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Hypersensitivity following intra-arterial injections:
are there differences between low osmolar and iso-osmolar iodinated contrast media?

Sohn KH et al. Immediate and delayed hypersensitivity after intra-arterial injection of iodinated contrast media: a prospective study in patients with coronary angiography. European Radiology (2019) ; 29: 5314–5321.

BACKGROUND | OBJECTIVES | METHODOLOGY | RESULTS | CONCLUSION & KEY MESSAGES

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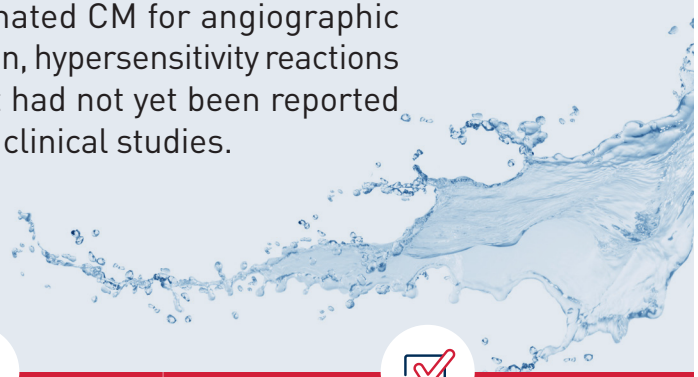
BACKGROUND

- Hypersensitivity reactions are categorized either as immediate reactions (onset within 1 hour after contrast media administration) or non-immediate or delayed reactions (onset beyond 1 hour after contrast media administration up to 10 days) [1]
- Some studies reported higher incidences of immediate and delayed adverse drug reactions after Intra-Arterial (IA) administration than after Intra-Venous (IV) administration of iodinated contrast media (CM). [2-3]
- Despite increasing use of iodinated CM for angiographic procedures with IA administration, hypersensitivity reactions (HSR) occurring in that context had not yet been reported from prospective observational clinical studies.



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OBJECTIVES

- To evaluate coronary angiography (CAG)-induced iodinated CM hypersensitivity incidence and severity related to intra-arterial administration of CM.
- To quantify the significant risk factor for immediate and delayed hypersensitivity.

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METHODOLOGY

A single-center prospective observational study

- Data were collected from the department of Internal Medicine in the National University Hospital of Seoul, Korea, between February 2015 and October 2015.
- 714 patients, undergoing CAG were enrolled in the study and were placed under nurse observation for one hour after iodinated CM administration. For assessment of delayed HSR directed telephone interviews were conducted by the Pharmacovigilance Center at 6-to 12h and 1-, 3-, 7-, and 14-days after the procedure. Both baseline and post-procedural serum creatinine were measured.

Contrast Media administration, assessment of HSR and renal function

- Two different CM were alternatively allocated:
  - IOCM, iodixanol, n=298 patients,
  - LOCM, ioversol, **Optiray®** 320, n=416 patients.
- Immediate HSR were classified according to ESUR Guidelines version 10.0 grading system.
- Delayed HSR were categorized as severe HSR in case of life-threatening reaction or reaction requiring hospitalization, moderate HSR when immediate response to treatment was obtained without hospitalization and mild HSR if no treatment was required.
- Both baseline and post-procedural serum creatinine measurements were used to search for possible acute kidney injury following CM administration.
- For comparison between sub-groups of patients with different prior exposure to ICM, chi-square test and Fisher's exact tests were used.
- Correlation between patient age and amount of CM was analyzed using Pearson's correlation.
- Logistic regression was conducted to evaluate risk factors.
- Results associated with p value of less than 0.05 were considered statistically significant.

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RESULTS (1,2)

Patients characteristics

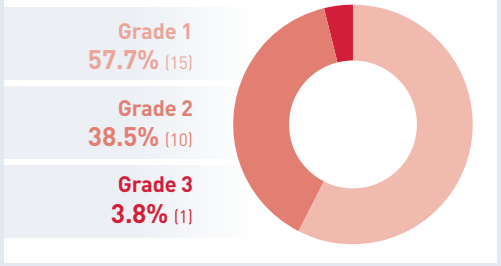
- Patients were separated into 3 groups:
  - No previous exposure to contrast
  - Previous CAG (IA exposure to CM): 343 (48.0%) patients
  - Previous IV exposure to CM: 428 (59.9%) patients

Clinical symptoms and severity of immediate and delayed HSR:

- 714 patients were enrolled and 26 (3.6%) of them experienced immediate HSR, and 108 (15.1%) experienced delayed HSR

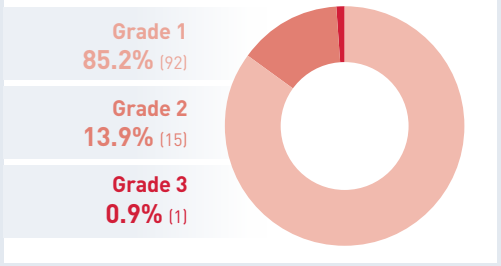
Among the 26 patients with immediate HSR, the authors noticed

Severity of reactions:



Among the 108 patients with delayed HSR, the authors noticed

Severity of reactions:



Risk factors for immediate and delayed HSR: Independent risk factors identified for development of HSR were:

- Previous exposure to intra-arterial iodinated contrast media for immediate HSR (OR 2.92, 95% CI 1.22-6.96; p=0.015)
- **Use of iodixanol compared to the use of Optiray® for delayed HSR (OR 1.61, 95% CI 1.07–2.43; p = 0.024)**
- This latter result is correlated with a higher incidence of delayed HSR of 18.8% (56/298) with iodixanol whereas **Optiray®** is associated with a significant lower incidence of 12.5% (52/416) (p = 0.022)

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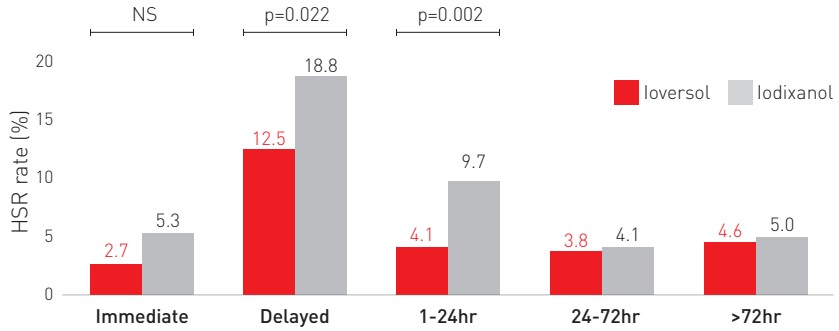
RESULTS (2,2)

Incidence of HSR based on the type of CM

- The authors analyzed the incidence of delayed HSR based on the different type of contrast media used in the study.

Figure: Immediate and delayed hypersensitivity reactions according to onset time, based on type of contrast media. HSR hypersensitivity reactions.



- For the delayed HSR, the study demonstrated a significant difference for the incidence of reactions within 24 h (p = 0.002) between the iodixanol subgroup and the two other subgroups.

Impact on renal function

- The authors measured serum creatinine to evaluate renal toxicity of the different contrast media. Serum creatinine was measured before examination and on days 2 or 3. Only five of the 711 patients showed an acute kidney injury defined as > 1.5 times baseline and/or an increase in serum creatinine > 0.3 mg/dL (incidence 0.7%), and there was no difference according to contrast type.

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CONCLUSION & KEY MESSAGES

- This is the first prospective study focused on HSR following iodinated CM exposure administered through IA route.
- This study confirmed that delayed hypersensitivity reactions were more frequently observed than immediate HSR.
- Delayed hypersensitivity reactions occurred at a higher rate but were less severe than immediate hypersensitivity reactions during coronary angiography.
- The risk factors identified for development of HSR were:
  - *Previous exposure to iodinated contrast media through IA route as risk factor for immediate HSR,*
  - *Use of iodixanol compared to the use of **Optiray®** (ioversol) as risk factor for delayed HSR.*
- **Optiray® is associated with a significantly lower incidence of delayed HSR than iodixanol.**
- No proven benefit of IOCM has been demonstrated to prevent contrast induced renal failure.[4]

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1. Brockow K, Ring J. Classification and pathophysiology of radiocontrast media hypersensitivity. Chem Immunol Allergy 2010 ; 95 : 157-169
2. Flinck A, Gottfridsson B (2001) Experiences with iohexol and iodixanol during cardioangiography in an unselected patient population.Int J Cardiol 80:143–151
3. Sutton AG, Finn P, Grech ED et al (2001) Early and late reactions after the use of iopamidol 340, ioxaglate 320, and iodixanol 320 in cardiac catheterization. Am Heart J 141:677–683
4. Azzalini. L. Incidence of contrast-induced acute kidney injury in a large cohort of all-comers undergoing percutaneous coronary intervention: Comparison of five contrast media. International Journal of Cardiology. 2018: 273: 69–73

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Optiray™ is a sterile, non-pyrogenic, aqueous solution intended for intravascular and subarachnoid administration.
Composition (*): Optiray™ 160 loversol, 339 mg/ml, which is equivalent to 160 mg/ ml of organically bound iodine. Optiray™ 240 loversol, 509 mg/ml, which is equivalent to 240 mg/ ml of organically bound iodine. Optiray™ 300 loversol, 636 mg/ml, which is equivalent to 300 mg/ml of organically bound iodine. Optiray™ 320 loversol, 678 mg/ml, which is equivalent to 320 mg/ml of organically bound iodine. Optiray™ 350 loversol, 741 mg/ml, which is equivalent to 350 mg/ml of organically bound iodine.
Indications (*): Optiray™ non-ionic X-ray contrast medium for diagnostic use only.
Optiray™ 350 is indicated in adults for angiography, including intra-arterial, digital subtraction angiography (IA-DSA), throughout the cardiovascular system, except selective cerebral angiography. Optiray™ 350 is also indicated for contrast enhanced computed tomographic imaging of the head and body, intravenous excretory urography, intravenous digital subtraction angiography and venography. Optiray™ 350 is indicated in children for angiocardiography.
Optiray™ 320 is indicated in adults for angiography, including digital subtraction angiography (DSA), throughout the cardiovascular system. The uses include but are not limited to cerebral, coronary, peripheral, visceral and renal arteriography, venography, aortography, and left ventriculography. Optiray™ 320 is also indicated for contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography. OPTIRAY™ 320 is indicated in children for angiocardiography, contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography.
Optiray™ 300 is indicated for cerebral, peripheral, and abdominal arteriography, including digital subtraction angiography (DSA), in adults. Optiray™ 300 is also indicated for contrast enhanced computed tomographic imaging of the head and body, venography, and intravenous excretory urography. Optiray™ 300 is indicated in children for cerebral, peripheral and abdominal angiography, including digital subtraction angiography (DSA), computed tomography of the head and body, and intravenous excretory urography.
Optiray™ 240 is indicated for cerebral, peripheral, and abdominal angiography, including intra-arterial, digital subtraction angiography (IA-DSA), and venography in adults. Optiray™ 240 is also indicated for contrast enhanced computed tomographic imaging of the head and body and intravenous excretory urography. Optiray™ 240 is indicated in children for cerebral, peripheral and abdominal angiography, including digital subtraction angiography (DSA), computed tomography of the head and body, and intravenous excretory urography. Optiray™ 240 is indicated for subarachnoid administration in adults for lumbar, thoracic and cervical myelography, in some countries.
Optiray™ 160 is only indicated for intra-arterial digital subtraction angiography (IADSA) in adults.
Posology and Method of Administration (*): The dosage may vary between 1 ml and 150 ml, maximum total dose 250 ml or less depending on the indications, the composition of Optiray™, the patient's factors and other technical factors. **Please refer to the Summary of Product Characteristics for the recommended dosage schedule.**
Contraindications: Hypersensitivity to ioversol ot to any of the excipients. Manifest hyperthyroidism. **Special Warnings and Precautions for Use:** Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration. Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients and in susceptible nondiabetic patients (often elderly with pre-existing renal disease). Patients should be well hydrated prior to and following the administration of Optiray. The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See Adverse Reactions). Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients administered Optiray. Early or late manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Increased risk is associated with a history of previous reaction to a contrast medium, and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities. The occurrence of severe idiosyncratic reactions has prompted the use of several pre-testing methods. However, pre-testing cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pre-testing in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Pre-medication with antihistamines or corticosteroids to avoid or minimize possible allergic reaction in such patients should be considered. Reports indicate that such pre-treatment does not prevent serious life-threatening reactions but may reduce both their incidence and severity. General anesthesia may be indicated in the performance of some procedures in selected patients. However, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia. In angiographic procedures, the risk of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are suggested. Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism. Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic disturbances which may be associated with a transitory increase in the circulating osmotic load. About procedural risks, selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure. Caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease. Specific warnings related to Intravascular administration: Caution must be exercised in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, severely impaired renal function, renal and hepatic disease, multiple myeloma or other paraproteinemia, anuria, pheochromocytoma, sickle cell disease and in neonates. Meticulous

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1. Brockow K, Ring J. Classification and pathophysiology of radiocontrast media hypersensitivity. Chem Immunol Allergy 2010 ; 95 : 157-169
2. Flinck A, Gottfridsson B (2001) Experiences with iohexol and iodixanol during cardioangiography in an unselected patient population.Int J Cardiol 80:143–151
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intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Specific warnings related to Subarachnoid administration: Myelography should not be performed in the presence of significant local or systemic infection where bacteremia is likely or when lumbar or cervical puncture is contraindicated. Myelography should be performed only in hospitalized patients under close medical observation, which is to be continued for 24 hours following the procedure.
Gravitational displacement of a concentrated bolus of Optiray™ above the level of C1 and especially into the intracranial subarachnoid spaces is to be avoided. Caution must be exercised in patients with history of seizure, epilepsy and elderly patients. **Please refer to the Summary of Product Characteristics for complete information about specific warnings.**
Interactions with other medicinal products and other forms of interaction: With metformine, vasopressor and the results of protein-bound iodine (PBI) and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. Please refer to summary of product characteristics.
Fertility, pregnancy and lactation: There are no adequate and well controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Although it has not been established that adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.
Effects on ability to drive and use machines: There is no known effect on the ability to drive and operate machines. However, because of the risk of early reactions, driving or operating machinery is not advisable for 30 to 60 min following administration.
Undesirable effects:
Adverse reactions following the use of Optiray™ are generally independent of the dose administered. Usually, they are mild to moderate, of short duration and resolve spontaneously (without treatment). However, even mild adverse reactions may be the first indication of a serious, generalized reaction that can occur rarely after iodinated contrast media. Such serious reactions may be life-threatening and fatal, and usually affect the cardiovascular system. Most adverse drug reactions to Optiray™ formulations occur within minutes after administration, however, contrast related hypersensitivity reactions may occur with a delay of some hours up to several days. Injections of contrast media are very commonly associated with sensations of warmth, and commonly associated with pain.
Adverse reactions may be classified as follows: • Hypersensitivity or anaphylactoid reactions are mostly mild to moderate with symptoms like rash, pruritus, urticaria, rhinitis and blister. These symptoms may occur independent of dose and route of administration and may be the first signs of an evolving shock with symptoms like pronounced decrease in blood pressure, tachycardia, dyspnoea, pallor and decrease in consciousness. Fatal cases were reported. • Vasovagal reactions with symptoms ranging from dizziness and hypotension to syncope. Vasovagal reactions may be caused either by the contrast media or by the procedure. • Cardiologic side effects during cardiac catheterization may include ECG changes, arrhythmia, conductivity disorders as well as coronary spasm. Such reactions may be caused by the contrast media or by the procedure. • Nephrotoxic reactions with acute renal failure may occur in patients with pre-existing renal damage. • Neurotoxic reactions after intra-arterial injection of the contrast medium like confusion, visual disorders, convulsions or fits. The symptoms are generally transient and abate spontaneously within several hours. • Local reactions at the injection site may occur and include rashes, swelling, inflammation and edema. Such reactions occur probably in most cases due to extravasation of the contrast agent. Extended paravasation may necessitate surgical treatment. For subarachnoid administration: Any adverse reactions known to occur with the intravascular use of Optiray™ can also occur during myelography, especially those which originate in the CNS. The most commonly observed adverse reaction was headache, which had an incidence of 8.6%.
Overdose: The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.
Pharmacological properties: Pharmacotherapeutic group: water-soluble, nephrotropic, low-osmolar X-ray contrast media ATC code: V08AB07.
Incompatibilities: No medicinal product should be mixed with Optiray™.
Nature and content of container: (*) Optiray™ is supplied in glass bottles and plastic pre-filled syringes.
Marketing authorization holder: (*) Information: Guerbet – BP 57400 – F-95943 Roissy CdG cedex - France. Tel: 33 (0) 1 45 91 50 00. Date of revision: 13/12/2020.

For current and complete prescribing information refer to the local Summary of Product Characteristics (SmPC) and /or contact your local Guerbet organization.
(*) Marketing Authorization Information: The marketing authorization holder, number and date of approval may differ from one country to another. Volume, presentation, indication and Posology and Method of Administration may also differ.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

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