Objective: To determine whether or not there is any interaction between iopamidol and gadopentetate dimeglumine (Gd-DTPA) in test tubes using the direct mixing manner.

Materials and Methods: The test solution was prepared by mixing iopamidol (Iopamiron 300) and Gd-DTPA (Magnevist) at a ratio of 1:1. The color, viscosity, and pH of the mixed solutions were assessed immediately after mixing and 1,3,6, and 24 hours after mixing. The concentration of aromatic primary amines, content of iopamidol, concentration of free iodine ion, and content of Gd-DTPA in the mixed solution were determined, and the presence or absence of spots, other than those resulting from iopamidol and Gd-DTPA, was determined using thin layer chromatography. These tests were carried out immediately, and 24 hours after mixing. Using iopamidol alone and Gd-DTPA alone as controls, the same items were examined.

Results: There was no significant change in the appearance or pH of the mixed iopamidol and Gd-DTPA solution immediately and 1, 3, 6, and 24 hours after direct mixing. The study of iopamidol alone or Gd-DTPA alone showed no apparently abnormal values or findings.

Conclusion: The direct mixing of iopamidol and Gd-DTPA in a test tube results in no significant interaction.

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Key words: contrast medium, CT, MRI, interaction

Introduction

The advance of diagnostic imaging, especially the introduction of CT and MRI in the clinical field, has enabled the correct diagnosis of many diseases. Contrast agents are frequently used in these techniques to identify the lesions more easily and to improve the accuracy of diagnosis. Generally, non-ionic iodine contrast agents are used in CT examination and gadolinium contrast agents are used in MRI. In recent clinical practice, both CT and

MRI examinations with the use of contrast materials are sometimes performed over a very short interval. In such cases, two kinds of contrast agents are present contemporaneously for a while in-vivo. Many studies have shown the safety of non-ionic iodine contrast agents¹⁻⁵ or gadolinium contrast agents⁶⁻⁹, respectively. However, the safety of those agents administered simultaneously or at a very short interval still remains to be studied.

The purpose of this experimental study was to determine whether or not there is any interaction

Correspondence to Hiromitsu Hayashi, MD, Department of Radiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan
E-mail: hhayashi@nms.ac.jp
Journal Website (<http://www.nms.ac.jp/jnms/>)

between the non-ionic iodine contrast agent iopamidol and the ionic gadolinium agent Gd-DTPA when the two agents are directly mixed in-vitro.

Materials and Methods

The contrast agents used in this study were Iopamiron 300 (main component: iopamidol, content: 612.4 mg/mL, Nihon Schering, Osaka, Japan. Lot No. 62287) as the non-ionic iodine contrast agent and Magnevist (Main component: gadopentetate dimeglumine (Gd-DTPA), content: 371.40 mg/mL, Nihon Schering, Osaka, Japan. Lot. No. 63230) as the ionic gadolinium contrast agent. Sixty mL of Iopamiron 300 and Magnevist were each put into a messcylinder and mixed fully to prepare a mixed solution, and this solution was then used as the test solution. The prepared solution was subjected to the following examination.

(I) In the appearance test of the mixed solution, (i) changes in the color and viscosity of the mixed solution were visually assessed and (ii) the hydrogen ion exponent (pH) was measured. These tests were carried out immediately and at 1, 3, 6, and 24 hours after mixing both contrast agents. The tests (i) were evaluated by three researchers (H.H, M.M and K.F) and the results were determined on the basis of consensus.

(II) For the study of Iopamidol in the mixed solution, (i) the concentration of aromatic primary amines that were detected after iodine contrast agents had been resolved, and (ii) that of Iopamidol were measured by high-performance liquid chromatography. Examination was carried out using a high-performance liquid chromatograph (CLASS-LC10A, Shimadzu Corporation, Kyoto, Japan) with an Inersil ODS-2 column (GL Science Inc., Tokyo, Japan) kept at around 40°C using a mixed solution of water and methanol (9:1) as the mobile phase, by the absolute calibration method at a wavelength of 256 nm. (iii) The concentration of free iodine ion was determined by the potentiometric titration method using a Potentiometric Automatic Titrator (AT-310J, Kyoto Electronics Co. Ltd, Kyoto, Japan). (iv) The presence or absence of spots other than of iopamidol spots was determined by thin layer

chromatography. The thin layer plate used was a Silica gel 60 F₂₅₄ (Merck Japan LTD, Tokyo, Japan) and the spotted amount was equal to a volume corresponding to 100 µg of iopamidol. The developing solutions used were ① methylethylketone / isopropanol / 25% aqueous ammonia (2:2:1), ② chloroform/methanol/25% aqueous ammonia (12:8:3), and ③ acetone/methylethylketone/25% aqueous ammonia (4:1:1), and the developing distance was 15 cm. Spots were detected using ultraviolet rays at 254 nm. Studies (i) to (iv) were performed twice: immediately and 24 hours after mixing. After the first experiment, the mixed solution was stored at room temperature in hermetic and light-shielded conditions until the second experiment.

(III) For the study of Gd-DTPA in the mixed solution, (i) the presence or absence of spots other than Gd-DTPA spots was determined by thin layer chromatography. The thin layer plate used was a high-performance thin layer chromatography pre-coated plate silica gel 60 (Merck Japan LTD, Tokyo, Japan) and the spotted amount was a volume corresponding to 15 µg of Gd-DTPA. The developing solutions were 1,4-dioxane/water/25% aqueous ammonia (35:15:1) and the developing distance was 8.5 cm. Spots were detected by the color development methods (1) with a xylenol orange solution and (2) with a ninhydrin/cadmium acetate solution. (ii) The concentration of Gd-DTPA was determined using a high-performance chromatograph (CLASS-LC10A, Shimadzu Corporation, Kyoto, Japan) with a Mos-Hypersil Column (Cemco Scientific Co. Ltd., Osaka, Japan) kept at around 40°C, using water/0.04M tetrabutylammonium perchlorate in methanol (3:1) as a mobile phase, by the internal standard method using p-oximethylbenzoate as a standard substance. Studies (i) and (ii) were performed immediately and 24 hours after mixing. After the first experiment, the mixed solution was stored at room temperature in light-shielded and hermetic conditions until the second experiment.

The controls were iopamidol alone and Gd-DTPA alone, respectively. Studies (I), (II), and (III) were performed on each control.

Table 1 Results of the direct mixing study of iopamidol and Gd-DTPA

		Mixed solution of iopamidol/Gd-DTPA (1 : 1)	
Appearance		Immediately after mixing	Colorless, transparent liquid with slight viscosity
		1 hour after mixing	Unchanged
		3 hours after mixing	Unchanged
		6 hours after mixing	Unchanged
		24 hours after mixing	Unchanged
pH		Immediately after mixing	7.4
		1 hour after mixing	7.4
		3 hours after mixing	7.4
		6 hours after mixing	7.4
		24 hours after mixing	7.5
Study of iopamidol	Aromatic primary amines	Immediately after mixing	Not more than 0.01%
		24 hours after mixing	Not more than 0.01%
	Concentration of free iodine ion	Immediately after mixing	0.7 $\mu\text{gI}^-/\text{mL}$
		24 hours after mixing	0.4 $\mu\text{gI}^-/\text{mL}$
	Thin layer chromatography	Immediately after mixing	No clear spot other than the iopamidol and Gd-DTPA spots obtained before mixing were detected, using any of 3 developing solutions with a different composition.
		24 hours after mixing	Unchanged
	Content of iopamidol	Immediately after mixing	303.4 mg/mL (100%)
		24 hours after mixing	300.1 mg/mL (99%)
Study of Gd-DTPA	Thin layer chromatography	Immediately after mixing	Detection method (1) showed no clear spot other than the iopamidol and Gd-DTPA spots obtained before mixing. Detection method (2) showed no spot other than the Gd-DTPA spots obtained before mixing.
		24 hours after mixing	Unchanged
	Content of Gd-DTPA	Immediately after mixing	185.6 mg/mL (100%)
		24 hours after mixing	188.3 mg/mL (101%)

Results

Study of the mixed solution (Table 1)

(I) Appearance test of the mixed solution

(i) The mixed solution was colorless, transparent, and slightly viscous. These were unchanged 1, 3, 6, and 24 hours after mixing. (ii) The pH value was 7.4, 7.4, 7.4, and 7.5 immediately and 1, 3, 6, and 24 hours after mixing, respectively, without a definite change.

(II) Study of iopamidol in the mixed solution

(i) The concentration of aromatic primary amines

was not more than 0.01% immediately and 24 hours after mixing. (ii) The concentration of iopamidol was 303.4 mg/mL immediately after mixing and 300.1 mg/mL at 24 hours, without a significant change. (iii) The concentration of free iodine ion was 0.7 $\mu\text{g}/\text{mL}$ immediately after mixing and 0.4 $\mu\text{g}/\text{mL}$ at 24 hours, without a remarkable change. (iv) The study of spots other than iopamidol spot produced one by thin layer chromatography using three developing solutions with a different composition showed no spots other than iopamidol spot and Gd-DTPA spot that usually appear using these three developing solutions.

Table 2 Results of the study of iopamidol alone or Gd-DTPA alone

		Iopamidol alone	Gd-DTPA alone
Appearance		Colorless, transparent liquid with slight viscosity	Colorless, transparent liquid with slight viscosity
pH		7.2	7.4
Study of iopamidol	Aromatic primary amines	0.01%	—
	Concentration of free iodine ion	1 $\mu\text{gI}^-/\text{mL}$	—
	Thin layer chromatography	An iopamidol spot was detected using any of the 3 developing solutions with a different composition.	A Gd-DTPA spot was detected using any of 3 developing solutions with a different composition.
	Content of iopamidol	609.7 mg/mL (100%)	—
Study of Gd-DTPA	Thin layer chromatography	Detection method (1) showed an iopamidol spot and detection method (2) showed no spot.	Detection methods (1) and (2) showed a Gd-DTPA spot.
	Content of Gd-DTPA	—	365.8 mg/mL (98%)

(III) Study of Gd-DTPA in the mixed solution

(i) The concentration of Gd-DTPA was 185.6 mg/mL immediately after mixing and 188.3 mg/mL at 24 hours, without a remarkable change. (ii) The study of spots by thin layer chromatography showed no spots other than Gd-DTPA spot and iopamidol spot that usually appear by detection method (1), and the study of spots showed no spots other than Gd-DTPA spot by detection method (2).

Control Studies (Table 2)

The control iopamidol alone was (I) (i) colorless, transparent, and slightly viscous and (ii) the pH value was 7.2. (II) (i) The concentration of aromatic primary amines was not more than 0.01% and (ii) the concentration of iopamidol was 609.7 mg/mL. (iii) The concentration of free iodine ion was 2 $\mu\text{g}/\text{mL}$ and (iv) the study by thin layer chromatography using three developing solutions with a different composition showed only a spot for iopamidol. (III) As the result of the study, (i) Gd-DTPA was not detected. (ii) The thin layer chromatography showed only an iopamidol spot by detection method (1) and no spot by detection method (2).

The other control Gd-DTPA was (I) (i) colorless and transparent and slightly viscous, and (ii) the pH value was 7.4. (II) Neither (i) aromatic primary

amines nor (ii) iopamidol were detected. (iii) No free iodine ion was detected and (iv) the study by thin layer chromatography using three developing solutions with a different composition showed only a Gd-DTPA spot. (III) (i) The content of Gd-DTPA was 365.8 g/mL. (ii) Thin layer chromatography showed only a Gd-DTPA spot by either of the detection methods (1) and (2).

Discussion

In many patients who are referred for diagnostic radiology, combinations of imaging studies are performed. The combination of CT and MRI is frequently performed, especially in correlative studies for efficacy assessment¹⁰. The low osmolar, non-ionic iodinated contrast agent, iopamidol, has been widely used in angiography, intravenous urography, and contrast-enhanced CT examinations. Adverse reactions after intravenous administration of non-ionic iodinated contrast agent are reported less frequently than with the use of ionic iodine contrast agents, with an incidence of 1.2%~3.13%³⁻⁵. The excretion route for iodinated X-ray contrast agents is mainly via the kidneys. In subjects with normal renal function, the blood concentration of iopamidol after injection exponentially declines over

time, and 97% of the injected iopamidol are excreted in the urine up to 24 hours after injection^{11,12}. Paramagnetic compounds such as MRI contrast agents cause contrast effect by shortening the relaxation time of protons or their environment, being quite different in their mechanism of action from iodinated contrast agents. The incidence of adverse reactions after intravenous injection of Gd-DTPA was reported to be 0.63%~2.4%^{8,9}. Gd-DTPA is excreted mainly through the kidneys. In subjects with normal renal function, injected Gd-DTPA is exponentially eliminated from the blood over time and 98.8% is excreted in the urine up to 24 hours after injection¹³.

Based on the main excretion route of both contrast agents, subjects with normal renal function excrete almost all of each agent administered in the urine up to 24 hours after injection. Thus, each injected contrast agent is thought to disappear from the body within a day, and the effect of the preceding contrast agent can be negligible the day after administration. When one agent is administered within 24 hours after injecting the other agent, however, both agents coexist for a while in the body. The shorter the interval is, the higher the dose of the first administered agent remaining in the body. This means both contrast agents exist and mix at high concentration in the body. Jinkins JR et al. have reported the proton relaxation enhancement effect of iodinated contrast agents in patients with brain tumors¹⁴, and Bloem JL et al. have studied the changes in CT attenuation numbers of urinary tracts after intravenous injection of Gd-DTPA¹⁰. However, to our knowledge, there is no study on the risk of interactions caused by both contrast agents administered simultaneously or at a very short interval. In the present study, we carried out a preliminary experimental study of directly mixing of the non-ionic iodine contrast agent iopamidol and the MRI contrast agent Gd-DTPA in test tubes to determine whether or not there is any interaction between them.

With respect to the mixed solution of iopamidol and Gd-DTPA, (I) the appearance and pH were unchanged immediately and 1, 3, 6, and 24 hours after mixing. (II) The study of iopamidol in the

mixed solution showed no remarkable findings indicative of changes due to interaction immediately and 24 hours after mixing. Similarly, (III) the study of Gd-DTPA showed no apparent abnormality immediately and 24 hours after mixing. Therefore, these results suggest that no interaction occurs between iopamidol and Gd-DTPA mixed in a test tube. However, this conclusion was derived from the results of the direct-mixing study with test tubes, providing no evidence that both agents do not interact in the body or that the two mixed agents produce no pathophysiological reaction. Further studies with animals are needed to examine whether or not the simultaneous or serial injections of the two agents at a very short interval may cause any physiological reaction. In addition, the effect of the two agents on the renal function should be studied precisely because both agents are excreted through the kidneys and they are obviously one of the main target organs for contrast-induced toxicity.

In conclusion, the present study confirmed that no interaction occurs between the non-ionic iodinated contrast agent iopamidol and the paramagnetic contrast agent Gd-DTPA when directly mixed in test tubes.

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