Pneumologia
REVISTA SOCIETĂȚII ROMÂNE DE PNEUMOLOGIE

Immediate and delayed hypersensitivity reactions to intravascular iodine based radiocontrast media – an update

Abstract

Used since 1929 in medical practice, nowadays four chemical varieties of intravascular iodine based radiocontrast media (I-RCM) are available: ionic monomers with high osmolarity, ionic dimers with low osmolarity, non-ionic monomers with low osmolarity and non-ionic iso-osmolar dimers. Increasing prescription of I-RCMs augments the number of reported hypersensitivity reactions. I-RCM induced hypersensitivity reactions can be clasified in two types: immediate hypersensitivity reactions (IHRs - occurring within the first hour) and delayed hypersensitivity reactions (DHRs - occurring between 1 hour and 7 days). IHRs usually present as urticaria and angioedema but may associate severe respiratory and cardiovascular symptoms. Risk factors for an IHRs include a prior immediate reaction, personal history of atopic diseases (mainly asthma) and treatment with beta blocking agents. Diagnostic tests for IHRs include blood tests (serum tryptase) and skin tests (prick and intradermal) performed 2 to 6 months after IHR. High osmolarity of the I-RCM is the factor most strongly associated with IHRs. Primary prevention of IHRs involves the use of non-ionic low-osmolar or iso-osmolar agents for all intravascular procedures. DHRs are usually mild to moderate in severity, transient and self-limiting, presenting as maculopapular rash in more than 50% of cases. As with IHRs, the most important risk factor for DHRs is a previous reaction to I-RCM. Assessment of DHRs includes skin prick tests, intradermal and patch tests. Due to extensive cross-reactivity between I-RCM, a change of product is no guarantee against a repeated reaction. Current premedication procedures in patients with previous severe reactions can reduce symptoms, but may not prevent recurrent reactions.
Keywords: *iodine, radiocontrast media, osmolarity, hypersensitivity reactions, skin tests, premedication*

Rezumat

Reacțiile de hipersensibilitate imediate și tardive la substanțele de contrast iodate intravenoase - actualizare

Utilizate încă din anul 1929 în practica medicală, în prezent sunt disponibile patru tipuri chimice de substanțe de contrast iodate (SCI): monomeri ionici cu osmolaritate mare, dimeri ionici cu osmolaritate scăzută, monomeri non-ionici cu osmolaritate scăzută și dimeri neionici izo-osmolari. Folosirea din ce în ce mai frecventă în practica medicală a SCI a dus la creșterea numărului de reacții de hipersensibilitate raportate. Reacțiile de hipersensibilitate induse de SCI pot fi clasificate în două tipuri: reacții de hipersensibilitate imediate (RHI), care apar în prima oră, și reacții de hipersensibilitate tardive (RHT), care apar între o oră și 7 zile. RHI se prezintă cel mai frecvent sub formă de urticarie și angioedem, dar pot asocia simptome respiratorii și cardiovasculare severe. Factorii de risc pentru RHI includ o reacție anterioară la SCI, antecedente personale de boli atopice (în principal astm) și tratamentul cu beta-blocante. Testele diagnostice pentru RHI includ teste de laborator (triptaza serică) și teste cutanate (prick și intradermice) efectuate la un interval optim de 2-6 luni după RHI. Osmolaritatea ridicată a SCI este factorul de risc cel mai puternic asociat cu RHI. Profilaxia primară a RHI implică utilizarea de agenți neionici cu osmolaritate scăzută sau izo-osmolari pentru toate procedurile intravasculare care implică folosirea SCI. RHT sunt, de obicei, ușoare până la moderate ca severitate, tranzitorii și autolimitante, prezentându-se ca erupții cutanate maculopapuloase în mai mult de 50% din cazuri. Ca și în cazul RHI, factorul de risc cel mai important pentru RHT este o reacție anterioară la SCI. Evaluarea RHT include teste cutanate prick, intradermice și epicutanate (patch-test). Din cauza reactivității încrucișate extinse între SCI, schimbarea tipului de produs utilizat nu reprezintă o garanție împotriva unei reacții de hipersensibilitate repetate. Protocoalele de premedicație actuale, recomandate la pacienții cu reacții severe de hipersensibilitate în antecedente, pot reduce simptomele, dar nu pot preveni recurența reacțiilor.
Cuvinte-cheie: *iod, substanțe de contrast, osmolaritate, reacții de hipersensibilitate, teste cutanate, premedicație*

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The authors report no conflict of interest.

Introduction

From their first use in 1929, iodine based radiocontrast media (I-RCM) have multiplied and diversified their indications, with over 50 million diagnostic radiographic examinations performed worldwide each year, including myelography, angiography, venography, urography, mamography, endoscopic retrograde cholangiopancreatography, arthrography and computed tomography[1, 2].

This increasing prescription of I-RCM augments the number of hypersensitivity reactions, some of them even fatal, with incomplete elucidated physiopatological mechanisms[3].

The purpose of this review is to present the most used I-RCM, to describe the clinical features of I-RCM induced hypersensitivity reactions, to propose a diagnostic algorithm based on allergological work-up, and to define risk factors, primary and secondary prevention measures.

Types of I-RCM

Iodine atom absorbs X-rays due to its elevated atomic weight, providing radio-opacity [4]. The other elements of the I-RCM molecule act as carriers of the iodine, increasing the hydro-solubility and reducing the toxicity of the whole molecule. Iodine concentration of products used for radiological investigations varies between 200 and 400 mg/ml. An I-RCM must contain the greatest possible number of iodine atoms for optimised radio-opacity and must have low osmolarity for reduced toxicity[5].

Table I I-RCM most frequently used in Romania: osmolarity, viscosity at 37°C for solutions with 300 mg/ml iodine

	Generic name	Registered trade name	Osmolarity (mOsmkg-1)	Viscosity (mPa s)
Ionic monomers with high osmolarity	Amidotrizoate Ioxitalamate Ioxaglate	Odiston, Urografin Telebrix Hexabrix	2100 1710 600	8,9 5,2 7,5
Ionic dimers with low osmolarity	Iopamidol Iohexol	Iopamiron Ominipaque	616 640	4,7 6,1
Non-ionic monomers with low osmolarity	Iomeprol Ioversol Iopromide Iobitridol	Iomeron Optiray Ultravist Xanatix	521 630 607 695	4,5 5 4,6 6
Non-ionic dimers iso-osmolar	Iodixanol	Visipaque	290	11,4

I-RCM: intravascular iodine based radiocontrast media

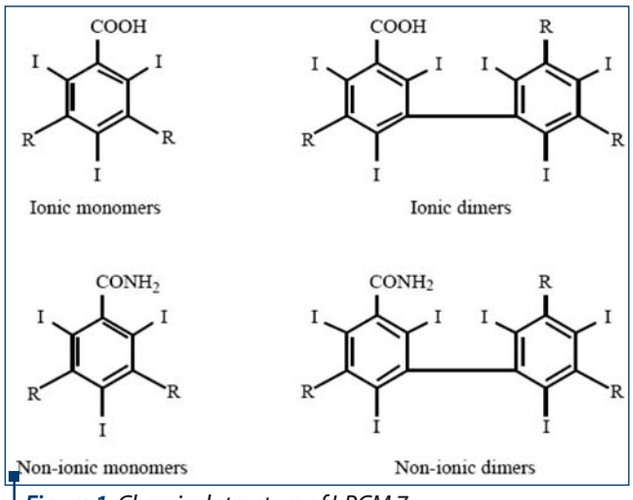

Figure 1. *Chemical structure of I-RCM 7*

Nowadays, four chemical varieties of I-RCM are available in clinical use: ionic monomers and dimers, non-ionic monomers and dimers. All four are tri-iodo benzyl ring derivatives with three atoms of iodine at 2, 4, 6 positions (in monomers) or six atoms of iodine per molecule of the ring anion (in dimers)[6] (Figure 1).

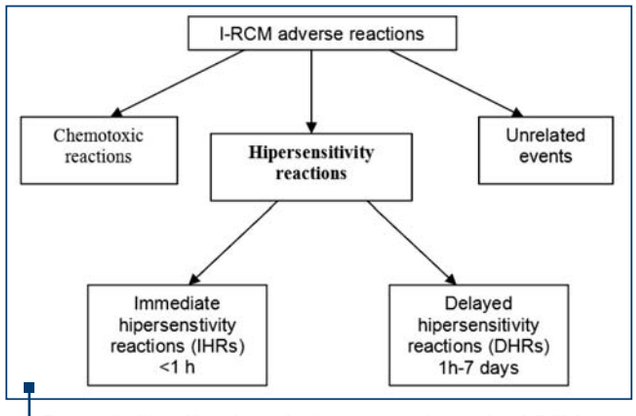

Figure 2. *Classification of adverse reactions after I-RCM administration[9]*

The main purpose of researchers was to reduce I-RCM osmolarity, first by dimerisation of ionic monomers, than by producing non-ionic monomers. Newest products are non-ionic dimers iso-osmolars (≈290 mOSm/kg H_2O), possesing an optimal ratio between radio-density and osmolarity[3]. Table I summarizes the I-RCM most frequently used in Romania.

Table II Symptoms of immediate and delayed hypersensitivity reactions to I-RCM[11]

Immediate reactions	Delayed reactions
Pruritus Urticaria Angioedema Flush Nausea, diarrhea, cramping Rhinitis (sneezing, rhinorrhea) Hoarsenes, cough Dyspnea (bronhospasm, laryngeal edema) Hypotension, tachycardia, arrhytmia Cardiovascular shock Cardiac arrest Respiratory arrest	Urticaria, angioedema Exanthema (macular, maculopapular eruption) Erythema multiforme minor Fixed drug eruption Stevens-Johnson Syndrome Toxic epidermal necrolysis Drug related eosinophilia with systemic symptoms (DRESS) Symetrical drug-related intertriginos and flexural exanthema (SDRIFE) Vasculitis

I-RCM: intravascular iodine based radiocontrast media

Table III Risk factors for IHRs and DHRs[3, 11, 13]

RISK FACTORS	
IHRs	**DHRs**
Previous IHRs to I-RCM Personal history of atopic diseases (asthma) Sex (women more predisposed than men) Age (severe reactions predomining in elderly) Treatment with beta-blockers/ IL-2 Cardiac disease Intravenous versus intraarterial route Anxiety	Previous DHRs to I-RCM Use of nonionic dimers Serum creatinine > 2 mg/dl History of drug intolerance reactions or allergic contact dermatitis Mastocitosis Current viral infections Autoimmune diseases (systemic lupus erythematosus)

IHR: immediate hypersensitivity reaction, DHR: delayed hypersensitivity reaction, I-RCM: intravascular iodine based radiocontrast media

Types of reactions induced by I-RCM

I-RCM can induce a large variety of adverse reactions, classified in 3 types: chemotoxic reactions (dose dependent and with organ toxicity), hypersensitivity reactions (idiosyncratic, independent of dose) and unrelated events (unspecified symptoms)[7] (Figure 2).

Immediate hypersensitivity reactions

The osmolarity of the agent is the factor most strongly associated with IHRs. Mild to moderate IHRs occur with 5% to 13% of procedures using ionic high-osmolar agents and 0.2% to 3% of those using non-ionic low-osmolar agents. Life-threatening immediate reactions occur in 0.04% to 0.22% of ionic high-osmolar agents infusions and in 0.004% to 0.04% of non-ionic low-osmolar agents administrations. However, it does not appear to be a difference in overall mortality between lower or higher osmolarity I-RCM[8, 9].

The iso-osmolar agent iodixanol may be associated with similar or even fewer IHRs than the nonionic low-osmolar agents[10].

The majority of clinical symptoms in IHRs develop in 5-15 minutes and resolve in 30-60 minutes with severe and fatal reactions occuring in the first 30 minutes. Clinical symptoms of IHRs to I-RCM are listed in Table II. Pruritus and mild urticaria are the most common immediate manifestations, occurring in up to 70% of affected patients[11].

The most important risk factor for an IHRs is a previous immediate reaction with a 21-60% risk of a repeated reaction when re-exposed to the same or a similar ionic I-RCM[12]. Personal history of atopic diseases is another important risk factor, with asthma as main predisposing factor of severe IHRs[13]. Other risk factors for IHRs are summarized in Table III.

The pathophysiology of IHRs remains controversial, including mechanisms non IgE-mediated (direct effect of osmolarity on mast cell membrane, activation of the coagulation, kinin, and/or complement cascades) and IgE-mediated (mainly in the cases of severe reactions)[14].

Tests performed immediately after reactions include serum tryptase (detected in blood between 30 minutes and 3 hours from the onset of symptoms) and urinary N-methylhistamine (in 24-hour urine sample). In case of positive results, these tests indicate massive activation and degranulation of mast cells and help distinguish anaphylaxis from other acute, severe events[15].

Skin tests are indicated in patients with severe IHRs with clinical features of IgE-mediated reactions and their results may also help guide the choice of RCM for future radiological investigations. Skin testing should be performed by an allergist, preferably within two to six months after hypersensitivity reaction, as the incidence of positive skin tests appears to decline prior to and after this time period[16]. Recommended concentrations for I-RCM skin tests are mentioned in Table IV.

As for I-RCM-specific IgE antibodies, no commercial assay is available for routine serum measurement. Recent studies demonstrated the potential role of basophil activaton test (BAT) as a diagnostic tool for an immediate RCM hypersensitivity, particularly as a confirmation test. However BAT is

Table IV Recomended I-RCM skin test concentrations[18]

TEST	CONCENTRATION	Time of reading in IHRs	Time of reading in DHRs
Prick test	Undiluted	20 minutes	20 minutes, 48 h, 72 h
Intradermal test	1/10	20 minutes	20 minutes, 48 h, 72 h
Patch test	Undiluted	-	20 minutes, 48 h, 72 h

I-RCM: intravascular iodine based radiocontrast media

Table V Premedication regimens for patients with previous reactions to I-RCM[18]

Elective premedication regimens	Emergency premedication regimens
50 mg Prednisone or 32 mg Metilprednisolone p.o. (13 h, 7 h and 1 h prior to procedure)* AND H1-antihistamine with rapid onset of action p.o. 1 h prior to procedure	40 mg Metilprednisolone sodium succinate or 200 mg Hydrocortizone hemisuccinate IV or 8 mg Dexametazone q4h until procedure AND Difenhidramine& 50 mg IV 1 h prior procedure

**Equivalent preparations can be used; some regimens include only doses at 12 hours and 1 hour prior procedure. &Not available in Romania. I-RCM: intravascular iodine based radiocontrast media*

available only in research centers, not in current practice[17].

The gold standard diagnostic test remains the drug provocation test, not routinely performed due to the risk of severe reactions.

Primary prevention of IHRs involves the use of non-ionic low-osmolar or iso-osmolar agents for all intravascular procedures. Considered that a non-ionic low-osmolar or iso-osmolar agent will be used, empiric premedication of patients who have not experienced problems with I-RCM in the past is not supported by the available evidence[11,13].

I-RCM that caused previous IHRs should be avoided. Skin tests (skin prick test and IDT) with RCM and reading after 20 minutes are recommended. In case of a positive reaction, a skin test-negative product should be chosen by testing a panel of several different I-RCM[16, 19].

Different premedications schemes, none generally accepted, are mentioned in literature for the patients with previous reactions to I-RCM including systemic corticosteroids, H1 and H2-antihistamines. Several elective and emergency premedications regimens are summarized in Table V.

Despite corticosteroid premedication, the recurrence rate of I-RCM reaction after administration has been estimated to be almost 10%, severe IHRs occuring even in patients with optimal premedication[20].

Delayed hypersensitivity reactions

The frequency of DHRs highly varies from 0.5% to 23% due to difficulty in verifying whether symptoms occurring hours or days after I-RCM exposure are actually caused by I-RCM[21]. The most frequent DHRs present as maculopapular rash in more than 50% of cases. Other frequently occurring DHRs include erythema, urticaria, angioedema, macular exanthema or scaling skin eruption, as mentioned in Table II.

Compared with IHRs, DHRs are usually mild to moderate in severity, transient and self-limiting. Majority of DHRs occur in 3-48 hours after I-RCM exposure and resolve after 1-7 days.

As with IHRs, the most important risk factor for DHRs is a previous reaction to I-RCM. Other reported risk factors are mentioned in Table III.

In terms of pathophysiology, most of the I-RCM-induced delayed skin eruptions appear to be T-cell mediated allergic reactions, skin biopsies of the affected areas showing a lymphocite-rich perivascular infiltrate (T cells CD45RO+, CD8+), sometimes asociated with eosinophils. The proposed pathogenic mechanism implies that I-RCM are chemically non-reactive (unable to form haptens) and might stimulate memory T-cells directly *via* their T-cell receptor[13].

Routine laboratory tests during or immediately after DHRs include CBC (eosinophilia), liver and renal function tests. Skin biopsy is not mandatory, and the results must be interpreted in the context of the whole clinical report[11, 13].

After recovery, *in vivo* tests including skin prick, intradermal and patch tests with I-RCM diluted and undiluted can be performed (Table III), intradermal tests proving more reliable, but larger studies are needed to draw a definite conclusion. As *in vitro* test lymphocite trasformation test (LTT) has occasionally been used in diagnosis of DHRs with inconsistent results, it cannot be recommended for routine use[22].

In patients with previous DHRs to I-RCM, another agent should be chosen if re-exposure is required. However, due to frequent cross-reactivity between different I-RCM, a change of product is no guarantee against a repeated reaction. It has not yet been proven whether skin testing is a suitable tool for the selection of an alternative RCM that can be used safely[11, 13].

In terms of premedication regimens, the guidelines from the Contrast Media Safety Committee of the European Society of Urogenital Radiology stated that patients with previous serious DHRs to I-RCM can be given oral steroid prophylaxis if new I-RCM exposure is required. However, DHRs have been reported despite corticosteroid premedication[23].

Conclusions

Despite the introduction in clinical practice of non-ionic I-RCM with low or iso-osmolarity, adverse reactions to I-RCM still represent a challenge to the treating physician.

Available evidence indicates that both severe IHRs and DHRs may be allergic reactions, involving IgE and T-cells mechanisms. Therefore prick, intradermal and patch tests can be useful both in diagnosis and in selection of alternative I-RCM. However, the specificity and sensitivity of these tests remain to be assessed.

For an I-RCM investigation in a patient with a previous I-RCM-induced hypersensitivity reaction, the clinician should choose a structurally different I-RCM and resuscitation equipement should be available during the radiological examination.

Also prophylactic regimens including corticosteroids and H1-antihistamines have to be considered. Current premedication procedures in patients with previous severe reactions can reduce symptoms, but may not prevent recurrent reactions.

In conclusion, hypersensitivity reactions to I-RCM still remain a hot topic in the field of drug allergy, with still open questions regarding the pathophysiology, diagnosis and prevention of these reactions. ■

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